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Standards of Care in Diabetes—2025

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THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

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[T]he simple word *Care* may suffice to express [the journal's] philosophical mission. The new journal is designed to promote better patient care by serving the expanded needs of all health professionals committed to the care of patients with diabetes. As such, the American Diabetes Association views *Diabetes Care* as a reaffirmation of Francis Weld Peabody's contention that "the secret of the care of the patient is in caring for the patient."

—Norbert Freinkel, *Diabetes Care*, January-February 1978

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Diabetes Care is a journal for the health care practitioner that is intended to increase knowledge, stimulate research, and promote better management of people with diabetes. To achieve these goals, the journal publishes original research on human studies in the following categories: Clinical Care/Education/Nutrition/Psychosocial Research, Epidemiology/Health Services Research, Emerging Technologies and Therapeutics, Pathophysiology/Complications, and Cardiovascular and Metabolic Risk. The journal also publishes ADA statements, consensus reports, clinically relevant review articles, letters to the editor, and health/medical news or points of view. Topics covered are of interest to clinically oriented physicians, researchers, epidemiologists, psychologists, diabetes educators, and other health professionals. More information about the journal can be found online at diabetesjournals.org/care.

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Introduction and Methodology: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2025;48(Suppl. 1):S1–S5 | https://doi.org/10.2337/dc25-SINT

Diabetes is a complex, chronic condition requiring continuous medical care with comprehensive risk-reduction strategies beyond glycemic management. Ongoing diabetes self-management education and support are critical to empowering people, preventing acute complications, and reducing the risk of long-term complications. Significant evidence exists that supports a range of interventions to improve diabetes outcomes.

The American Diabetes Association (ADA) "Standards of Care in Diabetes," referred to here as the Standards of Care, serves as a comprehensive resource to clinicians, researchers, policy makers, and other stakeholders. It outlines key elements of diabetes care, sets treatment goals, and provides tools to assess care quality, all aimed at improving diabetes care and outcomes across diverse populations.

The ADA Professional Practice Committee (PPC) updates the Standards of Care annually and includes discussion of emerging clinical considerations in the text, and as evidence evolves, clinical guidance is added to the recommendations in the Standards of Care. The Standards of Care is a "living" document where important updates are published online should the PPC determine that new evidence or regulatory changes (e.g., drug or technology approvals, label changes) merit immediate inclusion. More information on the "Living Standards" can be found on the ADA professional website DiabetesPro at professional.diabetes.org/standards-of-care/living-standards-update. The Standards of Care supersedes all previously published ADA statements—and the recommendations therein—on clinical topics within the purview of the Standards of Care; while still containing valuable analysis, ADA statements should not be considered the current position of the ADA. The Standards of Care receives annual review and approval by the ADA Board of Directors and is reviewed by the ADA scientific team and clinical leadership. The Standards of Care also undergoes external peer review annually.

SCOPE OF THE GUIDELINES

The recommendations in the Standards of Care include screening, diagnostic, and therapeutic actions that are scientifically proved or known based on expert clinical practice or believed to favorably affect health outcomes of people with diabetes. They also cover the prevention, screening, diagnosis, and management of diabetes-associated complications and comorbidities. The recommendations encompass care throughout the life span for youth (children aged birth to 11 years and adolescents aged 12–17 years), adults (aged 18–64 years), and older adults (aged ≥65 years). The recommendations cover the management of type 1 diabetes, type 2 diabetes, gestational diabetes mellitus, and other types of diabetes and/or hyperglycemic conditions.

The Standards of Care does not provide comprehensive treatment plans for complications associated with diabetes, such as diabetic retinopathy or diabetic foot ulcers, but offers guidance on how and when to screen for diabetes complications, management of complications in the primary care and diabetes care settings, and referral to specialists as appropriate. Similarly, regarding the psychosocial and behavioral health factors often associated with diabetes and that can affect diabetes care, the Standards of Care provides guidance on how and when to screen, management in the primary care and diabetes care settings, and referral but does not provide comprehensive management plans for conditions that require specialized care, such as mental illness.

INTENDED AUDIENCE

The intended audience for the Standards of Care includes primary care physicians, endocrinologists, nurse practitioners, physician associates/assistants, pharmacists, registered dietitian nutritionists, diabetes care and education specialists, and all members of the diabetes care team. The Standards of Care also provides guidance to specialists caring for people with diabetes and its multitude of complications, such as cardiologists, nephrologists, emergency physicians, internists, pediatricians, psychologists, neurologists, ophthalmologists, and podiatrists. Additionally, these recommendations help payors, policy makers, researchers, research funding organizations,

The "Standards of Care in Diabetes," formerly called "Standards of Medical Care in Diabetes," was originally published in 1988. The most recent full review and revision was in December 2024.

**A complete list of members of the American Diabetes Association Professional Practice Committee is provided in this section.*

Duality of interest information for each author is available at https://doi.org/10.2337/dc25-SDIS.

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and advocacy groups to align their policies and resources and deliver optimal care for people living with diabetes.

The ADA strives to improve and update the Standards of Care to ensure that clinicians, health plans, and policy makers can continue to rely on it as the most authoritative source for current guidelines for diabetes care. The Standards of Care recommendations are not intended to preclude clinical judgment. They must be applied in the context of excellent clinical care, with adjustments for individual preferences, comorbidities, and other patient factors. For more detailed information about the management of diabetes, please refer to *Medical Management of Type 1 Diabetes* (1) and *Medical Management of Type 2 Diabetes* (2).

METHODOLOGY AND PROCEDURE

The Standards of Care includes discussion of evidence and clinical practice recommendations intended to optimize care for people with diabetes by assisting health care professionals and individuals in making shared decisions about diabetes care. The recommendations are informed by a systematic review of evidence and an assessment of the benefits and risks of alternative care options.

Professional Practice Committee

The PPC of the ADA is responsible for the Standards of Care content. The PPC is an interprofessional expert committee comprising physicians, nurse practitioners, pharmacists, diabetes care and education specialists, registered dietitian nutritionists, behavioral health scientists, and others who have expertise in a range of areas including but not limited to adult and pediatric endocrinology, epidemiology, public health, behavioral health, cardiovascular risk management, microvascular complications, nephrology, neurology, ophthalmology, podiatry, clinical pharmacology, preconception and pregnancy care, weight management and diabetes prevention, and use of technology in diabetes management. Each year, ADA conducts a national call for applications to recruit members of the PPC. Appointment to the PPC is based on excellence in clinical practice and research, with attention to appropriate representation of members based on considerations including but not limited to demographic, geographic, work setting, or identity characteristics (e.g., gender, race and ethnicity, ability level). A PPC chair or co-chairs are appointed by the ADA (N.A.E. and R.G.M. are co-chairs for the 2025 Standards of Care) and oversee the committee. In addition to the PPC members, several professionals serve as designated subject matter experts to support the PPC in the development of specific content areas of the Standards of Care. While designated subject matter experts assist with content development, only PPC members formally vote on Standards of Care recommendations for final approval.

Additionally, several organizations have endorsed specific sections of the 2025 Standards of Care. The American College of Cardiology (ACC) reviewed and approved Section 10, "Cardiovascular Disease and Risk Management." The American Society for Bone and Mineral Research reviewed and approved the "Bone Health" subsection in Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities." The Obesity Society reviewed and approved Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes." New to the 2025 Standards of Care, the American Geriatrics Society reviewed and approved Section 13, "Older Adults."

Each section of the Standards of Care is reviewed annually and updated with the latest evidence-based recommendations by a subcommittee. The subcommittees perform systematic literature reviews and identify and summarize the scientific evidence. An information specialist with knowledge and experience in literature searching (a librarian) is consulted as necessary. A guideline methodologist (R.R.B. for the 2025 Standards of Care) with expertise and training in evidence-based medicine and guideline development methodology oversees all methodological aspects of the development of the Standards of Care and serves as a statistical analyst.

Disclosure and Duality of Interest Management

All members of the expert panel (the PPC members and subject matter experts) and ADA scientific team are required to comply with the ADA policy on duality of interest, which requires disclosure of any financial, intellectual, or other interests that might be construed as constituting an actual, potential, or apparent conflict, regardless of relevancy to the guideline topic. For transparency, ADA requires full disclosure of all relationships. Full disclosure statements from all committee members are solicited and reviewed during the appointment process. Disclosures are then updated throughout the guideline development process (specifically before the start of every meeting), and disclosure statements are submitted by every Standards of Care contributor upon submission of the updated Standards of Care section. Members are required to disclose conflicts for a time frame that includes 1 year prior to initiation of the committee appointment process until publication of that year's Standards of Care. Potential dualities of interest are evaluated by a designated review panel and, if necessary, the Legal Affairs Division of the ADA. The duality of interest assessment is based on the relative weight of the financial relationship (i.e., the monetary amount) and the relevance of the relationship (i.e., the degree to which an independent observer might reasonably interpret an association as related to the topic or recommendation of consideration). In addition, the ADA adheres to section 7 of the Council of Medical Specialty Societies "Code for Interactions with Companies" (3). The duality of interest review panel also ensures the majority of the PPC and the PPC chair or co-chairs are without potential conflict relevant to the subject area. Furthermore, the PPC chair or co-chairs are required to remain unconflicted for 1 year after the publication of the Standards of Care. Members of the committee who disclose a potential duality of interest pertinent to any specific recommendation are prohibited from participating in discussions related to those recommendations and their votes are excluded. No expert panel members were employees of any pharmaceutical or medical device company during the development of the 2025 Standards of Care. Members of the PPC, their employers, and their disclosed potential dualities of interest are listed in the section "Disclosures: Standards of Care in Diabetes—2025."

Funding Source

The Standards of Care guideline is funded by ADA general revenue. No other entity, including industry, provides financial support for the guideline. Committee members received no remuneration for their participation in development of this guideline.

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Evidence Review

The Standards of Care subcommittee for each section creates an initial list of relevant clinical questions that is reviewed and discussed by the expert panel. In consultation with a systematic review expert and librarian, each subcommittee devises and executes systematic literature searches. For the 2025 Standards of Care, PubMed, Medline, and EMBASE were searched for the time periods of 1 June 2023 to 19 July 2024. Searches are limited to studies published in English. Subcommittee members also manually search journals, reference lists of conference proceedings, and regulatory agency websites. All potentially relevant citations are then subjected to a full-text review. In consultation with the methodologist, the subcommittees prepare the evidence summaries and grading for each section of the Standards of Care. All PPC members discuss and review the evidence summaries and make revisions as appropriate. The final evidence summaries are then deliberated on by the PPC, and the recommendations that will appear in the Standards of Care are drafted.

Grading of Evidence and Recommendation Development

A grading system (**Table 1**) developed by the ADA and modeled after existing methods is used to clarify and codify the evidence that forms the basis for the recommendations in the Standards of Care. All recommendations in the Standards of Care are critical to comprehensive care regardless of rating. ADA recommendations are assigned ratings of **A**, **B**, or **C**, depending on the quality of the evidence in support of the recommendation. Expert opinion **E** is a separate category for recommendations in which there is no evidence from clinical trials, clinical trials may be impractical, or there is conflicting evidence. Recommendations assigned an **E** level of evidence are informed by key opinion leaders in diabetes (members of the PPC and external subject matter experts) and cover important elements of clinical care. All Standards of Care recommendations receive a rating for the strength of the evidence and not for the strength of the recommendation. Recommendations with **A**-level evidence are based on large, well-designed randomized controlled trials or well-done meta-analyses of randomized controlled trials. Generally, these recommendations have the best chance of improving outcomes when applied to the population for which they are appropriate. Recommendations with lower levels of evidence may be equally important but are not as well supported.

Of course, published evidence is only one component of clinical decision-making. Clinicians care for people, not populations; guidelines must always be interpreted with the individual person in mind. Individual circumstances, such as comorbid and coexisting diseases, age, education, disability, and, above all, the values and preferences of the person with diabetes, must be considered and may lead to different treatment goals and strategies. Furthermore, conventional evidence hierarchies, such as the one adapted by the ADA, may miss nuances important in diabetes care. For example, although there is excellent evidence from clinical trials supporting the importance of achieving multiple risk factor control, the optimal way to achieve this result is less clear. It is difficult to assess each component of such a complex intervention.

Table 1—ADA evidence-grading system for "Standards of Care in Diabetes"

Level of evidence	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies, including: • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies, including: • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

Evidence to Recommendations

All accumulated evidence was reviewed and discussed by all PPC members and external subject matter experts during multiple virtual meetings and a 2-day in-person meeting in Arlington, Virginia, in July 2024. Standards of Care recommendations were updated based on the newly acquired evidence, and each recommendation was voted on by the PPC, with 80% consensus required for any recommendation to be approved.

Revision Process

Public comment is particularly important in the development of clinical practice recommendations; it promotes transparency and provides key stakeholders, including people with diabetes and their caregivers, the opportunity to identify and address gaps in care. The ADA holds a year-long public comment period requesting feedback on the Standards of Care. The PPC reviews compiled feedback from the public in preparation for the annual update but considers more pressing updates throughout the year, which may be published as "living" Standards updates. Feedback from the larger clinical community and general public was invaluable for the revision of the 2024 Standards of Care. Readers who wish to comment on the 2025 Standards of Care are invited to do so at professional.diabetes.org/SOC.

Feedback for the Standards of Care is also obtained from external peer reviewers. The Standards of Care is reviewed by ADA clinical leadership and scientific and medical team and is approved by the ADA Board of Directors, which includes health care

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professionals, scientists, and other stakeholders. The ACC performs an independent external peer review, and the ACC provides endorsement of Section 10, "Cardiovascular Disease and Risk Management." In addition, the American Society for Bone and Mineral Research provides endorsement for the "Bone Health" subsection of Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," The Obesity Society provides endorsement for Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes," and the American Geriatrics Society provides endorsement for Section 13, "Older Adults." Feedback received from every stakeholder is adequately addressed by the committee, and the final version is approved by all parties prior to publication. The ADA adheres to the Council of Medical Specialty Societies revised "CMSS Principles for the Development of Specialty Society Clinical Guidelines" (4).

ADA STANDARDS, STATEMENTS, REPORTS, AND REVIEWS

The ADA has been actively involved in developing and disseminating diabetes care clinical practice recommendations and related documents for more than 35 years. The ADA Standards of Care is an essential resource for health care professionals caring for people with diabetes. ADA Statements, Consensus Reports, and Scientific Reviews support the recommendations included in the Standards of Care.

Standards of Care

The annual Standards of Care supplement to *Diabetes Care* contains the official ADA position, is authored by the ADA, and provides all of the ADA's current clinical practice recommendations.

ADA Statement

An ADA statement is an official ADA point of view or position that does not contain clinical practice recommendations and may be issued on advocacy, policy, economic, or medical issues related to diabetes. ADA statements undergo a formal review process, including external peer review and review by the appropriate ADA national committee, ADA clinical leadership, ADA scientific team, and, as warranted, the ADA Board of Directors.

Consensus Report

An ADA consensus report is a document on a particular topic that is authored by a technical expert panel under the auspices of ADA. The document does not reflect the official ADA position but rather represents the panel's collective analysis, evaluation, and expert opinion. The primary objective of a consensus report is to provide clarity and insight on a medical or scientific matter related to diabetes for which the evidence is contradictory, emerging, or incomplete. The report also aims to highlight evidence gaps and to propose avenues for future research. Consensus reports undergo a formal review process, including external peer review and review by the ADA PPC and ADA scientific team, for publication.

Scientific Review

A scientific review is a balanced review and analysis of the literature on a scientific or medical topic related to diabetes. A scientific review is not an ADA position and does not contain clinical practice recommendations but is produced under the auspices of the ADA by invited experts. The scientific review may provide a scientific rationale for clinical practice recommendations in the Standards of Care. The category may also include task force and expert committee reports.

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Summary of Revisions: Standards of Care in Diabetes—2025

American Diabetes Association Professional Practice Committee*

Diabetes Care 2025;48(Suppl. 1):S6–S13 | https://doi.org/10.2337/dc25-SREV

GENERAL CHANGES

The field of diabetes care is rapidly changing as new research, technology, and treatments that can improve the health and well-being of people with diabetes continue to emerge. With annual updates since 1989, the American Diabetes Association has long been a leader in producing guidelines that capture the most current state of the field.

The 2025 "Standards of Care in Diabetes" has continued to incorporate person-first and inclusive language. Efforts were made to consistently apply terminology that empowers people with diabetes and recognizes the individual at the center of diabetes care.

Although levels of evidence for several recommendations have been updated, these changes are not outlined below where the clinical recommendation has remained the same. That is, changes in evidence level from, for example, **E** to **C**, are not noted below. The 2025 Standards of Care contains, in addition to many minor changes that clarify recommendations or reflect new evidence, more substantive revisions detailed below.

SECTION CHANGES

Endorsements

For the second consecutive year, the "Bone Heath" subsection in Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," received endorsement from the American Society for Bone and Mineral Research and Section 8, "Obesity and Weight Management for the Prevention of Type 2 Diabetes," received endorsement from The Obesity Society. For the seventh consecutive year, Section 10, "Cardiovascular Disease and Risk Management," received endorsement from the American College of Cardiology. For the first time, Section 13, "Older Adults," received endorsement from the American Geriatrics Society.

Section 1. Improving Care and Promoting Health in Populations (https://doi.org/10.2337/dc25-S001)

Recommendation 1.1 was expanded to include people at risk for diabetes in addition to those with diabetes.

Recommendation 1.2 was revised to include, in addition to the Chronic Care Model, other evidence-based care delivery models and frameworks that have been demonstrated to improve diabetes care delivery and health outcomes. These include the Patient-Centered Medical Home model, Accountable Care Organizations, and value-based payment models and are discussed in the text.

Recommendation 1.5 was added to emphasize the importance of quality improvement initiatives and interprofessional teams for supporting sustainable and scalable process changes that improve quality of care and health outcomes. Implementation concepts were added throughout the section to provide actionable guidance on how to implement and sustain interventions that improve care delivery and population health.

Recommendation 1.6 was added to emphasize the importance of assessing and addressing disparities in diabetes care and health outcomes. The text includes actionable guidance on measuring health disparities and engaging interprofessional teams and community partners to address them.

Recommendation 1.7 was revised to emphasize the importance of screening for and addressing multiple social determinants of health that impact diabetes management, health outcomes, and quality of life.

The narrative text now includes an expanded discussion of cost and affordability considerations as well as health disparities and social determinants of health.

Table 1.1 was added to highlight the importance of engaging an interprofessional team approach to person-centered care for people with diabetes across the life span.

Section 2. Diagnosis and Classification of Diabetes (https://doi.org/10.2337/dc25-S002)

Table 2.3 was added to provide considerations related to the use and interpretation of laboratory measurement of glucose and A1C.

The "Classification" subsection has been updated to provide a pragmatic approach

*A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.

Duality of interest information for each author is available at 10.2337/dc25-SDIS.

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to management of individuals who have features of both type 1 and type 2 diabetes.

In the "Type 1 Diabetes" subsection, Recommendation 2.7 was added to emphasize the importance of antibody-based screening for presymptomatic type 1 diabetes in individuals with a family history of type 1 diabetes or otherwise known elevated genetic risk. The associated text was also updated and expanded to reflect these changes.

The "Gestational Diabetes Mellitus" subsection was completely updated to facilitate understanding and implementation of the current various approaches to screening for and diagnosis of gestational diabetes mellitus (GDM).

The text in various other subsections, including those that discuss diabetes and immune checkpoint inhibitors, the role of the gut microbiome in diabetes risk, and monogenic diabetes, was updated.

Section 3. Prevention or Delay of Diabetes and Associated Comorbidities

(https://doi.org/10.2337/dc25-S003)

In the "Lifestyle Behavior Change for Type 2 Diabetes Prevention" subsection, text pertaining to sleep health in relation to risk of type 2 diabetes was added. This addition highlights sleep as a central component in the management of prediabetes and type 2 diabetes, placing it on a level playing field with other lifestyle behaviors (e.g., physical activity and eating patterns).

In the "Pharmacologic Interventions to Delay Type 2 Diabetes" subsection, the text on the proposed use of vitamin D therapy to prevent type 2 diabetes was extensively updated. The text related to long-term metformin therapy and associated vitamin B12 deficiency was also updated.

The language in Recommendation 3.15 was strengthened to facilitate discussion with selected individuals aged ≥8 years with stage 2 type 1 diabetes about the role of teplizumab-mzwv infusion to delay the onset of symptomatic type 1 diabetes (stage 3).

Section 4. Comprehensive Medical Evaluation and Assessment of Comorbidities

(https://doi.org/10.2337/dc25-S004)

Language in **Fig. 4.1** was updated, and **Table 4.1** was modified to include changes made throughout Section 4.

Recommendation 4.3 was changed to include assessment for glycemic status and previous treatment at the initial visit and follow-up visits as appropriate.

Table 4.2 was amended to include essential components for assessment, planning, and referral as appropriate.

Changes were made in the "Immunizations" subsection to reflect updates for COVID-19, pneumococcal pneumonia, influenza, and respiratory syncytial virus. **Table 4.3** was revised to include important vaccination updates.

Recommendation 4.6 was modified to specify initial and repeat screening for autoimmune thyroid disease.

Recommendation 4.10 was updated to specify avoiding medications with known association with higher fracture risk.

Recommendation 4.12 was revised to include the recommended intake of calcium for people with diabetes.

Recommendation 4.13 was updated to specify when antiresorptive medications and osteoanabolic agents should be considered.

Table 4.4 was updated to specify when bone mineral density testing should be performed.

A new subsection, "Dental Care," was added and includes two new recommendations. Recommendation 4.15 was added to state people with diabetes should be referred for a dental exam at least once per year. Recommendation 4.16 was added to state that efforts between medical and dental teams should be coordinated so that glucose-lowering medications can be appropriately adjusted prior to and in the post–dental procedure period as needed.

Recommendation 4.17 was updated to reflect that an assessment for disability should be performed at the initial visit and an assessment for decline in function should be performed at each subsequent visit.

Recommendation 4.18 was modified to include inquiring about sexual health in men and to screen with a morning serum total testosterone if symptoms and/or signs of hypogonadism are present.

Recommendation 4.19 was added to specifically state that men with diabetes or prediabetes should be screened for erectile dysfunction, and new text was added on erectile dysfunction.

A new subsection, "Female Sexual Dysfunction," was added and includes two new recommendations. Recommendation 4.20 states that health care professionals should inquire about sexual health, particularly in women who experience depression and/or anxiety and those with recurrent urinary tract infections. Recommendation 4.21 was added to state that health care professionals should screen for symptoms and/or signs of genitourinary syndrome of menopause.

The terminology for nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) was updated to metabolic dysfunction–associated steatotic liver disease (MASLD) and metabolic dysfunction–associated steatohepatitis (MASH), respectively. This updated nomenclature was incorporated throughout the section.

Recommendation 4.22a was revised to specify when to screen for the risk of having or developing cirrhosis related to MASH using the calculated fibrosis-4 index (FIB-4).

Recommendation 4.23 was amended to state that adults with type 2 diabetes or prediabetes and a FIB-4 >1.3 should have additional risk stratification performed.

Recommendation 4.24 was revised to state that individuals with a higher risk for significant liver fibrosis should be referred to a gastroenterologist or hepatologist.

Recommendation 4.25 was revised to include an interprofessional team approach when promoting weight loss, particularly with a structured nutrition plan and physical activity program for cardiometabolic benefits and histological improvement.

Recommendation 4.26 was revised to include a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon like peptide 1 (GLP-1) receptor agonist (RA) with potential benefits in MASH as an adjunctive therapy to lifestyle interventions for weight loss in adults with type 2 diabetes, MASLD, and overweight or obesity.

Recommendation 4.27a was revised to state that in adults with type 2 diabetes and biopsy-proven MASH or those at high risk for liver fibrosis, use of pioglitazone or a GLP-1 RA or a dual GIP and GLP-1 RA is preferred for glycemic management due to potential beneficial effects on MASH.

Recommendation 4.27b was added to state that combination therapy with pioglitazone and a GLP-1 RA can be considered for treatment of hyperglycemia in adults with type 2 diabetes with biopsy-proven MASH or those at high risk of liver fibrosis because of potential beneficial effects of such a combination on MASH.

Recommendation 4.28 was added to state that treatment with a thyroid hormone receptor-β agonist in adults with

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type 2 diabetes or prediabetes with MASLD with moderate (F2) or advanced (F3) liver fibrosis may be considered and that the individual should be referred to a gastroenterologist or hepatologist with expertise in MASLD management for the initiation and monitoring of this therapy.

Recommendation 4.29 was added to emphasize that treatment initiation and monitoring should be individualized and within the context of an interprofessional team for MASLD and MASH management.

Figure 4.2 was revised to reflect important updates to the diagnostic algorithm for risk stratification and the prevention of cirrhosis in individuals MASLD, and new **Fig. 4.3** includes the MASLD treatment algorithm.

Section 5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes

(https://doi.org/10.2337/dc25-S005)

In the "Diabetes Self-Management Education and Support" subsection, Recommendation 5.1 was updated to emphasize that all people with diabetes should be advised to participate in diabetes self-management education and support (DSMES) rather than being just encouraged to participate.

Recommendation 5.2 was updated to clarify when to provide DSMES.

Recommendation 5.3 was revised to be more succinct and action-oriented, placing emphasis on routine assessment of key goals of DSMES.

Recommendation 5.4 was added to emphasize the importance of screening for behavioral health concerns at the same time points as evaluating the need for DSMES.

Language in Recommendation 5.5 was updated to state that DSMES should be culturally appropriate and responsive to individual preferences, needs, and values.

Recommendation 5.6 was updated to reflect the now-common practice of remote-delivery of DSMES and reimbursement for remotely delivered modalities.

Recommendation 5.9 was updated to reinforce the importance of screening for and including social determinants of health in guiding the design and delivery of DSMES.

In the "Medical Nutrition Therapy" subsection, Recommendation 5.12 was updated to emphasize the importance of providing treatment based on nutrition, physical activity, and behavioral therapy for individuals with overweight or obesity, aiming for at least 3–7% weight loss.

Recommendation 5.14 on eating patterns now has revised verbiage to include processed foods, lean proteins, and nondairy alternatives.

Recommendation 5.16 was updated to include actionable language and clarity regarding the use of dietary supplements for glycemic benefits.

Recommendations 5.17 and 5.18 were updated to have revised and actionable language, respectively.

Recommendation 5.19 was updated to use actionable language.

Recommendation 5.20 was revised to recommend limiting sodium as clinically appropriate, which can be done, in part, by limiting consumption of processed foods.

Recommendation 5.21 was modified to recommend water over nutritive and nonnutritive sweetened beverages, and Recommendation 5.22 was added to state that nonnutritive sweeteners can be used instead of sugar-sweetened products in moderation and for short term to reduce overall calorie and carbohydrate intake.

Recommendation 5.23 was added to emphasize the screening for malnutrition, especially for those who have undergone metabolic surgery and for those being treated with weight management pharmacological therapies.

Recommendation 5.25 was revised to use actionable language.

Recommendation 5.26 was added to address the issue of sodium–glucose cotransporter (SGLT) inhibition being associated with ketoacidosis under certain conditions. It provides guidance on awareness, prevention, risk mitigation, and dietary adjustments.

Recommendation 5.29 was added to encourage intake of plant-based proteins and fiber, and Recommendation 5.31 was added to encourage limiting foods high in saturated fats to reduce cardiovascular disease risk.

Two new recommendations were added for religious fasting. Recommendation 5.32 states to use the Diabetes and Ramadan International Alliance comprehensive prefasting risk assessment for risk stratification of people with diabetes prior to engaging in religious fasting. Recommendation 5.33 was created to provide guidance to health care professionals caring for people with diabetes who participate in religious fasting.

Additionally, newly added **Fig. 5.1** illustrates differences and similarities between religious and intermittent fasting for people with diabetes. **Table 5.4** includes a risk calculation and suggested risk score for people with diabetes who seek to fast during Ramadan, and **Table 5.5** includes information about medication changes during fasting.

In the "Physical Activity" subsection, Recommendation 5.34 was updated to include a statement about limiting the amount of time spent sedentary, which includes recreational screen time.

Recommendation 5.38 was modified to state that prolonged sitting should be interrupted at least every 30 min for glycemic benefits.

Recommendation 5.39 was added to counsel adults and youth receiving weight management pharmacotherapy or metabolic surgery to meet physical activity recommendations. The accompanying text addresses the concern of sarcopenic obesity with use of incretin therapies and metabolic surgery.

In the "Smoking Cessation: Tobacco, E-cigarettes, and Cannabis" subsection, Recommendation 5.42 was added to advise people with type 1 diabetes and those with other forms of diabetes at risk for diabetic ketoacidosis (DKA) to not use recreational cannabis in any form due to the risk of cannabis hyperemesis syndrome. The accompanying text describes cannabis hyperemesis syndrome and its diagnostic criteria.

Recommendation 5.43 in "Supporting Positive Health Behaviors" was updated to include health-related quality of life as an outcome when using behavioral health strategies to support self-management and healthy behaviors.

Recommendation 5.45 in "Psychosocial Care" was revised to state the specific psychosocial concerns health care professionals should screen for including diabetes distress, depression, anxiety, fear of hypoglycemia, and disordered eating behaviors.

Recommendation 5.48 in "Diabetes Distress" was updated to recommend the frequency of at least annual screening for diabetes distress in people with diabetes, caregivers, and family members.

Recommendation 5.49 in "Anxiety" was updated to recommend screening for anxiety, which is in accordance with the U.S. Preventive Services Task Force recommendation for screening for anxiety.

Recommendation 5.50 in "Anxiety" was added to include a recommendation for

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screening for fear of hypoglycemia in people with diabetes at risk for hypoglycemia or fear of hypoglycemia.

Recommendation 5.51 in "Depression" was modified to have more actionable language for the importance of depression rescreening.

Recommendation 5.54 in "Disordered Eating Behavior" was updated to recommend screening for disordered or disrupted eating using validated screening measures. The accompanying text describes the disordered or disrupted eating behaviors commonly reported in people with diabetes.

Tables 5.7 and **5.8** were added to illustrate psychosocial concerns and their association with diabetes-related outcomes in adults with type 1 and type 2 diabetes, respectively.

Section 6. Glycemic Goals and Hypoglycemia

(https://doi.org/10.2337/dc25-S006)

Recommendation 6.12 was added to promote routine screening for fear of hypoglycemia in individuals at risk for hypoglycemia.

A new subsection entitled "Hyperglycemic Crises: Diagnosis, Management, and Prevention" was added to cover the epidemiology, diagnostic criteria, and outpatient prevention of DKA and the hyperglycemic hyperosmolar state (HHS).

New recommendations on routine assessment of history of DKA and HHS (recommendation 6.20) and providing structured prevention education (Recommendation 6.21) in the outpatient setting were added.

Tables 6.9 and **6.10** were added and include risk factors for hyperglycemic crises as well as clinical presentation of DKA and HHS in people with diabetes, respectively.

Figure 6.2 was revised to provide a specific and actionable approach to selecting individual glycemic goals, accounting for health status and other person- and treatment-specific factors favoring more or less stringent goals.

Section 7. Diabetes Technology

(https://doi.org/10.2337/dc25-S007)

Recommendation 7.8 was modified to emphasize consideration for starting diabetes technology early, even at diagnosis.

Recommendation 7.9 was added to emphasize that reports for all continuous glucose monitoring (CGM) devices, connected insulin devices, and continuous subcutaneous insulin infusion and automated insulin delivery (AID) systems should be standardized with at a minimum the ambulatory glucose profile and weekly summary. In addition, there should be options for raw data or daily and weekly reports available to the health care professionals.

Recommendation 7.14 was modified to make the clinician aware of potential interference of medications and other substances on glucose levels measured by blood glucose meters.

Table 7.2 was modified to include the various potential substances or medical conditions that may affect glucose levels when measured by blood glucose meters.

Table 7.3 was modified to include the description of over-the-counter CGM devices.

Recommendation 7.15 was modified to support the use of real-time CGM (rtCGM) and intermittently scanned CGM (isCGM) for youth and adults with diabetes (type 1 or type 2) on any type of insulin therapy based on the most recent literature.

Recommendation 7.16 was added to consider the use of rtCGM or isCGM in adults with type 2 diabetes on glucose-lowering agents other than insulin to achieve and maintain individualized glycemic goals.

Recommendation 7.18 was modified to align with Section 15, "Management of Diabetes in Pregnancy," and reflect the update of CGM benefits in type 1 diabetes and pregnancy and other types of diabetes in pregnancy.

The text on CGM was expanded to include the updated sensors integrated with AID systems and to update the most recent literature evidence supporting the benefits of CGM in individuals with type 2 diabetes on glucose-lowering agents other than insulin from clinical trials and real-world studies. Furthermore, the CGM section was expanded to include the need to standardize any diabetes technology device reports and to provide clinicians not only with single page summaries but also with access to detailed reports and even raw data from devices, especially those reporting insulin dose modifications, such as AID systems.

The text on insulin pumps and AID systems was greatly expanded to discuss the features of the various AID systems and their data from pivotal trials and real-world studies in type 1 and type 2 diabetes.

Recommendation 7.29 was modified to include provision of support and diabetes management advice in people with diabetes using open-source closed-loop systems.

The text for open-source closed-loop systems was also expanded to include the most recent published evidence on the safety and effectiveness of these systems in people with type 1 diabetes.

Recommendation 7.30 was expanded to include the benefits of combining technology with online or virtual coaching to improve glycemic outcomes in individuals with diabetes and prediabetes.

Recommendation 7.32 was refined to emphasize the importance of continuing the use of insulin pumps or AID in people with diabetes while hospitalized when clinically appropriate and with confirmatory point-of-care blood glucose measurements for insulin dose adjustments and hypoglycemia assessment and treatment. The use of these devices in the inpatient setting should be contingent on the availability of infrastructure support and institutional diabetes technology protocols.

Section 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes

(https://doi.org/10.2337/dc25-S008)

Recommendation 8.2a was updated to clarify that additional measurements of body fat distribution are warranted if BMI is indeterminant.

Recommendation 8.2b was revised to recommend monitoring of obesity-related anthropometric measurements at least every 3 months during active weight management treatment.

Discussion of weight stigma and bias toward people living in larger bodies was added to the text.

Recommendation 8.11 was enhanced to reflect the importance of continued monitoring, support, and interventions for individuals who have achieved weight loss goals to support the maintenance of these goals long term.

Recommendation 8.18 was added to recommend screening for malnutrition for people with diabetes and obesity who have lost significant weight.

Recommendation 8.19 was added to recommend continuing weight management pharmacotherapy, as indicated, beyond reaching weight loss goals to maintain health benefits and avoid weight regain

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and worsening of cardiometabolic abnormalities that often result from sudden discontinuation of weight management pharmacotherapy.

Recommendation 8.25 was revised to emphasize use of a CGM device to improve safety in individuals with post–metabolic surgery hypoglycemia.

Updated **Tables 8.1** and **8.2** provide detailed information on the efficacy, common side effects, safety considerations, and costs of approved weight management pharmacotherapy options.

Discussion of medication cost and access barriers was added to the text, including suggestions to members of the interprofessional diabetes care team on mitigating financial barriers.

Section 9. Pharmacologic Approaches to Glycemic Treatment

(https://doi.org/10.2337/dc25-S009)

This section was reorganized and expanded with two new subsections: *1*) a subsection titled "Additional Recommendations for All Individuals With Diabetes" that includes new recommendations as well as recommendations previously listed with those for individuals with type 1 or type 2 diabetes if pertinent to individuals regardless of their type of diabetes, and *2*) a subsection titled "Special Circumstances and Populations."

Figure 9.1 was revised for clarity, and a general statement was added to **Table 9.1** on dose adjustments when using AID systems.

The subsection on insulin administration technique was expanded to address inhaled insulin and use of insulin bolus patches.

Recommendation 9.8 was revised to emphasize the importance of selecting glucose-lowering medications that provide sufficient effectiveness and achieve and maintain multiple treatment goals simultaneously, including improving cardiovascular, kidney, weight, and other relevant outcomes, reducing hypoglycemia risk, and considering cost, access, risk for adverse reactions, and individual preferences.

Recommendations were revised to explicitly advise on choice of pharmacotherapy for individuals with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease (ASCVD) (Recommendation 9.10), heart failure (Recommendation 9.11), and chronic kidney disease (CKD) (Recommendation 9.12) to improve health outcomes for individuals with these conditions irrespective of A1C.

Recommendation 9.12 was added to recommend use of GLP-1 RA with demonstrated benefits in individuals with type 2 diabetes, symptomatic heart failure with preserved ejection fraction, and obesity.

Recommendation 9.13 was revised to recommend use of either SGLT2 inhibitor or GLP-1 RA with demonstrated benefits in individuals with type 2 diabetes and CKD.

Recommendations 9.15 and 9.16 were added to recommend treatment of individuals with type 2 diabetes and MASLD or MASH with GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone, or a combination of GLP-1 RA and pioglitazone based on the staging of liver disease risk and need for weight management.

Figure 9.3 and the text discussing choice of glucose-lowering therapy in adults with type 2 diabetes were extensively revised to facilitate evidence-based selection of glucose-lowering therapies based on individualized treatment goals. Considerations of glucose-lowering medication effects on MASLD and MASH were added to **Fig. 9.3**.

Table 9.2 was simplified and revised to better highlight important considerations when choosing medications for lowering glucose in type 2 diabetes.

Recommendation 9.20 was clarified to recommend reassessing the need for and/or dose of medications with higher hypoglycemia risk (i.e., sulfonylureas, meglitinides, and insulin) when initiating a new glucose-lowering medication to minimize the risk of hypoglycemia and treatment burden.

Recommendation 9.21 was added to advise against concurrent use of a dipeptidyl peptidase 4 inhibitor with a GLP-1 RA due to lack of additional glucose lowering beyond that of a GLP-1 RA alone.

Recommendation 9.24 was clarified by specifying that a GLP-1 RA or a dual GIP and GLP-1 RA is preferred to insulin in adults with type 2 diabetes only in the absence of evidence of insulin deficiency.

Text in the "Basal Insulin" section was revised to provide guidance on switching between different basal insulin formulations.

Figure 9.4 was revised for clarity, and the list of options for prandial insulin was expanded.

Recommendation 9.27 was revised to remove consideration of basal insulin doses exceeding 0.5 units/kg/day as evidence of overbasalization. Instead, signs of overbasalization including significant bedtime-to-morning or postprandial-to-preprandial glucose differential, occurrences of hypoglycemia (aware or unaware), and high glycemic variability should be used.

Tables 9.3 and **9.4** were updated with glucose-lowering medication and insulin costs as of 1 July 2024, and an expanded discussion on medication costs and affordability was added to the text.

In the new subsection "Special Circumstances and Populations," Recommendations 9.31a, 9.31b, and 9.31c were added to advise on actions to take when medications are not available (such as medication shortages); Recommendations 9.32a and 9.32b were added to address care considerations for individuals of childbearing potential; and Recommendation 9.33 was added to provide guidance on mitigating risk of ketoacidosis when individuals at risk for ketoacidosis or who follow a ketogenic eating pattern are treated with SGLT inhibition. Additional text in this subsection discusses considerations for glucose-lowering pharmacotherapy for individuals with diabetes secondary to chemotherapy and with other types of diabetes (i.e., pancreatogenic diabetes, cystic fibrosis–related diabetes, posttransplant diabetes, maturity-onset diabetes of the young, and neonatal diabetes).

Section 10. Cardiovascular Disease and Risk Management

(https://doi.org/10.2337/dc25-S010)

Recommendation 10.1 was updated with details on the frequency of recommended blood pressure monitoring.

Figure 10.2 was updated to provide clarity on medication classes for the treatment of confirmed hypertension in nonpregnant people with diabetes.

Recommendation 10.12 was modified to specify appropriate monitoring for increased serum creatinine levels, serum potassium levels, and hypokalemia when ACE inhibitors, angiotensin receptor blockers (ARBs), or mineralocorticoid receptor antagonists are used.

Recommendation 10.13 was added to specify hypertension treatment options that should be avoided during pregnancy and in sexually active individuals of childbearing potential not using reliable contraception.

Recommendation 10.26 was added to recommend that in most cases lipid-lowering agents should be discontinued prior to conception and avoided in sexually

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active individuals of childbearing potential not using reliable contraception, unless the benefits may outweigh the risk.

Figures 10.3 and **10.4** were added to illustrate recommendations for primary prevention and secondary prevention of ASCVD, respectively, in people with diabetes using cholesterol-lowering therapy.

Triglyceride thresholds were updated in Recommendations 10.31 and 10.32.

The criteria for coronary artery disease investigations in Recommendation 10.39b were revised to include signs or symptoms of cardiac or associated vascular disease or electrocardiogram abnormalities.

Recommendation 10.41 was modified to include screening for peripheral artery disease (PAD) with ankle-brachial index testing in asymptomatic people with diabetes aged ≥65 years, microvascular disease in any location, or foot complications or any end-organ damage from diabetes if a PAD diagnosis would change management. PAD screening should also be considered in individuals with diabetes duration ≥10 years and high cardiovascular risk.

For individuals with type 2 diabetes, obesity, and symptomatic heart failure with preserved ejection fraction, Recommendation 10.46d was added to recommend treatment with a GLP-1 RA with demonstrated benefit in this population to reduce heart failure–related symptoms, reduce physical limitations, and improve exercise function.

Figure 10.5 was added to illustrate recommendations for screening for asymptomatic and undiagnosed cardiovascular disease, and **Fig. 10.6** was added to provide an overview of recommendations for the prevention of the development of symptomatic heart failure in people with diabetes.

Section 11. Chronic Kidney Disease and Risk Management

(https://doi.org/10.2337/dc25-S011)

Recommendation 11.3 was amended for clarity about optimizing blood pressure management goals.

Recommendation 11.4a was revised to clarify that ACE inhibitors or ARBs should be titrated to the maximally tolerated dose to prevent the progression of CKD and reduce cardiovascular events in nonpregnant individuals with diabetes and hypertension.

Recommendation 11.4b was modified to specify appropriate monitoring for increased serum creatinine levels, serum potassium levels, and hypokalemia when ACE inhibitors, ARBs, or mineralocorticoid receptor antagonists are used.

Recommendation 11.5b was updated to state that for people with type 2 diabetes and CKD, a GLP-1 RA with demonstrated benefit in this population should be used to reduce cardiovascular risk and kidney disease progression.

Recommendation 11.6 was added to state that potentially harmful antihypertensive medications in pregnancy should be avoided in sexually active individuals of childbearing potential not using reliable contraception and to switch to options considered safer prior to conception and during pregnancy.

Recommendation 11.7 was updated to specify reducing urinary albumin by ≥30% to slow progression of CKD.

Recommendation 11.8 was updated to specify protein goals for individuals with stage 3 or higher CKD and those who are treated with dialysis.

Table 11.1 was added to include reasons to consider non–diabetes-related kidney diseases in a person with CKD and diabetes, and **Table 11.3** was added to include suggestions for interventions that lower albuminuria.

Section 12. Retinopathy, Neuropathy, and Foot Care

(https://doi.org/10.2337/dc25-S012)

Recommendation 12.5 was updated to specify involvement of an ophthalmologist for more frequent examinations if retinopathy is progressing or sight threatening.

Recommendation 12.8 wording was changed to reflect that a dilated eye exam should be performed before and in the first trimester, rather than one or the other.

Recommendation 12.19 was modified to include additional screening criteria for symptoms and signs of autonomic neuropathy.

Recommendation 12.22 was updated to recommend against opioid use for neuropathic pain treatment due to the potential for adverse events, and the narrative text was updated to expand on this.

A short discussion on the role of weight management and neuropathy was added to the narrative text.

Recommendation 12.24 was updated to include the Ipswich touch test as an option for neurological assessment.

Recommendation 12.29 was expanded to include the importance of smoke cessation and referral for counseling for individuals who smoke and have a prior history of lower-extremity complications, loss of protective sensation, structural abnormalities, or PAD.

Increasing role of surgery in diabetic foot management was added to the narrative text of foot care section.

Section 13. Older Adults

(https://doi.org/10.2337/dc25-S013)

The 4Ms framework of age-friendly health systems (Mentation, Medications, Mobility, and What Matters Most) as it applies to diabetes management in older adults was introduced and illustrated in the new **Fig. 13.1**.

Recommendation 13.8a was modified to include time in range and time below range in addition to A1C treatment goals for older adults who are otherwise healthy with few and stable chronic conditions and intact cognitive functional status.

Recommendation 13.8b was modified to include time in range and time below range in addition to A1C treatment goals for older adults who have intermediate or complex health who are clinically heterogeneous with variable life expectancy.

Table 13.1 was modified to include a column on reasonable CGM goals for each health status category.

In the "Treatment" section, the appropriate selection and use of SGLT2 inhibitors in older adults was expanded.

Section 14. Children and Adolescents

(https://doi.org/10.2337/dc25-S014)

Recommendation 14.4 in the "Type 1 Diabetes" section was added to emphasize key nutrition principles.

Recommendation 14.10 was altered to emphasize limits on sedentary activity.

Recommendation 14.21 was changed to state that insulin pumps should be offered to anyone with type 1 diabetes who can use the devices safely.

Recommendation 14.24 was modified to remove lack of access as a reason for less stringent A1C goals.

Recommendation 14.26 was altered to include weight gain as a balancing measure for more stringent A1C goals.

Recommendation 14.36 was changed to exclude secondary causes of hypertension.

Recommendation 14.41 was updated to include the use of age-approved statins.

Recommendation 14.50 was modified to state that screening should be repeated at a minimum of 2-year intervals

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or more frequently if screening is normal and BMI is increasing.

Recommendation 14.57 was revised to include the key nutritional principles and provide specific examples of healthy food choices and what foods should be avoided.

Recommendation 14.60 was changed to recommend an A1C goal of <6.5% (<48 mmol/mol) for most children and adolescents with type 2 diabetes who have a low risk of hypoglycemia and a higher risk of complications.

Recommendation 14.65 was revised to change the terminology from "hyperglycemic hyperosmolar nonketotic syndrome" to "hyperglycemic hyperosmolar state" and include intravenous fluid as the initial step to treat severe hyperglycemia (blood glucose ≥600 mg/dL) once the diagnosis is confirmed.

The narrative was updated to reinforce the benefits and safety of GLP-1 RAs in decreasing A1C, weight, blood pressure, and insulin dose reduction. **Figure 14.1** was updated to reflect the revision in this recommendation.

Recommendation 14.73 was modified to reflect that excluding secondary hypertension is an essential step in hypertension management.

Recommendation 14.104 was revised to state that vaping and electronic cigarettes are both discouraged.

Recommendation 14.105 in the "Substance Use in Pediatric Diabetes" section was added to state that all youth with diabetes should be advised not to use cannabis recreationally in any form.

Recommendation 14.108 was modified to encourage pediatric diabetes specialists to partner with youth with diabetes and their caregivers to engage in shared decision-making.

Tables 14.1*A* and **14.1*B*** were modified to include changes made throughout Section 14.

Section 15. Management of Diabetes in Pregnancy

(https://doi.org/10.2337/dc25-S015)

Section 15 was restructured to discuss the care of pregnant individuals with type 1 diabetes, type 2 diabetes, and GDM in all sections and to discuss aspects of management in each relevant subsection (e.g., preconception care and pharmacotherapy); consequently, the order of appearance of some of the recommendations changed.

Recommendation 15.7 wording was changed to reflect that a dilated eye exam should be performed before and in the first trimester, rather than one or the other.

Table 15.1 was updated with a folic acid supplement recommendation of 400–800 μg/day and clarification for which checklist items are only for individuals with preexisting diabetes and not for individuals with prediabetes or a history of GDM, and specific immunizations were omitted and referenced.

In Recommendation 15.10, the benefits of CGM use in type 1 diabetes and pregnancy were clarified, and an addition of its potential to be beneficial in other types of diabetes in pregnancy was added.

Recommendation 15.12 no longer states that CGM metrics should not be used as a substitute for blood glucose monitoring; the recommendation now states that CGM may be used in conjunction with blood glucose monitoring to achieve glycemic goals.

Glucose goals for preexisting diabetes, GDM treated with insulin, and GDM not treated with insulin are consolidated into a new **Table 15.2**.

"Management of Gestational Diabetes Mellitus" and "Management of Preexisting Type 1 Diabetes and Type 2 Diabetes Pregnancy" were merged into one subsection, titled "Management of Diabetes in Pregnancy," which includes all aspects of management for all types of diabetes (e.g., nutrition, physical activity, and pharmacotherapy).

Recommendation 15.14 provides more clarification on the recommended eating pattern in pregnancy.

Insulin recommendations that were previously split into separate recommendations for preexisting diabetes and GDM were merged.

There are two new recommendations regarding AID use in type 1 diabetes and pregnancy. Recommendation 15.19 states that AID systems are recommended if the system has a pregnancy-specific glucose goal. Recommendation 15.20 states that AID systems may be considered for select individuals with an experienced health care team if the system does not have a pregnancy-specific glucose goal or algorithm.

Recommendation 15.21 provides more clarification for why metformin and glyburide should not be first-line agents for management of diabetes in pregnancy.

The narrative for subsection "Physical Activity" includes recommended activity levels for pregnancy, as these pertain to individuals with any type of diabetes in pregnancy.

The "Insulin" subsection includes information on different insulin delivery modalities used during labor and delivery or postpartum.

The recommendation to explicitly measure blood pressure during pregnancy is now mentioned in the narrative of the "Preeclampsia and Aspirin" subsection per the recent guidelines of the U.S. Preventive Services Task Force.

Recommendation 15.25 was split into two recommendations. Recommendation 15.25a provides more examples of potentially harmful medications in pregnancy. Recommendation 15.25b recommends that lipid-lowering medications be avoided in most circumstances in pregnancy but that statins may be considered for use in high-risk individuals (such as those with prior ASCVD and familial hypercholesterolemia) when benefits outweigh risks. The narrative discusses Recommendation 15.25b in more detail and includes discussion of studies of pravastatin use in pregnancy.

Section 16. Diabetes Care in the Hospital

(https://doi.org/10.2337/dc25-S016)

Diabetes care in the hospital stresses identification and treatment of dysglycemia and provides glycemic goals. For the treatment of persistent hyperglycemia starting at a threshold of ≥180 mg/dL (≥10.0 mmol/L), Recommendation 16.4a was amended to reflect that insulin should be initiated or intensified for the majority of critically ill individuals, and Recommendation 16.4b was added to state that insulin and/or other glucose-lowering therapies should be initiated or intensified for the majority of noncritically ill individuals.

Recommendation 16.5a was updated to state that a glycemic goal of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for most critically ill individuals, but more stringent individualized glycemic goals may be appropriate if they can be achieved without significant hypoglycemia. Recommendation 16.5b was updated to recommend a glycemic goal of 100–180 mg/dL (5.6–10.0 mmol/L) for most noncritically ill individuals if it can be achieved without significant hypoglycemia.

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Recommendation 16.7 was amended for clarity on the use of insulin pump or AID continuation and their use in people with diabetes who are hospitalized, when clinically appropriate.

Recommendation 16.8a was added to state that continuous intravenous insulin infusion is recommended for achieving glycemic goals and avoiding hypoglycemia in critically ill individuals.

The language regarding a hypoglycemia management surveillance protocol for health systems was updated for clarity in Recommendation 16.12.

Guidance regarding use of GLP-1 RA and dual GIP and GLP-1 RA medications in the perioperative setting and regarding instructions in preparation for procedures or surgery has been added to the narrative text.

Recommendations 16.14 and 16.15 were added for DKA and HHS management; transition to maintenance subcutaneous insulin administration and discharge planning were added. Additionally, the newly added **Fig. 16.1** includes treatment pathways for DKA and HHS.

Section 17. Diabetes Advocacy
(https://doi.org/10.2337/dc25-S017)
The subsections "Diabetes Care in the School Setting" and "Diabetes and Driving" were updated with information from recently published advocacy statements. The subsection "Diabetes Management in Detention Facilities" was added with information from a recently published advocacy statement.

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1. Improving Care and Promoting Health in Populations: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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DIABETES AND POPULATION HEALTH

Recommendations

1.1 Ensure treatment decisions are timely, rely on evidence-based guidelines, capture key elements within the social determinants of health, and are made collaboratively with people with or at risk for diabetes and caregivers based on individual preferences, prognoses, comorbidities, and informed financial considerations. **B**

1.2 Align approaches to diabetes management with evidence-based care models. These models emphasize person-centered team care, integrated long-term treatment approaches to diabetes and comorbidities, and ongoing collaborative communication and goal setting between all team members and with people with diabetes. **A**

1.3 Care systems should facilitate in-person and virtual team-based care, include those knowledgeable and experienced in diabetes management as part of the team, and utilize patient registries, decision support tools, proactive care planning, and community involvement to meet needs of individuals with diabetes. **B**

1.4 Assess diabetes management, risk factors, and complications (**Table 4.1**) using reliable and relevant data metrics to improve processes of care and health outcomes, with attention to care costs, individual preferences and goals for care, and treatment burden. **B**

1.5 Health systems should adopt a culture of quality improvement, implement benchmarking programs, and engage interprofessional teams to support sustainable and scalable process changes to improve quality of care and health outcomes. **A**

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.*

Duality of interest information for each author is available at https://doi.org/10.2337/dc25-SDIS.

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Population health is defined as "the health outcomes of a group of individuals, including the distribution of health outcomes within the group" (1). These outcomes can be measured in terms of health indicators (mortality, morbidity, and functional status), disease epidemiology (incidence and prevalence), and behavioral and metabolic factors (physical activity, nutrition, A1C, time in range, etc.) (1). Clinical practice recommendations are tools for health care professionals who seek to improve health across populations; however, for optimal outcomes, diabetes care must also be individualized for each person with diabetes and for each person's context, as well as across the life span. Thus, efforts to improve population health will require a combination of policy-level, system-level, and person-level approaches. With such an integrated approach in mind, the American Diabetes Association (ADA) highlights the importance of person-centered care, defined as care that considers an individual's comorbidities and prognoses; is respectful of and responsive to individual preferences, needs, and values; and ensures that the individual's values guide all clinical decisions (2). Social determinants of health (SDOH)—factors often beyond an individual's direct control and potentially representing lifelong risks—play a significant role in both clinical and psychosocial outcomes. To improve health, support overall well-being, and eliminate disparities, it is crucial to address these determinants, particularly for individuals from racial and ethnic minority communities, underserved geographic areas (rural or urban), and those facing socioeconomic barriers to care and health (3). This section discusses the current state of diabetes and diabetes care in the U.S. and provides guidance for health care professionals as well as health systems, community partners, payors, and policymakers on improving the delivery of diabetes care to improve the health of all people at risk for or living with diabetes.

To provide actionable guidance for improving the care for and health outcomes of people with and at risk for diabetes, this section examines care delivery and payment models demonstrated to support high-quality, evidence-based care; offers guidance on practical strategies for system-level improvement; and discusses opportunities to expand access to health care and diabetes self-management education and support (DSMES) through telehealth, mobile platforms, interprofessional team care, and engagement of community-based care partners and resources. As SDOH have a central role in diabetes burden, management, and outcomes, the subsection TAILORING TREATMENT FOR SOCIAL CONTEXT discusses the importance of screening individuals for SDOH, advises on strategies to identify disparities in diabetes management and outcomes experienced by at-risk populations, and offers actionable guidance for addressing SDOH and health disparities at the individual and population levels.

State of Diabetes Care

The proportion of people with diabetes who achieve recommended A1C, blood pressure, and LDL cholesterol levels has fluctuated over the years, with some improvement over time (4,5). In 2015–2018 (the most recent time period with population-level data available), just 50.5% of U.S. community-dwelling adults with diabetes achieved A1C $<$7% and 75.4% achieved A1C $<$8% (5). The goal blood pressure of $<$130/80 mmHg was achieved by just 47.7% of adults with diabetes, while 70.4% achieved blood pressure $<$140/90 mmHg (5). Lipid goals, defined in these studies as non-HDL cholesterol $<$130 mg/dL, was achieved by 55.7% of adults with diabetes, and all three risk factors were treated to goal in just 22.2% (5). Importantly, many people who did not attain A1C, blood pressure, and lipid goals were not receiving any or adequate pharmacotherapy for glycemic, hypertension, and dyslipidemia management, respectively, which underscores the urgent need for care delivery systems and structural facilitators (i.e., health and public health policies and payment models) that enable timely and equitable delivery of evidence-based care and address diabetes prevention and treatment in communities (5). Many segments of the population, such as children, young adults, and individuals with complex health needs, financial or other social hardships, and/or limited English proficiency, as well as individuals in groups that have been historically marginalized, face particular challenges to diabetes management (6–8). A U.S. population–based study based on National Health and Nutrition Examination Survey (NHANES) data showed that younger people with diabetes, Mexican American people, non-Hispanic Black people, those with a lower level of educational attainment, and those who are underinsured are most likely to be undertreated, particularly for glycemic management (5).

Gaps and disparities in diabetes management and outcomes are also prevalent among youth with diabetes in the U.S. Data from SEARCH for Diabetes in Youth (SEARCH), a population-based registry network of five centers across five U.S. states, showed that in 2014–2019, mean A1C was 9.1% (SD 2.0) among youth and young adults with type 1 diabetes and 8.9% (SD 2.9) in youth and young adults with type 2 diabetes; these values increased from 8.5% (SD 1.5) and 8.4% (SD 2.8), respectively, in 2002–2007 (9). In youth and young adults with type 1 diabetes, identifying as a non-Hispanic Black person or a Native American person (compared with identifying as a non-Hispanic White person), being younger, not being treated with insulin pump therapy, and having low annual household income were associated with a higher A1C level (9). Data from the T1D Exchange Quality Improvement Collaborative (T1DX-QI), a learning health network of pediatric and adult centers across the U.S., revealed that between 2016 and 2018, mean A1C was 8.1% (65 mmol/mol) among children with type 1 diabetes 5 years of age and 9.3% (78 mmol/mol) among children 15–18 years of age. Only 17% of youth under 18 years of age with type 1 diabetes achieved the recommended A1C goal of $<$7.5% ($<$58 mmol/mol), and A1C levels for non-Hispanic Black youth were higher than those for non-Hispanic or Hispanic White youth—a disparity that persisted after adjustment for socioeconomic status (10).

Diabetes and its associated health complications pose a significant financial hardship to individuals and society. It is estimated that the annual cost of diagnosed diabetes in the U.S. in 2022 was $413 billion, including $307 billion in direct health care costs and $106 billion in reduced productivity (11). After adjusting for inflation, the economic costs of diabetes increased by 7% between 2017 and 2022 and by 35% between 2012 and 2022 (11). This is attributed to both the increased prevalence of diabetes and the higher cost per person with diabetes. People living with diabetes also face financial hardship, which is correlated

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with higher A1C, diabetes distress, and depressive symptoms (12).

The growing gaps in diabetes care quality and outcomes, the high and rising costs of diabetes care across the U.S., and the disparities experienced by individuals from racial and ethnic minoritized backgrounds and those facing socioeconomic barriers to care call for urgent, substantial, and multisectoral system-level improvements to care delivery (13).

Evidence-Based Care Models to Improve Population Health

A major barrier to optimal and comprehensive diabetes care is a delivery system that is often fragmented, lacks clinical information capabilities, is not appropriately incentivized and funded, does not adequately engage people with diabetes and the communities where they live, and is poorly designed for the coordinated and longitudinal delivery of chronic care (14). Several models have been demonstrated to improve aspects of diabetes care delivery and health outcomes.

The Chronic Care Model (CCM) is a commonly used framework for describing diabetes care programs (15). It includes six core elements to optimize the care of people with chronic disease:

1. Delivery system design (moving from a reactive to a proactive care delivery system where planned visits are coordinated through a team-based approach)
2. Self-management support
3. Decision support, particularly at the point of care during a clinical encounter (basing care on evidence-based, effective care guidelines)
4. Clinical information systems (using registries that can provide person-specific and population-based support to the care team)
5. Community resources and policies (identifying or developing resources to support healthy lifestyles)
6. Health systems (to create a quality-oriented culture)

Randomized controlled trials of CCM interventions have shown that while interventions vary, programs that include core components of the CCM decrease A1C (mean difference –0.21% [95% CI –0.30 to –0.13], $P < 0.001$ compared with usual care), with greater improvements seen among adults with higher baseline A1C and with interventions that include four or more CCM elements (16). CCM-aligned programs also improved blood pressure levels and processes of diabetes care (e.g., screening for complications of diabetes), though there was no impact on cholesterol levels, tobacco use, or weight (17). Multiple studies have examined individual components of the CCM with respect to diabetes management and have found inconsistent levels of benefit with case management, team-based care, use of electronic patient registries, clinician education, clinician and patient reminders, and patient education and promotion of individual self-management (18). The inconsistencies in findings may be driven by heterogeneity of interventions, settings, and evaluation strategies.

Collaborative, interprofessional teams, which can bring together multiple disciplines within the health care system, payors, and community partners, are best suited to provide care for people with chronic conditions such as diabetes and to facilitate individuals' self-management (**Table 1.1**) (19–25). The care team, which centers around the person with diabetes, should avoid therapeutic inertia and prioritize timely and appropriate intensification of behavior change (nutrition and physical activity), pharmacologic therapy, and/or social and financial support systems for individuals who have not achieved recommended metabolic goals or are experiencing high burden of treatment.

Initiatives such as the Patient-Centered Medical Home (PCMH) model can improve health outcomes by fostering comprehensive primary care and offering new opportunities for team-based chronic disease management (26–28). Accountable Care Organizations (ACOs), a primary care–centered delivery and payment model, can support the implementation of the CCM and ultimately improve diabetes-related metrics in participating organizations (29). The Accountable Health Communities Model was introduced to support identifying and addressing health-related social needs to improve disease management and health outcomes (30); early evidence showed reduction in emergency department use among Medicare and Medicaid beneficiaries, but diabetes-specific metrics were not examined, and program effectiveness has been limited by scarcity of resources to meet identified health-related social needs (31). Alternative Payment Models (APMs) have had mixed effects on diabetes care delivery and outcomes, with higher-risk APMs (i.e., models with greater financial risk assumed by the provider, such as capitated payment models) generally associated with greater improvements in diabetes care processes than lower-risk APMs (32). Value-based payment models are hypothesized to better support the implementation and sustainability of innovative care delivery models seeking to improve population health (26,33), though evidence for currently available value-based insurance designs is limited (32).

Telehealth

Telehealth uses digital tools like video conferencing, mobile apps, and remote monitoring to deliver a range of health services remotely, including clinical care, education, and administrative support. Telemedicine, a subset of telehealth, focuses specifically on remote clinical care, such as diagnosis, treatment, and consultations through real-timecommunication. Increased access to and effective use of telehealth services, alongside in-person care, can enhance timely access to diabetes care and DSMES services for individuals with diabetes (34–38).

Telehealth should be used to complement but not replace in-person visits for optimal glycemic management (39,40). Increasingly, evidence suggests that various telehealth modalities may facilitate reducing A1C in people with type 2 diabetes compared with usual care or in addition to usual care (41), and findings suggest that telemedicine is a safe method of delivering care for people with type 1 diabetes in rural areas (42). For rural populations or those with limited physical access to health care, telehealth has a growing body of evidence for its effectiveness, particularly with regard to glycemic management as measured by A1C (43–46). In addition, evidence supports the effectiveness of telehealth in hypertension and dyslipidemia interventions (47). Interactive strategies that facilitate communication between health care professionals and people with diabetes, including the use of web-based portals or text messaging and those that incorporate medication adjustment, appear to be effective in improving outcomes (44,48). Telehealth and other virtual environments can be used to offer diabetes self-management education and clinical support and remove geographic and transportation barriers for individuals living in underresourced

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Table 1.1—Considerations for engaging interprofessional members of a comprehensive, person-centered diabetes care team to identify and meet the needs of people with diabetes across the life span

Subpopulation of a person with diabetes	Team members to engage in care	Unique care considerations
All adults with diabetes	Primary care clinician, CDCES, RDN, and other specialists as available and appropriate to treat comorbidities (**Table 4.1**)	Assess for and address social determinants of health.
Adults treated with intensive insulin therapy, including multiple daily injections of insulin and insulin pump therapy	Clinicians and other health care team members experienced in advanced diabetes management, including technology use	
All youth with diabetes	Primary care clinician, pediatric endocrinologist, CDCES, RDN, other specialists as available and appropriate to treat comorbidities (**Table 14.1**), daycare or school nurse or other professional, behavioral health professional (as needed), and parent(s) or caregiver(s)	Assess for and address social determinants of health and barriers to safety, well-being, and academic performance in school. Engage professionals within the school and extracurricular/after-school activities to ensure safe diabetes management. An individualized diabetes medical management plan should be developed in collaboration with school professionals and parent(s) or caregiver(s). Support gradual developmentally appropriate transfer of self-management from caregivers to the youth with diabetes.
Individuals with diabetes and diabetes-related complications or comorbidities	Specialist referrals as appropriate and available (e.g., behavioral health professional, cardiologist, eye specialist, gastroenterologist or hepatologist, neurologist, nephrologist, obesity medicine specialist, or podiatrist), care coordinator/navigator or case manager, and clinical pharmacist (for those with polypharmacy or complex medication plans)	Screen for functional, cognitive, financial, and logistical barriers to self-management and evidence that self-care demands exceed capacity and available resources and support systems.
Individuals with social and/or structural barriers to care	Care coordinator/navigator, social services professional, insurance specialist/navigator, peer-to-peer support (as available), community health worker and/or community paramedic (as available), public health professional, and interpreter (as applicable)	Consider each person's psychosocial needs, available resources, and support systems.
Older adults	Geriatric medicine specialist, social services professional, case manager, community services provider, and physical and/or occupational therapist as available and appropriate based on functional status and independence	Consider the older adult's nutritional status, including ability to afford (financial barriers), acquire (accessibility), prepare (cooking), and consume (oral health) nutritious food. Assess for and address needs related to vision, hearing, dexterity, cognition, mobility, and other challenges.
Individuals in long-term care settings	Long-term care facility clinicians, nurses, other health care professionals, physical and occupational therapists, and RDN	Engage professionals within the long-term care facility to ensure safe and appropriate diabetes management.
Pregnant individuals with diabetes	Maternal-fetal medicine specialist or obstetrician experienced in the care of pregnant individuals with diabetes (particularly for individuals with type 1 diabetes or requiring intensive insulin therapy), CDCES, RDN, eye specialist (particularly for individuals with preexisting type 1 or type 2 diabetes), other specialists as appropriate, and lactation consultant as appropriate	Ensure appropriate postpartum follow-up and care, including transition from obstetric care to established primary care.
Individuals with behavioral health conditions	Behavioral health professional, care coordinator/navigator, and social services professional as age and situation appropriate	Use age- and situation-appropriate screening protocols for general and diabetes-related psychosocial concerns.

CDCES, certified diabetes care and education specialist; RDN, registered dietitian nutritionist.

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areas or with disabilities (49). Telehealth resources can also have a role in improving diabetes management in children and adolescents with type 1 diabetes (50) and addressing SDOH in young adults with diabetes (51). Optimally leveraging telehealth to improve diabetes management requires anticipating and addressing barriers posed by cost, capacity, and resources (including broadband internet access) of people with diabetes and the existing clinical infrastructure into which telehealth approaches are being integrated (52).

Strategies for System-Level Improvement

Optimal diabetes management requires a systematic approach and coordinated team of health care professionals working in an environment where person-centered, high-quality care is a priority (8,17,53,54). While many diabetes care processes and access to technologies have improved nationally in the past decade, the overall quality of care for people with diabetes remains suboptimal (5). Efforts to increase the quality of diabetes care include providing care that is concordant with evidence-based guidelines (54), expanding the role of teams to implement more intensive disease management strategies (19), tracking medication-taking behavior (55), redesigning care processes (56), implementing electronic health record (EHR) population health tools (57), empowering and educating people with diabetes (58), reducing financial barriers (59), leveraging telehealth to improve access to care (43), assessing and addressing psychosocial issues (60,61), and engaging community resources and public policies that support healthy lifestyles (62). The National Diabetes Education Program maintains an online resource (cdc.gov/diabetes/php/toolkits/index.html) to help health care professionals design and implement more effective health care delivery systems for people with diabetes. Given the pluralistic needs of people with diabetes and that the challenges they experience (complex insulin treatment plans, new technologies, changes in capacity for self-management, etc.) vary over the course of disease management and life span, engagement of an interprofessional team with complementary expertise is essential (20).

Behaviors and Well-being

Successful diabetes care also requires a systematic approach to supporting the behavior-change efforts of people with diabetes. High-quality DSMES has been shown to improve a person's self-management, satisfaction, and glycemic outcomes (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for a detailed review of the evidence supporting DSMES). National DSMES standards call for an integrated approach that includes clinical content and skills, behavioral strategies (goal setting, problem-solving, etc.), and engagement with psychosocial concerns (61). Increasingly, such support is available through online or mobile platforms that can support user access and effectiveness. These curricula should be tailored to the needs of their intended populations, including addressing the "digital divide," i.e., access to the technology required for implementation (46,63).

Cost Considerations for Medication-Taking Behaviors

The cost of diabetes medications and devices is an ongoing barrier to achieving glycemic goals. Based on a national survey conducted in 2021, 18.6% of U.S. adults with type 1 diabetes and 15.8% of adults with insulin-treated type 2 diabetes reported rationing (i.e., skipping, taking less, and/or delaying) their insulin to save money (64). Insulin underuse due to cost has been termed "cost-related medication nonadherence" (here referred to as cost-related barriers to medication use). The ADA Insulin Access and Affordability Working Group has recommended system-level approaches to address this issue, including concepts such as cost-sharing for insured people with diabetes based on the lowest price available, a list price for insulins that closely reflects the net price, and health plans that ensure people with diabetes can access insulin without undue administrative burden or excessive cost (65). In 2021, the Centers for Medicare & Medicaid Services (CMS) launched the Part D Senior Savings Model (66), which requires participating plans to cover insulins with a $35 maximum monthly out-of-pocket payment. In 2022, 43% of stand-alone Part D plan enrollees and 60% of Medicare Advantage Part D plan enrollees participated in the Senior Savings Model (67). Most recently, the Inflation Reduction Act of 2022 capped out-of-pocket payments for insulin at $35 per insulin per month for all Medicare beneficiaries. A patchwork of solutions has also been introduced for individuals with commercial insurance and those without health insurance. Over the past 5 years, 25 states and the District of Columbia have capped out-of-pocket expenditures for insulin in select state-regulated commercial health plans (68). Between 2023 and 2024, three major insulin manufacturers similarly lowered the price of insulin to $35 per month in select circumstances (69). These programs may help reduce the financial hardship of diabetes management, though many are challenging to navigate, not all people with diabetes can benefit, and costs for insulin delivery and glucose monitoring remain high. Thus, all people with diabetes should be screened for financial hardship of treatment, cost-related barriers to medication use, and rationing of other essential services due to medical costs (70).

The cost of medications (not only insulin) influences prescribing patterns and medication use because of the financial strain on the person with diabetes and the lack of secondary payor support (public and private insurance) for effective approved glucose-lowering, cardiovascular and kidney disease risk–reducing, and weight management therapies. There is robust evidence of disparities in the use of evidence-based therapies among individuals from racial and ethnic minoritized backgrounds, those with lower income levels, those living in rural areas, and those with limited insurance coverage (4,71–80). Financial barriers remain a major source of health disparities, and costs should be a focus of treatment goals and clinical decisions (81). (See TAILORING TREATMENT FOR SOCIAL CONTEXT.) Reduction in cost-related barriers to medication use is associated with better health outcomes and quality of life (82).

Access to Care

The Affordable Care Act and Medicaid expansion have increased access to care for many individuals with diabetes, emphasizing the protection of people with preexisting conditions, health promotion, and disease prevention (83). In fact, health insurance coverage increased from 84.7% in 2009 to 90.1% in 2016 for adults with diabetes aged 18–64 years. As of early 2022, more than 35 million people in the U.S. were enrolled in some form of Affordable Care Act–related health insurance (84). Coverage for those aged ≥65 years remained nearly universal (85). People with diabetes who have either

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private or public insurance coverage are more likely to meet quality indicators for diabetes care (86). However, even individuals with insurance coverage can experience financial barriers to care, particularly if enrolled in high-deductible health plans. In 2021, 28% of individuals with employer-sponsored health plans were enrolled in high-deductible health plans (87). Such plans are increasing in popularity; by 2023, 51% of private industry employees had the option to enroll in a high-deductible health plan, although only 36% had access to health savings accounts, which can offset some of the out-of-pocket costs incurred with high-deductible plans (88). Switching to a high-deductible health plan has been shown to increase financial hardship among people with diabetes (89), decrease and delay screening for retinopathy (90), decrease blood pressure and A1C monitoring (90), and increase the risks of experiencing both acute (severe hypoglycemia, hyperglycemic crises) (91) and chronic (myocardial infarction, stroke, hospitalization for heart failure, kidney failure, lower-extremity complications, proliferative retinopathy, and blindness) (92) diabetes complications. Insurance coverage and formulary design influence treatment decisions; it is essential that payors cover evidence-based diabetes care with minimal cost sharing by the person with diabetes. Health care teams should also discuss insurance coverage and financial barriers to care with all individuals with diabetes and pursue therapeutic strategies that minimize financial hardship.

Access to primary and specialty care is also essential for people with diabetes. While most adults with diabetes have access to a primary care clinician (a 2016 nationally representative population-based study found that 88% of adults with diabetes saw a primary care clinician in the prior year) (93), fewer have access to specialty endocrinology/diabetes care (94). A study of Medicare beneficiaries found that just 33% of older adults with type 1 diabetes, 14% of adults with type 2 diabetes and history of severe hypoglycemia, and 9% of other adults with type 2 diabetes saw an endocrinologist in 2019 (94). Racial and ethnic minoritized individuals, those with low income, those living in rural areas, and those residing in a long-term care facility were less likely to receive endocrinology care. Improving health outcomes for people with diabetes will therefore require improving availability of and access to primary and specialty services necessary to meet the full range of their health care needs (**Table 1.1**).

Quality Improvement

A recent Cochrane systematic review concluded that quality improvement (QI) can significantly improve outcomes for people with diabetes (18). As mandated by the Affordable Care Act, the Agency for Healthcare Research and Quality developed a National Quality Strategy based on three aims: improving the health of populations, improving overall quality and the personal experience of care, and reducing per capita cost (95). QI methods have been documented to improve diabetes device uptake, increase screening for psychosocial care, and reduce inequities in access to diabetes technologies (96–99). Information and guidance specific to quality improvement and practice transformation for diabetes care are available from the National Institute of Diabetes and Digestive and Kidney Diseases guidance on diabetes care and quality (100).

A successful QI team should include a clinical champion, administrative leader, QI/data specialist, and an individual living with or impacted by diabetes. Using patient registries and EHRs, health systems can evaluate the quality of diabetes care being delivered, benchmark metrics, and perform intervention cycles as part of QI strategies (13,57,101). QI can also be used as an effective strategy to support application of clinical practice recommendations by health care professionals.

In addition to QI approaches, other strategies that simultaneously improve the quality of care and potentially reduce costs are gaining momentum and include reimbursement structures that, in contrast to visit-based billing, reward the provision of appropriate and high-quality care to achieve metabolic goals (102); value-based payments; and incentives that accommodate personalized care goals (8,103). See EVIDENCE-BASED CARE MODELS TO IMPROVE POPULATION HEALTH, above, for more information.

TAILORING TREATMENT FOR SOCIAL CONTEXT

Recommendations

1.6 Health systems should assess and address disparities in diabetes care and health outcomes (e.g., by stratifying clinical quality data by factors such as insurance status, race, ethnicity, preferred language for health care discussions, disability, and other social determinants of health). **C** (104)

1.7 During clinical encounters, assess for social determinants of health, including food insecurity, **A** housing insecurity, financial barriers, health insurance and health care access, environmental and neighborhood factors, and social capital/social community support, **B** to inform treatment decisions, with referral to appropriate local community resources.

1.8 Provide people with diabetes additional self-management support from lay health coaches, navigators, or community health workers when available. **A**

1.9 Consider the involvement of community health workers to support management of diabetes and cardiovascular risk factors, especially in underserved communities and health care systems. **B**

Health inequities related to diabetes and its complications are well documented, are heavily influenced by SDOH, and have been associated with greater risk for developing diabetes, higher disease prevalence, and worse diabetes-related outcomes (104–106). SDOH are defined as the economic, environmental, political, and social conditions in which people live and are responsible for a major part of health inequality worldwide (107). Greater exposure to adverse SDOH over the life course results in poor health (108). Interventions to address SDOH can improve diabetes-related outcomes (104,109). Using clinical quality data to identify inequities and opportunities for improvement is valuable for health care professionals, health systems, payors, policymakers, and people with diabetes (110). The Joint Commission requires that all accredited organizations in its ambulatory health care, behavioral health care and human services, critical access hospital, and hospital accreditation programs collect race and ethnicity information and implement specific steps to reduce health care disparities. The Joint Commission specifically requires that organizations designate an individual or individuals) to lead efforts to reduce health care disparities, assess

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health-related social needs and provide information on community resources to meet these needs, identify health care disparities by stratifying quality and safety data using sociodemographic characteristics, develop an action plan to address health care disparities, work to actively reduce health care disparities, and inform key stakeholders about progress to reduce health care disparities (111). The CMS Framework for Health Equity similarly prioritizes collection, reporting, and analysis of standardized individual-level demographic (including race, ethnicity, language, gender identity, sex, sexual orientation, and disability status) and SDOH data as well as assessing for and addressing disparities through improved access to culturally tailored services, team-based care, and community resources (112). Quality measures assessing SDOH screening and intervention have been introduced by the National Committee for Quality Assurance (focused on food, housing, and transportation insecurity) (113) and CMS (focused on food, housing, and transportation insecurity, utility difficulties, and interpersonal safety) (114).

Outside of SDOH, there are several contributors to inequities, including bias, institutional practices, and systemic factors (115–117). The ADA recognizes the association between interpersonal, social, and environmental factors and the prevention and treatment of diabetes and has issued a call for research that seeks to better understand how social determinants influence behaviors and how the relationships between these variables might be modified for enhancing the prevention and management of diabetes (104). While a comprehensive strategy to reduce diabetes-related health disparities in populations is yet to be formally studied, general recommendations from other chronic disease management and prevention models can be drawn upon to inform system-level strategies in diabetes (118). For example, the National Academy of Medicine has published a framework for educating health care professionals on the importance of SDOH (119). Furthermore, there are resources available for the inclusion of standardized sociodemographic variables in EHRs to facilitate the measurement of health disparities and the impact of interventions designed to reduce those disparities (95,119,120).

SDOH are not consistently recognized and often go undiscussed—and are ultimately not addressed—during the clinical encounter (106). Among people with chronic illnesses, two-thirds of those who reported not taking medications as prescribed due to cost-related barriers never shared this information with their physician (121). A study using data from the National Health Interview Survey (NHIS) (106) found that half of adults with diabetes reported financial stress and about 20% reported food insecurity. Studies of both type 1 diabetes and type 2 diabetes have noted an association of one or more adverse SDOH with health care utilization and poor diabetes outcomes among individuals with diabetes (121,122). It is therefore important for people with diabetes to be screened for SDOH during clinical encounters and be referred to appropriate clinical and community resources to address these needs (**Table 1.1**). Furthermore, health systems may benefit from compiling an inventory of such resources to facilitate referrals at the point of care. Policies and payment models that support addressing SDOH, both within and outside the health care setting, are needed to ensure that these efforts are both feasible and sustainable. One example of a statewide payment model that incentivizes value-based care, addressing SDOH and funding community-based health care professionals, is the Maryland Total Cost of Care Model, although it is currently limited by a narrow focus on preventing diabetes and does not consider diabetes care quality or health outcomes in people with diabetes (110,123).

Another population in which such issues must be considered is older adults, for whom social difficulties may further impair quality of life and increase the risk of functional dependency (124) (see Section 13, "Older Adults," for a detailed discussion of social considerations in older adults).

Creating system-level mechanisms to screen for SDOH may help overcome structural barriers and communication gaps between people with diabetes and health care professionals (106,125). A number of studies have proven the effectiveness of identifying SDOH by using validated screening tools (126). In addition, brief, validated screening tools for some SDOH exist and could facilitate discussion around factors that significantly impact treatment during the clinical encounter.

Food Insecurity

Food insecurity is a household-level economic and social condition of limited or uncertain access to adequate food (127). In 2022, almost 13% of Americans were food insecure (127), and food insecurity is associated with increased risk of type 2 diabetes and higher-than-recommended glycemia (128,129). The rate is disproportionately higher among some groups that have been historically marginalized, low-income households, and households headed by single mothers. Additionally, those facing food insecurity have lower engagement in self-care behaviors and medication use, have higher rates of depression and diabetes distress, and have worse glycemic management compared with individuals who are food secure (128,129). Older adults with food insecurity are more likely to have emergency department visits and hospitalizations compared with older adults who do not report food insecurity (130). Risk for food insecurity can be assessed with a validated two-item screening tool (131) that includes the following statements: *1*) "Within the past 12 months, we worried whether our food would run out before we got money to buy more" and *2*) "Within the past 12 months the food we bought just didn't last, and we didn't have money to get more." Interventions such as food prescription programs are considered promising to address food insecurity by integrating community resources into primary care settings and directly dealing with food deserts in underserved communities (132).

In those with diabetes and food insecurity, the priority is mitigating the increased risk for severe hyperglycemia and hypoglycemia (133,134). The reasons for the increased risk of hyperglycemia can include the consumption of inexpensive carbohydrate-rich processed foods, binge eating, financial constraints to filling diabetes medication prescriptions, anxiety and depression, and poor sleep, all contributing to hyperglycemia and poor diabetes self-care behaviors. Hypoglycemia can occur due to inadequate or inconsistent carbohydrate consumption following the administration of sulfonylurea or insulin. Health care professionals should consider these factors when making treatment decisions for people with food insecurity and seek local resources to help people with diabetes and their

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family members obtain nutritious food more regularly (135).

Housing Insecurity

Housing insecurity has been shown to be directly associated with a person's ability to maintain their diabetes self-management (136). Housing insecurity often accompanies other barriers that challenge diabetes self-management. Food insecurity, lack of insurance, cognitive impairment, behavioral health concerns, and low literacy and numeracy skills are also factors (135). The prevalence of diabetes among people experiencing housing insecurity is estimated to be around 8% (137). Additionally, people with diabetes and housing insecurity need secure places to keep their diabetes medications and supplies as well as refrigerator access to safely store insulin. The risk for housing insecurity can be ascertained using a brief risk assessment tool developed and validated for use among veterans (138). Given the potential challenges, health care professionals who care for housing-insecure individuals should be familiar with resources to support these individuals or have access to social workers who can facilitate stable housing as a way to improve diabetes care (139).

Refugee, Migrant, and Seasonal Agricultural Workers

Refugee status, like having a diabetes diagnosis, is an independent risk factor for cardiovascular disease (140). In areas undergoing humanitarian crises, refugees are at greater risk for obstacles to achieving optimal chronic disease management, but unfortunately there are few quality investigations into the particular situations of refugees with diabetes. There have been efforts to develop models of care specifically aimed at improving the health of refugee populations, but more work is needed to demonstrate effectiveness of those care models and approaches (141).

Migrant and seasonal agricultural workers likely have a higher risk of type 2 diabetes than the general population. While migrant farmworker–specific data are lacking, most agricultural workers in the U.S. are Latino, a population with a high rate of type 2 diabetes. In addition, living in severe poverty brings with it food insecurity, high chronic stress, and an increased risk of diabetes; there is also an association between the exposure to certain pesticides and the incidence of diabetes (142).

Data from the Department of Labor indicate that there are approximately 2.18 million agricultural workers in the U.S. (143). These agricultural workers often travel throughout the country seasonally (144), although less so than in past decades. According to 2022 health center data, 175 health centers across the U.S. reported providing care to 843,071 adult migrant farmworkers, and 91,839 had encounters for diabetes (142). In a 2023 report on the National Agricultural Workers Survey, age-adjusted self-reported diabetes prevalence was 13.51% (95% CI 10.0–17.1) among migrant farmworkers and 10.8% (95% CI 9.0–12.6) among nonmigrant farmworkers (142).

Migrant farmworkers and other agricultural workers encounter numerous and overlapping barriers to receiving care. Migration, which might occur as frequently as every few weeks for some, disrupts care. Common barriers to adequate diabetes care include those related to cost, culture, language, literacy, transportation, geographic distance, food access, long work hours, unfamiliarity with new communities, the complexity of the U.S. health care system, and limited access to various other resources like medications and DSMES (144). Without regular care, farmworkers with diabetes can experience severe and often expensive complications that incur morbidity and mortality and affect quality of life. Nontraditional care delivery models, including mobile integrated health and telehealth, should be leveraged to improve access to high-quality care.

Health care professionals need to be attuned to the working and living conditions of people with diabetes. For example, if a farmworker with diabetes presents for care, appropriate referrals should be initiated to social workers and community resources, as available, to assist with removing barriers to care.

Language Barriers

Health systems and health care professionals caring for those with limited English proficiency should develop or offer educational programs and materials in culturally appropriate languages. Professional language assistance (i.e., interpreters) should be provided to individuals with limited English proficiency and/or other communication needs at no cost to them (145). Use of untrained interpreters, including family members, should be avoided when possible, as this can result in confusing or inaccurate conveyance of information. Accompanying written materials should be in the language appropriate for the individual being supported and at a reading level that is not overly complicated—typically this is defined as a sixth-grade reading level. The National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care (National CLAS Standards) provide guidance on how health care professionals can reduce language barriers by improving their cultural competency, addressing health literacy, and ensuring communication with professional language assistance (145). In addition, the National CLAS Standards website offers several resources and materials that can be used to improve the quality of care delivery to individuals with limited English proficiency (145).

Health Literacy and Numeracy

Health literacy is the degree to which individuals can obtain, process, and understand basic health information and services needed to make appropriate decisions (146,147). Health literacy is strongly associated with individuals engaging in complex disease management and self-care (148). Approximately 9 out of 10 American adults are estimated to have limited or low health literacy (146,149). Clinicians and diabetes care and education specialists should provide easy-to-understand information and reduce unnecessary complexity when developing care plans. Interventions addressing low health literacy in populations with diabetes seem effective in improving diabetes outcomes, including ones focusing primarily on education, self-care training, or disease management. Combining easily adapted materials with formal diabetes education demonstrates effectiveness on clinical and behavioral outcomes in populations with low literacy (150). However, more research is needed to establish the most effective strategies for enhancing retention and application of diabetes knowledge among various populations of people with diabetes (148,151).

Health numeracy is also essential in diabetes prevention and management. Health numeracy requires primary numeric skills,

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applied health numeracy, and interpretive health numeracy, which is especially important for people using diabetes technologies like insulin pumps (152). An emotional component also affects a person's ability to understand concepts of risk, probability, and communication of scientific evidence (153). People with prediabetes or diabetes often need to perform numeric tasks such as interpreting food labels and blood glucose levels to make treatment decisions. Thus, both health literacy and numeracy are necessary for enabling effective communication between people with diabetes and health professionals, arriving at a treatment plan, and making diabetes self-management task decisions. If people with diabetes appear not to understand concepts associated with treatment decisions, both can be assessed using standardized screening measures (154). Adjunctive education and support may be indicated if limited health literacy and numeracy are barriers to optimal care decisions (60).

Social Capital and Community Support

Social capital, which comprises community and personal network instrumental support, promotes better health, whereas lack of social support is associated with poorer health outcomes in individuals with diabetes (104). Of particular concern are the SDOH, including, among others, racism and discrimination (155). These factors are rarely addressed in routine clinical practice but may be underlying reasons for adverse health outcomes and lower engagement in beneficial self-care behaviors and medication use. Optimally identifying and leveraging community resources are core components of chronic care management (15).

Health care community linkages are receiving increasing attention from the American Medical Association, the Agency for Healthcare Research and Quality, and others to promote the translation of clinical recommendations for nutrition and physical activity in real-world settings (156). Community health workers (CHWs) (157), community paramedics (158), peer supporters (159,160), and lay leaders (161) may assist in the delivery of DSMES services (119,162), particularly in underserved communities. The American Public Health Association defines a CHW as a "frontline public health worker who is a trusted member of and/or has an unusually close understanding of the community served" (163). CHWs can be part of an evidence-based strategy to improve the management of diabetes and cardiovascular risk factors in underserved communities and health care systems (164). The CHW scope of practice in areas such as outreach and communication, advocacy, social support, basic health education, referrals to community clinics, and other services has successfully provided social and primary preventive services to underserved populations in rural and hard-to-reach communities. Even though CHWs' core competencies are not clinical in nature, in some circumstances, clinicians may delegate limited clinical tasks to CHWs. If such is the case, these tasks must always be performed under the direct supervision of the delegating health professional and following state health care laws and statutes (165,166). Community paramedics are advanced paramedics with training in chronic disease monitoring and education, medication management, care coordination, and SDOH in addition to their emergency medical services expertise. While their scope of practice varies across states, community paramedics can engage and support people living with diabetes under the direction of a medical director by delivering diabetes education, assisting with medication management, performing health assessments and wound care, and connecting people with diabetes and care partners with clinical and community resources (158).

SUMMARY

Improving individual and population health for people with and at risk for diabetes requires engagement of and collaboration between people with diabetes and their caregivers, interprofessional health care teams, health systems, community partners, payors, policymakers, and public health agencies. This section provides guidance to facilitate implementation of evidence-based diabetes care recommendations that are discussed in the Standards of Care with the goal of improving health, eliminating health disparities, and reducing the impact of diabetes and its complications on individuals and society.

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2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is both underutilized as an energy source and overproduced due to inappropriate gluconeogenesis and glycogenolysis, resulting in hyperglycemia (1). Diabetes can be diagnosed by demonstrating increased concentrations of glucose in venous plasma or increased A1C in the blood. Diabetes is classified conventionally into several clinical categories (e.g., type 1 or type 2 diabetes, gestational diabetes mellitus, and other specific types derived from other causes, such as monogenic diabetes, exocrine pancreatic disorders, and high-risk medications) (2).

DIAGNOSTIC TESTS FOR DIABETES

Diabetes may be diagnosed based on A1C or plasma glucose criteria. Plasma glucose criteria include either the fasting plasma glucose (FPG), 2-h plasma glucose (2-h PG) during a 75-g oral glucose tolerance test (OGTT), or random glucose accompanied by classic hyperglycemic symptoms (e.g., polyuria, polydipsia, and unexplained weight loss) or hyperglycemic crises (i.e., diabetic ketoacidosis [DKA] and/or hyperglycemic hyperosmolar state [HHS]) (**Table 2.1**).

Recommendations

2.1a Diagnose diabetes based on A1C or plasma glucose criteria. Plasma glucose criteria include either the fasting plasma glucose (FPG), 2-h plasma glucose (2-h PG) during a 75-g oral glucose tolerance test (OGTT), or random glucose accompanied by classic hyperglycemic symptoms/crises (**Table 2.1**). **B**

2.1b In the absence of unequivocal hyperglycemia (e.g., hyperglycemic crises), diagnosis requires confirmatory testing (**Table 2.1**). **B**

Screening and Diagnosis of Diabetes

FPG, 2-h PG during 75-g OGTT, and A1C are appropriate for screening and diagnosis. It should be noted that detection rates of different screening tests vary in both

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.*

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Table 2.1—Criteria for the diagnosis of diabetes in nonpregnant individuals

A1C ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (≥7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (≥11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal results from different tests which may be obtained at the same time (e.g., A1C and FPG), or the same test at two different time points.

populations and individuals. FPG, 2-h PG, and A1C reflect different aspects of glucose metabolism, and diagnostic cut points for the different tests will identify groups with incomplete concordance (3). Compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with prediabetes and diabetes (4). Moreover, the efficacy of interventions for primary prevention of type 2 diabetes (i.e., preventing conversion of prediabetes to type 2 diabetes) has been demonstrated mainly among individuals with prediabetes who have impaired glucose tolerance (IGT) with or without elevated fasting glucose, not for individuals with isolated impaired fasting glucose (IFG) or for those with prediabetes defined by A1C criteria (5–8).

The same tests may be used to screen for and diagnose diabetes and to detect individuals with prediabetes (9) (**Table 2.1** and **Table 2.2**). Diabetes may be identified anywhere along the spectrum of clinical scenarios—in seemingly low-risk individuals who happen to have glucose testing, in individuals screened based on diabetes risk assessment, and in symptomatic individuals. There is presently insufficient evidence to support the use of continuous glucose monitoring (CGM) for screening or diagnosis of prediabetes or diabetes. For additional details on the evidence used to establish the criteria for the diagnosis of diabetes or prediabetes, see the American Diabetes Association (ADA) position statement "Diagnosis and Classification of Diabetes Mellitus" (2) and other reports (1,3,10,11).

Table 2.2—Criteria defining prediabetes in nonpregnant individuals

A1C 5.7–6.4% (39–47 mmol/mol)
OR
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range. FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose.

Use of Fasting Plasma Glucose or 2-Hour Plasma Glucose for Screening and Diagnosis of Diabetes

In the less common clinical scenario where a person has classic hyperglycemic symptoms (e.g., polyuria, polydipsia, unexplained weight loss) or presents with hyperglycemic crisis, measurement of random plasma glucose is sufficient to diagnose diabetes (symptoms of hyperglycemia or hyperglycemic crisis plus random plasma glucose ≥200 mg/dL [≥11.1 mmol/L]). In these cases, knowing the plasma glucose level is critical because, in addition to confirming that symptoms are due to diabetes, it will inform management decisions. Health care professionals may also want to know the A1C to determine the chronicity of hyperglycemia. However, in an individual without symptoms, FPG or 2-h PG can be used for screening and diagnosis of diabetes. In nonpregnant individuals, FPG (or A1C) is typically preferred for routine screening due to the ease of administration (**Table 2.3**); however, the 2-h PG (OGTT) testing protocol diagnoses more diabetes than the other two tests and is preferentially recommended for screening for some conditions (e.g., cystic fibrosis-related diabetes or posttransplantation diabetes mellitus). In the absence of classic hyperglycemic symptoms, repeat testing is required to confirm the diagnosis regardless of the test used (see CONFIRMING THE DIAGNOSIS, below).

An advantage of glucose testing is that these assays are inexpensive and widely available. Disadvantages include the high diurnal variation in glucose and fasting requirement. Individuals may have difficulty fasting for the full 8-h period or may misreport their fasting status (**Table 2.3**). Recent physical activity, illness, or acute stress can affect glucose concentrations. Glycolysis is also an important and underrecognized concern with glucose testing. Glucose concentrations will be falsely low if samples are not handled properly and promptly prior to analysis (1).

People should follow a mixed eating pattern with at least 150 g of carbohydrates on the 3 days prior to OGTT (12–14). Antecedent carbohydrate restriction in the days prior to OGTT can falsely elevate postchallenge glucose levels, potentially resulting in a false-positive OGTT (12).

Use of A1C for Screening and Diagnosis of Diabetes

Recommendations

2.2a The A1C test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) as

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Table 2.3—Considerations related to the use and interpretation of laboratory measurements of glucose and A1C

	Glucose	A1C
Cost	Inexpensive and available in most laboratories across the world	More expensive than glucose and not as widely available globally
Time frame of hyperglycemia	Acute measure	Chronic measure of glucose exposure over the past ~2–3 months
Preanalytic stability	Poor; plasma must be separated immediately or samples must be kept on ice to prevent glycolysis	Good
Sample	Measurement can vary depending on sample type (plasma, serum, whole blood) and source (capillary, venous, arterial)	Requires whole-blood sample
Assay standardization	Not standardized	Well standardized
Fasting	Fasting or timed samples required	Nonfasting test; no participant preparation is needed
Within-person variability	High	Low
Acute factors that can affect levels	Food intake, stress, recent illness, activity	Unaffected by recent food intake, stress, illness, activity
Other individual factors that can affect test results	Diurnal variation, medications, alcohol, smoking, bilirubin	Altered erythrocyte turnover (e.g., anemia, iron status, splenectomy, blood loss, transfusion, hemolysis, glucose-6-phosphate dehydrogenase deficiency, erythropoietin), HIV, cirrhosis, renal failure, dialysis, pregnancy
Test interferences	Depends on specific assay: sample handling/processing time, hemolysis, severe hypertriglyceridemia, severe hyperbilirubinemia	Depends on specific assay: hemoglobin variants, severe hypertriglyceridemia, severe hyperbilirubinemia

Data are from Selvin (217).

traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. **B**

2.2b Point-of-care A1C testing for diabetes screening and diagnosis should be restricted to devices approved for diagnosis by the U.S. Food and Drug Administration at Clinical Laboratory Improvement Amendments–certified laboratories that perform testing of moderate complexity or higher by trained personnel. **B**

2.3 Evaluate for the possibility of a problem or interference with either test when there is consistent and substantial discordance between blood glucose values and A1C test results. **B**

2.4 In conditions associated with an altered relationship between A1C and glycemia, such as some hemoglobin variants, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, hemolysis, or erythropoietin therapy, plasma glucose criteria should be used to diagnose diabetes. **B**

The A1C test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) (ngsp.org) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Outside the U.S., some assays are NGSP certified but many more are International Federation of Clinical Chemistry (IFCC) certified (a similarly stringent process) (1).

Point-of-care A1C assays may be NGSP certified and cleared by the U.S. Food and Drug Administration (FDA) for use in monitoring glycemic management in people with diabetes in both Clinical Laboratory Improvement Amendments (CLIA)–regulated and CLIA-waived settings. FDA-approved point-of-care A1C testing can be used in laboratories or sites that are CLIA certified, are inspected, and meet the CLIA quality standards. These standards include specified personnel requirements (including documented annual competency assessments) and participation three times per year in an approved proficiency testing program (15–18).

A1C has several advantages compared with FPG and OGTT, including greater convenience (fasting is not required), greater preanalytical stability, and fewer day-to-day perturbations during stress, changes in nutrition, or illness. However, it should be noted that there is lower sensitivity of A1C at the designated cut point compared with that of 2-h PG as well as limited access in some parts of the world (**Table 2.3**).

A1C reflects glucose bound to hemoglobin over the life span of the erythrocyte (~120 days) and is thus a "weighted" average that is more heavily affected by recent blood glucose exposure. This means that clinically meaningful changes in A1C can be seen in <120 days. A1C is an indirect measure of glucose exposure, and factors that affect hemoglobin concentrations or erythrocyte turnover can affect A1C

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(e.g., thalassemia or folate deficiency) (**Table 2.3**). A1C may not be a suitable diagnostic test in people with anemia, people treated with erythropoietin, or people undergoing hemodialysis or HIV treatment (1,19,20). Some hemoglobin variants can interfere with A1C test results, but this depends on the specific assay. For individuals with a hemoglobin variant but normal red blood cell turnover, such as those with the sickle cell trait, an A1C assay without interference from hemoglobin variants should be used. An updated list of A1C assays with interferences is available at ngsp.org/interf.asp. Another genetic variant, X-linked glucose-6-phosphate dehydrogenase G202A, carried by 11% of African American individuals in the U.S., is associated with a decrease in A1C of about 0.8% in homozygous men and 0.7% in homozygous women compared with levels in individuals without the variant (21).

There is controversy regarding racial differences in A1C. Studies have found that African American individuals have slightly higher A1C levels than non-Hispanic White or Hispanic people (22–25). The glucose-independent racial difference in A1C is small (~0.3 percentage points) and may reflect genetic differences in hemoglobin or red cell turnover that vary by ancestry. There is an emerging understanding of the genetic determinants of A1C (21), but the field lacks adequate genetic data in diverse populations (26,27). While some genetic variants might be more common in certain race or ancestry groups, it is important that we do not use race or ancestry as proxies for poorly understood genetic differences. Reassuringly, studies have shown that the association of A1C with risk for complications appears to be similar in African American and non-Hispanic White populations (28).

Confirming the Diagnosis

Unless there is a clear clinical diagnosis (e.g., individual with classic symptoms of hyperglycemia or hyperglycemic crisis and random plasma glucose ≥200 mg/dL [≥11.1 mmol/L]), confirmation is necessary to establish the diagnosis. This can be accomplished by two abnormal screening test results, measured either at the same time (29) or at two different time points. If using samples at two different time points, it is recommended that the second test, which may be either a repeat of the initial test or a different test, be performed in a timely manner. For example, if the A1C is 7.0% (53 mmol/mol) and a repeat result is 6.8% (51 mmol/mol), the diagnosis of diabetes is confirmed. Two different tests (such as A1C and FPG) both having results above the diagnostic threshold when collected at the same time or at two different time points would also confirm the diagnosis. On the other hand, if an individual has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated, with careful consideration of factors that may affect measured A1C or glucose levels. The diagnosis is made based on the confirmatory screening test. For example, if an individual meets the diabetes criterion of A1C (two results ≥6.5% [≥48 mmol/mol]) but not FPG (<126 mg/dL [<7.0 mmol/L]), that person should nevertheless be considered to have diabetes.

If individuals have test results near the margins of the diagnostic threshold, the health care professional should educate the individual about the onset of possible hyperglycemic symptoms and repeat the test in 3–6 months.

Consistent and substantial discordance between glucose values and A1C test results should prompt additional follow-up to determine the underlying reason for the discrepancy (including evaluation for the possibility of a problem or interference with either test) and whether it has clinical implications for the individual (**Table 2.3**). In addition, consider other biomarkers, such as fructosamine and glycated albumin, which are alternative measures of chronic hyperglycemia that are approved for clinical use for monitoring glycemic management in people with diabetes.

CLASSIFICATION

Recommendation

2.5 Classify people with hyperglycemia into appropriate diagnostic categories to aid in personalized management. **E**

Diabetes is classified conventionally into several clinical categories, although these are being reconsidered based on genetic, metabolomic, and other characteristics and pathophysiology (1):

1. Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes in adults)
2. Type 2 diabetes (due to a nonautoimmune progressive loss of adequate β-cell insulin secretion, frequently on the background of insulin resistance)
3. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes, diseases of the exocrine pancreas, and drug- or chemical-induced diabetes
4. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation or other types of diabetes occurring throughout pregnancy, such as type 1 diabetes).

Type 1 diabetes and type 2 diabetes are heterogeneous diseases in which clinical presentation and disease progression may vary considerably. Classification is important for determining personalized therapy, but some individuals cannot be clearly classified as having type 1 or type 2 diabetes at the time of diagnosis. The traditional paradigms of type 2 diabetes having onset only in adults and type 1 diabetes having onset only in children are not accurate, as both diseases occur in all age-groups. Children with type 1 diabetes often present with the hallmark symptoms of polyuria/polydipsia, and approximately half present with DKA (30–32). The onset of type 1 diabetes may be more variable in adults; they may not present with the classic symptoms seen in children and may progress to insulin replacement more slowly (33–35). The features most useful in determination of type 1 diabetes include younger age at diagnosis (<35 years) with lower BMI (<25 kg/m^2), unintentional weight loss, ketoacidosis, and plasma glucose >360 mg/dL (>20 mmol/L) at presentation (36) (**Fig. 2.1**). Other features classically associated with type 1 diabetes, such as ketosis without acidosis, osmotic symptoms, family history, or a history of autoimmune diseases, are weak discriminators. Occasionally, people with type 2 diabetes may present with DKA (37), particularly members of certain racial, ethnic, and ancestral groups (e.g., African American and Hispanic/Latino

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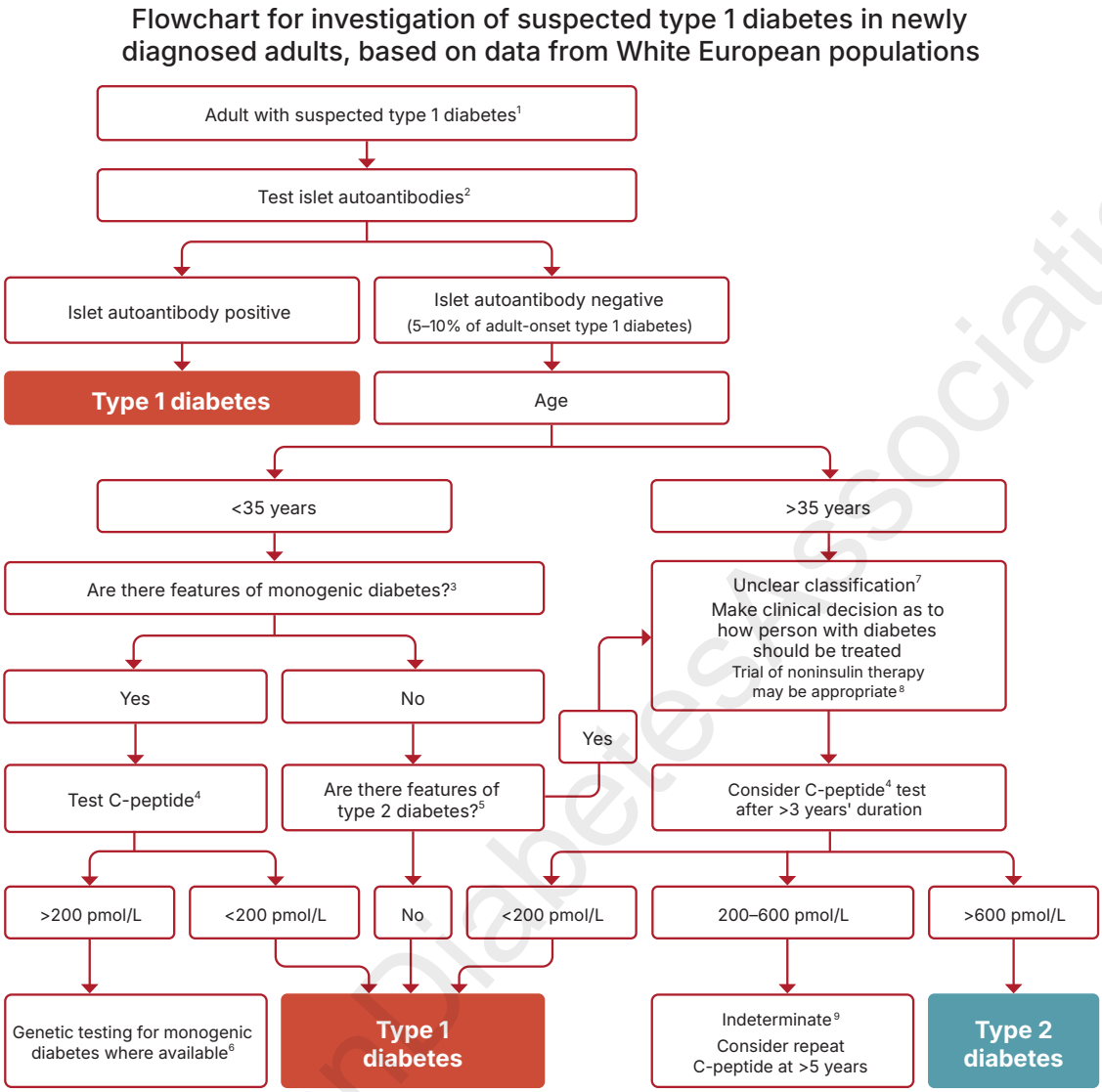

Figure 2.1—Flowchart for investigation of suspected type 1 diabetes in newly diagnosed adults, based on data from White European populations. [1]No single clinical feature confirms type 1 diabetes in isolation. [2]Glutamic acid decarboxylase (GAD) should be the primary antibody measured and, if negative, should be followed by islet tyrosine phosphatase 2 (IA-2) and/or zinc transporter 8 (ZnT8) where these tests are available. In individuals who have not been treated with insulin, antibodies against insulin may also be useful. In those diagnosed at <35 years of age who have no clinical features of type 2 diabetes or monogenic diabetes, a negative result does not change the diagnosis of type 1 diabetes, since 5–10% of people with type 1 diabetes do not have antibodies. [3]Monogenic diabetes is suggested by the presence of one or more of the following features: A1C <58 mmol/mol (<7.5%) at diagnosis, one parent with diabetes, features of a specific monogenic cause (e.g., renal cysts, partial lipodystrophy, maternally inherited deafness, and severe insulin resistance in the absence of obesity), and monogenic diabetes prediction model probability >5% (diabetesgenes.org/exeter-diabetes-app/ModyCalculator). [4]A C-peptide test is only indicated in people receiving insulin treatment. A random sample (with concurrent glucose) within 5 h of eating can replace a formal C-peptide stimulation test in the context of classification. If the result is ≥600 pmol/L (≥1.8 ng/mL), the circumstances of testing do not matter. If the result is <600 pmol/L (<1.8 ng/mL) and the concurrent glucose is <4 mmol/L (<70 mg/dL) or the person may have been fasting, consider repeating the test. Results showing very low levels (e.g., <80 pmol/L [<0.24 ng/mL]) do not need to be repeated. Where a person is insulin treated, C-peptide must be measured prior to insulin discontinuation to exclude severe insulin deficiency. Do not test C-peptide within 2 weeks of a hyperglycemic emergency. [5]Features of type 2 diabetes include increased BMI (≥25 kg/m^2), absence of weight loss, absence of ketoacidosis, and less marked hyperglycemia. Less discriminatory features include non-White ethnicity, family history, longer duration and milder severity of symptoms prior to presentation, features of metabolic syndrome, and absence of a family history of autoimmunity. [6]If genetic testing does not confirm monogenic diabetes, the classification is unclear and a clinical decision should be made about treatment. [7]Type 2 diabetes should be strongly considered in older individuals. In some cases, investigation for pancreatic or other types of diabetes may be appropriate. [8]A person with possible type 1 diabetes who is not treated with insulin will require careful monitoring and education so that insulin can be rapidly initiated in the event of glycemic deterioration. [9]C-peptide values 200–600 pmol/L (0.6–1.8 ng/mL) are usually consistent with type 1 diabetes or maturity-onset diabetes of the young but may occur in insulin-treated type 2 diabetes, particularly in people with normal or low BMI or after long duration. Reprinted and adapted from Holt et al. (36).

adults), who may present with ketosis-prone type 2 diabetes (30). This form of diabetes is strongly inherited and is not HLA associated. An absolute requirement for insulin replacement therapy in affected individuals may be intermittent. It is important for health care professionals to realize that classification of diabetes type is not always straightforward at presentation

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and that misdiagnosis is common and can occur in ~40% of adults with new type 1 diabetes (e.g., adults with type 1 diabetes misdiagnosed as having type 2 diabetes). In comparison, individuals with maturity-onset diabetes of the young (MODY) may be misdiagnosed as having type 1 diabetes (36). Although difficulties in distinguishing diabetes type may occur in all age-groups at onset, the diagnosis generally becomes more obvious over time in people with β-cell deficiency as the degree of β-cell deficiency becomes clear (**Fig. 2.1**). One useful clinical tool for distinguishing diabetes type is the **AABBCC** approach: **A**ge (e.g., for individuals <35 years old, consider type 1 diabetes); **A**utoimmunity (e.g., personal or family history of autoimmune disease or polyglandular autoimmune syndromes); **B**ody habitus (e.g., BMI <25 kg/m^2); **B**ackground (e.g., family history of type 1 diabetes); **C**ontrol (preferred term is "goal," i.e., the inability to achieve glycemic goals on noninsulin therapies); and **C**omorbidities (e.g., treatment with immune checkpoint inhibitors for cancer can cause acute autoimmune type 1 diabetes) (36).

In both type 1 and type 2 diabetes, genetic and environmental factors can result in the progressive loss of β-cell mass and/or function that manifests clinically as hyperglycemia. Once hyperglycemia occurs, people with all forms of diabetes are at risk for developing the same chronic complications, although rates of progression may differ. The identification of individualized therapies for diabetes in the future will be informed by better characterization of the many paths to β-cell demise or dysfunction (38). Across the globe, many groups are working on combining clinical, pathophysiological, and genetic characteristics to more precisely define the subsets of diabetes that are currently clustered into the type 1 diabetes versus type 2 diabetes nomenclature with the goal of optimizing personalized treatment approaches (39). A diagnosis of type 1 diabetes does not preclude also having features classically associated with type 2 diabetes (e.g., insulin resistance, obesity, and other metabolic abnormalities), and until more precise subsets are used in clinical practice, it may be appropriate to categorize such an individual as having features of both type 1 and type 2 diabetes to facilitate access to appropriate treatment (e.g., glucagon-like peptide 1 receptor agonist [GLP-1 RA] or sodium–glucose cotransporter 2 [SGLT2] inhibitor therapies for potential weight and other cardiometabolic benefits) and monitoring systems.

Characterization of the underlying pathophysiology is more precisely developed in type 1 diabetes than in type 2 diabetes. It is clear from prospective studies that the persistent presence of two or more islet autoantibodies is a near-certain predictor of clinical diabetes (40). In at-risk cohorts followed from birth or a very young age, seroconversion rarely occurs before 6 months of age and there is a peak in seroconversion between 9 and 24 months of age (41–43). The rate of progression is dependent on the age at first detection of an autoantibody, number of autoantibodies, autoantibody specificity, and autoantibody titer. Glucose and A1C levels may rise well before the clinical onset of diabetes (e.g., changes in FPG and 2-h PG can occur about 6 months before diagnosis) (44), making diagnosis feasible under ideal situations of serial monitoring of individuals at high risk of type 1 diabetes before the onset of DKA. Three distinct stages of type 1 diabetes have been defined (**Table 2.4**) and serve as a framework for research and regulatory decision-making (38,45).

There is debate as to whether slowly progressive autoimmune diabetes with an adult onset should be termed latent autoimmune diabetes in adults (LADA) or type 1 diabetes. The clinical priority with detection of LADA is awareness that slow autoimmune β-cell destruction can occur in adults, leading to a long duration of marginal insulin secretory capacity. For this classification, all forms of diabetes mediated by autoimmune β-cell destruction independent of age of onset are included under the rubric of type 1 diabetes. Use of the term LADA is common and acceptable in clinical practice and has the practical impact of heightening awareness of a population of adults likely to have progressive autoimmune β-cell destruction (46), thus accelerating insulin initiation prior to deterioration of glucose management or development of DKA (34,47). At the same time, there is evidence that application of only a single imperfect autoantibody test for determining LADA classification may lead to misclassification of some individuals with type 2 diabetes. Diagnostic accuracy may be improved by using higher-specificity tests, using confirmatory testing for other autoantibodies, and restricting testing to those with clinical features suggestive of autoimmune diabetes (48).

The paths to β-cell demise and dysfunction are less well defined in type 2 diabetes, but deficient β-cell insulin secretion, frequently in the setting of insulin resistance, appears to be the common denominator. Type 2 diabetes is associated with insulin secretory defects related to genetic predisposition, epigenetic changes, inflammation, and metabolic stress. Future classification schemes for diabetes will likely focus on the pathophysiology of the underlying β-cell dysfunction (38,49–52).

TYPE 1 DIABETES

Recommendations

2.6 Screening for presymptomatic type 1 diabetes may be done by detection of autoantibodies to insulin, glutamic acid decarboxylase (GAD), islet antigen 2 (IA-2), or zinc transporter 8 (ZnT8). **B**

2.7 Autoantibody-based screening for presymptomatic type 1 diabetes should be offered to those with a family history of type 1 diabetes or otherwise known elevated genetic risk. **B**

2.8 Having multiple confirmed islet autoantibodies is a risk factor for clinical diabetes. Testing for dysglycemia may be used to further forecast near-term risk (**Table 2.4**). When multiple islet autoantibodies are identified, referral to a specialized center for further evaluation and/or consideration of a clinical trial or approved therapy to potentially delay development of clinical diabetes should be considered. **B**

2.9 Standardized islet autoantibody tests are recommended for classification of diabetes in adults who have phenotypic risk factors that overlap with those for type 1 diabetes (e.g., younger age at diagnosis, unintentional weight loss, ketoacidosis, or short time to insulin treatment). **E**

Immune-Mediated Diabetes

Autoimmune type 1 diabetes accounts for 5–10% of diabetes and is caused by

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Table 2.4—Staging of type 1 diabetes

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple islet autoantibodies • No IGT or IFG, normal A1C	• Islet autoantibodies (usually multiple) • Dysglycemia: ◦ IFG: FPG 100–125 mg/dL (5.6–6.9 mmol/L) or ◦ IGT: 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) or ◦ A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Autoantibodies may become absent • Diabetes by standard criteria

Adapted from Skyler et al. (38). FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose. Alternative additional stage 2 diagnostic criteria of 30-, 60-, or 90-min plasma glucose on oral glucose tolerance test ≥200 mg/dL (≥11.1 mmol/L) and confirmatory testing in those aged ≥18 years have been used in clinical trials (84). Dysglycemia can be defined by one or more criteria as outlined in the table.

autoimmune destruction of the pancreatic β-cells. Autoimmune markers include islet cell autoantibodies and autoantibodies to glutamic acid decarboxylase (GAD) (such as GAD65), insulin, the tyrosine phosphatases islet antigen 2 (IA-2) and IA-2b, and zinc transporter 8 (ZnT8). Numerous clinical studies are being conducted to test various methods of preventing or delaying type 1 diabetes in those with evidence of islet autoimmunity (trialnet.org/our-research/prevention-studies) (40–42, 47,53,54). The disease has strong HLA associations, with linkage to the *DQB1* and *DRB1* haplotypes, and genetic screening has been used in some research studies to identify high-risk populations. Specific alleles in these genes can be either predisposing (e.g., DRB1*0301-DQB1*0201 [DR3-DQ2] and DRB1*0401-DQB1*0302 [DR4-DQ8]) or protective (e.g., DRB1*1501 and DQA1*0102-DQB1*0602). Stage 1 of type 1 diabetes is defined by the presence of two or more of these autoantibodies and normoglycemia (**Table 2.4**). At stage 1, the 5-year risk of developing symptomatic type 1 diabetes is ∼44% overall but varies considerably based on number, titer, and specificity of autoantibodies as well as age of seroconversion and genetic risk (45). Stage 2 includes individuals with multiple islet autoantibodies and dysglycemia not yet diagnostic of diabetes (dysglycemia can be defined by one or more criteria as outlined in **Table 2.4**). At stage 2 of the disease, there is ∼60% risk by 2 years and ∼75% risk within 5 years of developing a clinical diagnosis of type 1 diabetes (55,56). A consensus guidance provides expert recommendations on what should be monitored and how often these factors should be monitored in individuals with presymptomatic type 1 diabetes (57).

The rate of β-cell destruction is quite variable, being rapid in some individuals (particularly but not exclusively in infants and children) and slow in others (mainly but not exclusively adults) (44,58). Children and adolescents often present with DKA as the first manifestation of the disease, and rates in the U.S. have increased over the past 20 years (30–32). Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or DKA with infection or other stress. Adults may retain sufficient β-cell function to prevent DKA for many years; such individuals may have remission characterized by decreased insulin needs for months or years, eventually become dependent on insulin for survival, and are at risk for DKA (33–35, 59,60). At this later stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes is the most common form of diabetes in childhood and adolescence, but it can occur at any age. Autoimmune destruction of β-cells has multiple genetic factors and is also related to environmental factors that are still poorly defined. Although individuals did not classically have obesity when they presented with type 1 diabetes, obesity is increasingly common in the general population; as such, obesity should not preclude testing for type 1 diabetes. People with type 1 diabetes are also prone to other autoimmune disorders, such as Hashimoto thyroiditis, Graves disease, celiac disease, Addison disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities"). Type 1 diabetes can be associated with monogenic polyglandular autoimmune syndromes, including immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome, which is an early-onset systemic autoimmune, genetic disorder caused by mutation of the forkhead box protein 3 (*FOXP3*) gene, and another disorder caused by the autoimmune regulator (*AIRE*) gene mutation (61,62).

Introduction of immunotherapy, specifically checkpoint inhibitors, for cancer treatment has led to unexpected adverse events, including immune system activation precipitating autoimmune disease. Fulminant onset of type 1 diabetes can occur, with DKA and low or undetectable levels of C-peptide as a marker of endogenous β-cell function (63–65). Fewer than half of these individuals have autoantibodies that are seen in type 1 diabetes, supporting alternate pathobiology. This immune-related adverse event occurs in just under 1% of checkpoint inhibitor–treated individuals but most commonly occurs with agents that block the programmed cell death protein 1/programmed cell death ligand 1 pathway alone or in combination with other checkpoint inhibitors (66). To date, the majority of immune checkpoint inhibitor–related cases of type 1 diabetes occur in people with high-risk HLA susceptibility haplotype for type 1 diabetes; however, people with either a neutral or typically protective

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HLA haplotype for type 1 diabetes can also develop checkpoint inhibitor–associated type 1 diabetes (67). To date, risk cannot be predicted by family history or autoantibodies, so all health care professionals administering these medications or caring for people who have a history of current or past exposure to these agents should be mindful of this adverse effect and educate and monitor individuals appropriately.

A number of viruses have been associated with type 1 diabetes, including enteroviruses such as Coxsackievirus B. During the coronavirus disease 2019 (COVID-19) pandemic, numbers of cases of hyperglycemia, DKA, and new diabetes increased, suggesting that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a trigger for or can unmask type 1 diabetes (68). Possible mechanisms of β-cell damage include virus-triggered β-cell death, immune-mediated loss of pancreatic β-cells, and damage to β-cells because of infection of surrounding exocrine cells. The cytokine storm associated with COVID-19 infection is a highly inflammatory state that could also contribute. To better characterize and understand the pathogenesis of new-onset COVID-19–related diabetes, a global registry, CoviDIAB, has been established (69).

Idiopathic Type 1 Diabetes

Some forms of type 1 diabetes have no known etiologies. Individuals have permanent insulinopenia and are prone to DKA but have no evidence of β-cell autoimmunity. However, only a minority of people with type 1 diabetes fall into this category.

Screening for Type 1 Diabetes Risk

The incidence and prevalence of type 1 diabetes are increasing (70). People with type 1 diabetes often present with acute symptoms of diabetes and markedly elevated blood glucose levels, and 25–50% are diagnosed with life-threatening DKA (30–32). Family history of type 1 diabetes increases the risk of developing type 1 diabetes compared with the general population, but the majority, ∼90%, of individuals who develop type 1 diabetes do not have a known relative with the disease. Multiple studies indicate that measuring islet autoantibodies in relatives of those with type 1 diabetes (45), in children from the general population (71,72), or in children from the general population with high genetic risk (73) can identify many individuals who will develop type 1 diabetes. A study reported the risk of progression to type 1 diabetes from the time of seroconversion to autoantibody positivity in three pediatric cohorts from Finland, Germany, and the U.S. Of the 585 children who developed more than two autoantibodies, nearly 70% developed type 1 diabetes within 10 years and 84% within 15 years (40). These findings are highly significant, because while the German group was recruited from offspring of parents with type 1 diabetes, the Finnish and American groups were recruited from the general population. Remarkably, the findings in all three groups were the same, suggesting that the same sequence of events led to clinical disease in both "sporadic" and familial cases of type 1 diabetes. Indeed, the risk of type 1 diabetes increases as the number of relevant autoantibodies detected increases (53,74,75). In The Environmental Determinants of Diabetes in the Young (TEDDY) study, type 1 diabetes developed in 21% of 363 subjects with at least one autoantibody at 3 years of age (76). Such testing, coupled with education about diabetes symptoms and close follow-up, has been shown to enable earlier diagnosis and to prevent DKA (77,78). In several cohort studies, up to 50% of children with only a single autoantibody revert to being islet autoantibody negative during follow-up (79,80). Therefore, it is recommended that the first autoantibody-positive test be confirmed with a second test within 3 months, preferably in a laboratory that meets the performance standards set by the Islet Autoantibody Standardization Program (IASP) (57).

Type 1 diabetes genetic risk scores have been used in newborn screening to identify those at risk for future presentation of the disease. In a simulation using one such genetic risk score, the majority of those who would go on to develop type 1 diabetes, >77%, could be identified within just 10% of the general population, identifying a subset who may most benefit from autoantibody testing (81). As many genetic risk studies have been performed in populations of European ancestry and discriminatory ability may differ in those of different ancestry, more large case-control cohorts from non-European populations are still needed (82).

Screening programs are available in Europe (e.g., Fr1da and gppad.org), Australia (e.g., type1screen.org), and the U.S. (e.g., trialnet.org, askhealth.org, and cascadekids.org). General population-based screening programs may offer broader testing where high-quality, validated assays and resources for appropriate follow-up of results are available, with several countries considering making such testing part of standard care. In 2023, Italy introduced nationwide screening for type 1 diabetes and celiac disease in the general population aged 1–17 years (83). Individuals who test autoantibody positive should be provided with or referred for counseling about the risk of developing diabetes, diabetes symptoms, and DKA prevention and should be given consideration for referral to a specialized center for further evaluation and/or consideration of a clinical trial or approved therapy to potentially delay development of clinical diabetes (84).

PREDIABETES AND TYPE 2 DIABETES

Recommendations

2.10 Screening for risk of prediabetes and type 2 diabetes with an assessment of risk factors or validated risk calculator should be done in asymptomatic adults. **B**

2.11a Testing for prediabetes or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity who have one or more risk factors (**Table 2.5**). **B**

2.11b For all other people, screening should begin at age 35 years. **B**

2.11c In people without prediabetes or diabetes after screening, repeat screening recommended at a minimum of 3-year intervals is reasonable, sooner with symptoms or change in risk (e.g., weight gain). **C**

2.12 To screen for prediabetes and type 2 diabetes, FPG, 2-h PG during 75-g OGTT, and A1C are each appropriate (**Table 2.1** and **Table 2.2**). **B**

2.13 When using OGTT as a screening tool for prediabetes or diabetes, adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to testing. **E**

2.14 Risk-based screening for prediabetes or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever

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Table 2.5—Criteria for screening for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in individuals of Asian ancestry) who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race, ethnicity, and ancestry (e.g., African American, Latino, Native American, Asian American)
   - History of cardiovascular disease
   - Hypertension (≥130/80 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (<0.9 mmol/L) and/or triglyceride level >250 mg/dL (>2.8 mmol/L)
   - Individuals with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans, metabolic dysfunction–associated steatotic liver disease)
2. People with prediabetes (A1C ≥5.7% [≥39 mmol/mol], IGT, or IFG) should be tested yearly.
3. People who were diagnosed with GDM should have testing at least every 1–3 years.
4. For all other people, testing should begin at age 35 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
6. Individuals in other high-risk groups (e.g., people with HIV, exposure to high-risk medicines, evidence of periodontal disease, history of pancreatitis) should also be closely monitored

GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

occurs earlier, in children and adolescents with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more risk factors for diabetes. (See **Table 2.6** for evidence grading of risk factors.) **B**

2.15a Consider screening people for prediabetes or diabetes if they are on certain medications, such as glucocorticoids, statins, thiazide diuretics, some HIV medications, and second-generation antipsychotic medications, as these agents are known to increase the risk of these conditions. **C**

2.15b In people who are prescribed second-generation antipsychotic medications, screen for prediabetes and diabetes at baseline and repeat 12–16 weeks after medication initiation or sooner, if clinically indicated, and annually thereafter. **B**

2.16 People with HIV should be screened for diabetes and prediabetes with an FPG test before starting antiretroviral therapy, at the time of switching antiretroviral therapy, and 3–6 months after starting or switching antiretroviral therapy. If initial screening results are normal, FPG should be checked annually. **E**

Table 2.6—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting

Screening should be considered in youth* who have overweight (≥85th percentile) or obesity (≥95th percentile) and who have one or more additional risk factors:
- Maternal history of diabetes or GDM during the child's gestation
- Family history of type 2 diabetes in first- or second-degree relative
- High-risk race, ethnicity, and ancestry (see **Table 2.5**)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, large- or small-for-gestational-age birth weight)

GDM, gestational diabetes mellitus. *After the onset of puberty or after 10 years of age, whichever occurs earlier. If tests are normal, repeat testing at a minimum of 3-year intervals (or more frequently if BMI is increasing or risk factor profile is deteriorating) is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors.

Prediabetes

Prediabetes is the term used for individuals whose glucose or A1C levels do not meet the criteria for diabetes yet have abnormal carbohydrate metabolism that results in elevated glucose levels (dysglycemia) intermediate between normoglycemia and diabetes (28,85). People with prediabetes are defined by the presence of IFG and/or IGT and/or A1C 5.7–6.4% (39–47 mmol/mol) (**Table 2.2**). As prediabetes is an intermediate state between normoglycemia and diabetes, it is a significant risk factor for progression to diabetes as well as cardiovascular disease and several other cardiometabolic outcomes. Criteria for screening for diabetes or prediabetes in asymptomatic adults are outlined in **Table 2.5**. Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension. The presence of prediabetes should prompt comprehensive screening for cardiovascular risk factors.

Diagnosis of Prediabetes

IFG is defined as FPG levels from 100 to 125 mg/dL (from 5.6 to 6.9 mmol/L) (78,84) and IGT as 2-h PG levels during 75-g OGTT from 140 to 199 mg/dL (from 7.8 to 11.0 mmol/L) (10). It should be noted that the World Health Organization and a number of diabetes organizations define the IFG lower limit at 110 mg/dL (6.1 mmol/L). The ADA also initially endorsed this IFG lower limit in 1997 (10). However, in 2003 the ADA adopted the new range of 100–125 mg/dL (5.6–6.9 mmol/L) to better define IFG so that the population risk of developing diabetes with IFG would be similar to that with IGT (11).

As with the glucose measures, several prospective studies that used A1C to predict the progression to diabetes demonstrated a strong, continuous curvilinear association between A1C and subsequent diabetes. In a systematic review of 44,203 individuals from 16 cohort studies with a follow-up interval averaging 5.6 years (range 2.8–12 years), those with A1C between 5.5% and 6.0% (between 37 and 42 mmol/mol) had a substantially increased risk of diabetes (5-year incidence from 9% to 25%). Those with an A1C range of 6.0–6.5% (42–48 mmol/mol) had a 5-year risk of developing diabetes between 25% and 50% and a relative risk

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20 times higher than that with A1C of 5.0% (31 mmol/mol) (86). In a community-based study of African American and non-Hispanic White adults without diabetes, baseline A1C was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose (87). Other analyses suggest that A1C of 5.7% (39 mmol/mol) or higher is associated with a diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP) (88), and A1C at baseline was a strong predictor of the development of glucose-defined diabetes during the DPP and its follow-up (7).

An A1C range of 5.7–6.4% (39–47 mmol/mol) identifies a group of individuals at high risk for diabetes and cardiovascular outcomes. These individuals should be informed of their increased risk for diabetes and cardiovascular disease and counseled about effective strategies to lower their risks (see Section 3, "Prevention or Delay of Diabetes and Associated Comorbidities"). Similar to glucose measurements, the continuum of risk is continuous and curvilinear: as A1C rises, the diabetes risk rises disproportionately (86). Aggressive interventions and vigilant follow-up should be pursued for those considered at very high risk (e.g., those with A1C >6.0% [>42 mmol/mol] and individuals with both IFG and IGT).

Table 2.5 outlines the criteria for screening for prediabetes. The ADA risk test is an additional option (i.e., an awareness tool for the layperson and the health care professional) for assessment to determine the appropriateness of screening for diabetes or prediabetes in asymptomatic adults (**Fig. 2.2**) (diabetes.org/diabetes-risk-test). For additional background regarding risk factors and screening for prediabetes, see screening and testing for prediabetes and type 2 diabetes in asymptomatic adults and screening and testing for prediabetes and type 2 diabetes in children and adolescents, below. For details regarding individuals with prediabetes most likely to benefit from a formal behavioral or lifestyle intervention, see Section 3, "Prevention or Delay of Diabetes and Associated Comorbidities."

Type 2 Diabetes

Type 2 diabetes accounts for 90–95% of all diabetes. This form encompasses individuals who generally have relative (rather than absolute) insulin deficiency and have insulin resistance (i.e., decreased biological responses to insulin).

There are various causes of type 2 diabetes. Although the specific etiologies are not known, individuals do not have any of the other known causes of diabetes. Most, but not all, people with type 2 diabetes have overweight or obesity. Excess weight itself causes some degree of insulin resistance. Individuals who do not have obesity or overweight by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region, including sites involved in metabolic dysfunction–associated steatotic liver disease (MASLD) and/or ectopic sites (e.g., skeletal muscle).

DKA seldom occurs spontaneously in type 2 diabetes (30); when seen, it usually arises in individuals who are insulinopenic and already treated with insulin (e.g., missed or inadequate doses); in people with ketosis-prone type 2 diabetes; in association with the stress of another illness such as infection (e.g., COVID-19) or myocardial infarction; in association with illicit drug use (e.g., cocaine); in association with certain social determinants of health; or with the use of certain medications such as glucocorticoids, second-generation antipsychotics, or SGLT2 inhibitors (89,90). HHS is more typically associated with type 2 diabetes (existing or new diagnosis) and is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis. People with diabetes can also have mixed clinical features of both DKA and HHS (30).

Type 2 diabetes frequently goes undiagnosed for many years, because hyperglycemia develops gradually and, at earlier stages, is often not severe enough for the individual to notice the classic diabetes symptoms caused by hyperglycemia, such as dehydration or unintentional weight loss. Nevertheless, even undiagnosed people with diabetes are at increased risk of developing macrovascular and microvascular complications.

People with type 2 diabetes early in the disease course may have insulin levels that appear normal or elevated, yet the failure to normalize blood glucose reflects a relative defect in glucose-stimulated insulin secretion that is insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction, physical activity, and/or pharmacologic treatment of hyperglycemia but is seldom restored to normal. Recent interventions with intensive nutritional changes and exercise, newer pharmacological agents (e.g., GLP-1 RAs), or surgical weight loss can lead to diabetes remission (91–94) (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes").

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity (95,96). It occurs more frequently in individuals with prediabetes, prior gestational diabetes mellitus, or polycystic ovary syndrome. It is also more common in people with hypertension or dyslipidemia and in certain racial, ethnic, and ancestral subgroups (**Table 2.5**). It is often associated with a strong genetic predisposition or family history in first-degree relatives (more so than type 1 diabetes). However, the genetics of type 2 diabetes are poorly understood and under intense investigation in this era of precision medicine (50). The composition of the gut microbiome may also affect the likelihood of developing type 2 diabetes (97). In adults without traditional risk factors for type 2 diabetes and/or of younger age, consider islet autoantibody testing (e.g., GAD autoantibodies) to exclude the diagnosis of type 1 diabetes (36) (**Fig. 2.1**).

Screening and Testing for Prediabetes and Type 2 Diabetes in Asymptomatic Adults

Screening for prediabetes and type 2 diabetes risk through a targeted assessment of risk factors (**Table 2.5**) or with an assessment tool, such as the ADA risk test (**Fig. 2.2**) (diabetes.org/diabetes-risk-test), is recommended to guide health care professionals on whether performing a diagnostic test (**Table 2.1**) is appropriate. Prediabetes and type 2 diabetes meet criteria for conditions in which early detection via screening is appropriate. Both conditions are common and impose significant clinical and public health burdens. There is often a long presymptomatic phase before the diagnosis of type 2 diabetes. Simple tests to detect preclinical disease are readily available (98). The duration of glycemic burden is a strong predictor of adverse outcomes. There are effective interventions that prevent progression from prediabetes to diabetes. It is important to individualize the risk-to-benefit ratio of formal intervention for

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Are you at risk for type 2 diabetes?

Diabetes Risk Test

1. How old are you?.....

Less than 40 years (0 points)
40–49 years (1 point)
50–59 years (2 points)
60 years or older (3 points)

2. Are you a man or a woman?.....

Man (1 point) Woman (0 points)

3. If you are a woman, have you ever been diagnosed with gestational diabetes? .....

Yes (1 point) No (0 points)

4. Do you have a mother, father, sister or brother with diabetes? .....

Yes (1 point) No (0 points)

5. Have you ever been diagnosed with high blood pressure?.....

Yes (1 point) No (0 points)

6. Are you physically active?.....

Yes (0 points) No (1 point)

7. What is your weight category?.....

See chart at right.

WRITE YOUR SCORE IN THE BOX.

Height	Weight (lbs.)		
4′ 10″	119–142	143–190	191+
4′ 11″	124–147	148–197	198+
5′ 0″	128–152	153–203	204+
5′ 1″	132–157	158–210	211+
5′ 2″	136–163	164–217	218+
5′ 3″	141–168	169–224	225+
5′ 4″	145–173	174–231	232+
5′ 5″	150–179	180–239	240+
5′ 6″	155–185	186–246	247+
5′ 7″	159–190	191–254	255+
5′ 8″	164–196	197–261	262+
5′ 9″	169–202	203–269	270+
5′ 10″	174–208	209–277	278+
5′ 11″	179–214	215–285	286+
6′ 0″	184–220	221–293	294+
6′ 1″	189–226	227–301	302+
6′ 2″	194–232	233–310	311+
6′ 3″	200–239	240–318	319+
6′ 4″	205–245	246–327	328+
	1 point	**2 points**	**3 points**

If you weigh less than the amount in the left column: **0 points**

Adapted from Bang et al., Ann Intern Med 151:775–783, 2009 • Original algorithm was validated without gestational diabetes as part of the model

ADD UP YOUR SCORE

If you scored 5 or higher:

You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes, a condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanic/Latino individuals, Native Americans, Asian Americans, and Native Hawaiians and Pacific Islanders.

Higher body weight increases diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weight than the rest of the general public (about 15 pounds lower).

Lower your risk:

The good news is you can manage your risk for type 2 diabetes. Small steps make a big difference in helping you live a longer, healthier life.

If you are at high risk, your first step is to visit your doctor to see if additional testing is needed.

Visit diabetes.org or call 1–800–DIABETES (800–342–2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk

Diabetes Risk Test | American Diabetes Association®

Learn more at diabetes.org/diabetes-risk-test | 1-800-DIABETES (800-342-2383)

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Figure 2.2—ADA risk test (diabetes.org/diabetes-risk-test).

people with prediabetes and consider person-centered goals. Risk models have explored the benefit, in general finding higher benefit of intervention in those at highest risk (99) (see Section 3, "Prevention or Delay of Diabetes and Associated Comorbidities") and reduced risk of diabetes complications (100) (see Section 10, "Cardiovascular Disease and Risk Management," Section 11, "Chronic Kidney Disease and Risk Management," and Section 12, "Retinopathy, Neuropathy, and

Foot Care"). In the National Institutes of Health (NIH) Diabetes Prevention Program Outcomes Study (DPPOS) report, prevention of progression from prediabetes to diabetes (101) resulted in lower rates of developing retinopathy and nephropathy (102). Similar impact on diabetes complications was reported with screening, diagnosis, and comprehensive risk factor management in the U.K. Clinical Practice Research Datalink database (100). In that report, progression from prediabetes to diabetes augmented risk of complications.

Despite the numerous benefits of screening and early diagnosis for prediabetes or diabetes, unfortunately many people in the U.S. and globally either remain undiagnosed or are diagnosed late, when complications have already arisen.

Additional considerations regarding testing for type 2 diabetes and prediabetes in asymptomatic individuals are described below.

Age

Age is a major risk factor for diabetes. Testing should begin at no later than age 35 years for all people (103). Screening should be considered in adults of any age with overweight or obesity and one or more risk factors for diabetes.

Medications

Certain medications, such as glucocorticoids, statins (104), thiazide diuretics, some HIV medications (19), and second-generation antipsychotic medications (105), should be considered when deciding whether to screen for prediabetes or diabetes, as these medications are known to increase the risks of these conditions.

For example, people taking second-generation antipsychotic medications require greater monitoring because of an increase in risk of type 2 diabetes associated with this medication (105). There is a range of effects on metabolic parameters (e.g., hyperglycemia, dyslipidemia, and weight gain) across second-generation antipsychotic medications. People treated with these agents should be screened for prediabetes or diabetes at baseline, rescreened 12–16 weeks after medication initiation, and screened annually thereafter (105). Repeat testing can occur sooner if clinically warranted.

People With HIV

People with HIV are at higher risk for developing prediabetes and diabetes. In addition, some antiretroviral (ARV) therapies may further increase the risk. Therefore, a screening protocol for prediabetes and type 2 diabetes is recommended (106). As the A1C test may underestimate glycemia in people with HIV, plasma glucose criteria are preferred to diagnose prediabetes and diabetes (20).

Diabetes risk is increased with certain protease inhibitors (PIs) and nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). New-onset diabetes is estimated to occur in more than 5% of individuals infected with HIV on PIs, whereas more than 15% may have prediabetes (107). PIs are associated with insulin resistance and may also lead to apoptosis of pancreatic β-cells. NRTIs also affect fat distribution (both lipohypertrophy and lipoatrophy), which is associated with insulin resistance. For people with HIV and ARV-associated hyperglycemia, it may be appropriate to consider discontinuing the problematic ARV agents if safe and effective alternatives are available (108). Before making ARV substitutions, carefully consider the possible effect on HIV virological control and the potential adverse effects of new ARV agents. In some cases, antihyperglycemic agents may still be necessary.

Testing Interval

The appropriate interval between screening tests is not known (109). The rationale for the 3-year interval is that with this interval, the number of false-positive tests that require confirmatory testing will be reduced, and individuals with false-negative tests will be retested before substantial time elapses and complications develop (109). In especially high-risk individuals such as those with previous values nearer to the diabetes diagnostic cut point, shorter intervals between screenings may be useful.

Community Screening

Ideally, screening should be carried out within a health care setting (including appropriately resourced pharmacies) because of the need for follow-up and treatment. Community screening outside a health care setting is generally not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. However, in specific situations where an adequate referral system is established beforehand for positive tests, community screening may be considered. Community screening may also be poorly targeted; i.e., it may fail to reach the groups most at risk and inappropriately test those at very low risk or even those who have already been diagnosed (110).

Screening in Dental Practices

Because of the bidirectional relationship between periodontal disease and diabetes, the utility of screening in a dental setting and referral to primary care as a means to improve the diagnosis of prediabetes and diabetes has been explored (111,112). For example, one study estimated that 30% of individuals ≥30 years of age seen in general dental practices (including both people with and without periodontal disease) had newly diagnosed dysglycemia (112). Further research is needed to demonstrate the feasibility, effectiveness, and cost-effectiveness of screening in this setting. For additional background on oral health in relation to prediabetes and type 2 diabetes, see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities."

Screening and Testing for Prediabetes and Type 2 Diabetes in Children and Adolescents

The epidemiologic studies that formed the basis for the recommendations to use A1C and plasma glucose criteria to diagnose prediabetes and diabetes included only adult populations (113). However, ADA clinical guidance concluded that A1C, FPG, or 2-h PG also could be used to test for prediabetes or type 2 diabetes in children and adolescents (114).

In the last decade, the incidence and prevalence of type 2 diabetes in children and adolescents has increased dramatically, especially in certain high-risk racial, ethnic, and ancestral subgroups (115). See **Table 2.6** for recommendations on risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting (114). See **Table 2.1** and **Table 2.2** for the criteria for the diagnosis of diabetes and prediabetes, respectively, that apply to children, adolescents, and adults. See Section 14, "Children and Adolescents," for

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additional information on type 2 diabetes in children and adolescents.

PANCREATIC DIABETES OR DIABETES IN THE CONTEXT OF DISEASE OF THE EXOCRINE PANCREAS

Recommendation

2.17 Screen people for diabetes within 3–6 months following an episode of acute pancreatitis and annually thereafter. Screening for diabetes is recommended annually for people with chronic pancreatitis. **E**

Pancreatic diabetes (also termed pancreatogenic diabetes or type 3c diabetes) includes both structural (e.g., destruction or removal of normal pancreatic tissue) and functional loss of glucose-normalizing insulin secretion in the context of exocrine pancreatic dysfunction and is commonly misdiagnosed as type 2 diabetes. The diverse set of etiologies includes pancreatitis (acute and chronic pancreatic inflammation and associated fibrosis leading to loss of functional exocrine and endocrine pancreatic function), trauma or pancreatectomy, neoplasia, cystic fibrosis (addressed later in this section), hemochromatosis, fibrocalculous pancreatopathy, rare genetic disorders, and idiopathic forms (2); as such, pancreatic diabetes is the preferred umbrella term (116).

Acute (even a single bout) and chronic pancreatitis can lead to postpancreatitis diabetes mellitus (117). A distinguishing feature is concurrent pancreatic exocrine insufficiency (consider screening individuals with acute and chronic pancreatitis for exocrine pancreatic insufficiency by measuring fecal elastase), pathological pancreatic imaging (endoscopic ultrasound, MRI, and computed tomography), and absence of type 1 diabetes–associated autoimmunity (118–122). There is loss of both insulin and glucagon secretion and often higher-than-expected insulin requirements. Risk for microvascular complications appears to be similar to that of other forms of diabetes.

For people with pancreatitis and diabetes, therapy should be advanced if A1C goals are not met. Glucose-lowering therapies potentially associated with increased risk of pancreatitis (i.e., incretin-based therapies) should be avoided. Early initiation of insulin therapy should be considered. In the context of pancreatectomy, islet autotransplantation can be considered for selected individuals with medically refractory chronic pancreatitis in specialized centers to preserve endogenous islet function and insulin secretion (123,124). In some cases, autotransplant can lead to insulin independence. In others, it may decrease insulin requirements (125).

Cystic Fibrosis–Related Diabetes

Recommendations

2.18 Annual screening for cystic fibrosis–related diabetes (CFRD) with an OGTT should begin by age 10 years in all people with cystic fibrosis not previously diagnosed with CFRD. **B**

2.19 A1C is not recommended as a screening test for CFRD due to low sensitivity. However, a value of ≥6.5% (≥48 mmol/mol) is consistent with a diagnosis of CFRD. **B**

2.20 Beginning 5 years after the diagnosis of CFRD, annual monitoring for complications of diabetes is recommended. **E**

Cystic fibrosis is a multisystem condition arising from recessive mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Pancreatic exocrine damage, which can begin as early as infancy, ultimately leads to pancreatic exocrine insufficiency (126). Cystic fibrosis–related diabetes (CFRD) is a common comorbidity in people with cystic fibrosis, occurring in about 20% of adolescents and 40–50% of adults (127). The relevance of CFRD is highlighted by its association with increased morbidity, mortality, and patient burden. Diabetes in this population, compared with individuals with type 1 or type 2 diabetes, is associated with worse nutritional status, more severe inflammatory lung disease, and greater mortality. Insulin insufficiency is the primary defect in CFRD. Genetically determined β-cell function and insulin resistance associated with infection and inflammation may also contribute to the development of CFRD.

Milder abnormalities of glucose tolerance are even more common and occur at earlier ages than CFRD. Whether individuals with IGT should be treated with insulin replacement has not currently been determined. Although screening for diabetes before the age of 10 years can identify risk for progression to CFRD in those with abnormal glucose tolerance, no benefit has been established with respect to weight, height, BMI, or lung function. OGTT is the recommended screening test for CFRD. Not unexpectedly, annual OGTTs are perceived as burdensome, and engagement in current CFRD screening guidelines is poor, with only 30% of adults with cystic fibrosis having annual OGTTs (128). A1C is not recommended for screening due to low sensitivity; however, a value of ≥6.5% (≥48 mmol/mol) is consistent with a diagnosis of CFRD and reduces patient screening burden (129–131). Regardless of age, weight loss or failure of expected weight gain is a risk for CFRD and should prompt screening (129,130). The Cystic Fibrosis Foundation Patient Registry (132) evaluated 3,553 people with cystic fibrosis and identified 445 (13%) with CFRD. Early diagnosis and treatment of CFRD was associated with preservation of lung function. The European Cystic Fibrosis Society Patient Registry reported an increase in CFRD with age (10% increase per decade), genotype, decreased lung function, and female sex (133). CGM or HOMA of β-cell function (134) may be more sensitive than OGTT to detect risk for progression to CFRD; however, evidence linking these results to long-term outcomes is lacking, and these tests are not recommended for screening outside the research setting (127). There is inadequate evidence presently to alter CFRD screening based on use of highly effective CFTR modulator therapy, which uses small-molecule compounds that directly correct the basic defect of the CFTR channel and restore channel function (127).

CFRD mortality has significantly decreased over time, and the gap in mortality between people with cystic fibrosis with and without diabetes has considerably narrowed (135). There are limited clinical trial data on optimal therapy for CFRD. People with CFRD should be treated with insulin to attain individualized glycemic goals. See Section 9, "Pharmacologic Approaches to Glycemic Treatment," for further information.

Additional resources for the clinical management of CFRD can be found in the position statement "Clinical Care Guidelines for Cystic Fibrosis-Related Diabetes" (136) and in the International Society for Pediatric

Standards of Medical Care in Diabetes—2021 Abridged for Primary Care Providers

and Adolescent Diabetes (ISPAD) 2022 clinical practice consensus guidelines (127).

POSTTRANSPLANTATION DIABETES MELLITUS

Recommendations

2.21 After organ transplantation, screening for hyperglycemia should be done. A formal diagnosis of posttransplantation diabetes mellitus (PTDM) is best made once the individual is stable on an immunosuppressive plan and in the absence of an acute infection. **B**

2.22 The OGTT is the preferred test to make a diagnosis of PTDM. **B**

2.23 Immunosuppressive plans shown to provide the best outcomes for individuals and graft survival should be used, irrespective of PTDM risk. **E**

Several terms are used in the literature to describe the presence of diabetes following organ transplantation (137). New-onset diabetes after transplantation (NODAT) is one such designation that describes individuals who develop new-onset diabetes following transplant. NODAT excludes people with pretransplant diabetes that was undiagnosed as well as posttransplant hyperglycemia that resolves by the time of discharge (138). Another term, posttransplantation diabetes mellitus (PTDM) (138,139), describes the presence of diabetes in the posttransplant setting irrespective of the timing of diabetes onset (140). The clinical importance of PTDM lies in its impact as a significant risk factor for cardiovascular disease and chronic kidney disease in solid-organ transplantation (137).

Hyperglycemia is very common during the early posttransplant period, with ~90% of kidney allograft recipients exhibiting hyperglycemia in the first few weeks following transplant (138,139,141,142). In most cases, such stress- or steroid-induced hyperglycemia resolves by the time of discharge (142,143). Although the use of immunosuppressive therapies is a major contributor to the development of PTDM, the risks of transplant rejection outweigh the risks of PTDM, and the role of the diabetes health care professional is to treat hyperglycemia appropriately regardless of the type of immunosuppression (138). Risk factors for PTDM include both general diabetes risks (such as age, family history of diabetes, and obesity) and transplant-specific factors, such as use of immunosuppressant agents (144–146). Whereas posttransplantation hyperglycemia is an important risk factor for subsequent PTDM, a formal diagnosis of PTDM is optimally made once the individual is stable on maintenance immunosuppression (usually at least 45 days) and in the absence of acute infection (138,142–144,147).

The OGTT is recommended for the diagnosis of PTDM (1 year posttransplant) (138,139,148). However, screening people with FPG and/or A1C can identify high-risk individuals who require further assessment and may reduce the number of overall OGTTs required.

Few randomized controlled studies have reported on the short- and long-term use of antihyperglycemic agents in the setting of PTDM (144,149,150). Most studies have reported that transplant individuals with hyperglycemia and PTDM after transplantation have higher rates of rejection, infection, and rehospitalization (142,144,151). Insulin therapy is the agent of choice for the management of hyperglycemia and diabetes in the hospital setting and can be continued postdischarge. Noninsulin glucose-lowering therapies can also be used for long-term management. The choice of agent is usually made based on the side effect profile of the medication, possible interactions with the individual's immunosuppression plan, and potential cardiovascular and renal benefits in individuals with PTDM (144). See Section 9, "Pharmacologic Approaches to Glycemic Treatment," for further information.

MONOGENIC DIABETES SYNDROMES

Recommendations

2.24a Regardless of current age, all people diagnosed with diabetes in the first 6 months of life should have genetic testing for neonatal diabetes. **B**

2.24b Children and young adults who do not have typical characteristics of type 1 or type 2 diabetes and family history of diabetes in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young (MODY). **B**

2.24c In both instances, consultation with a center specializing in diabetes genetics is recommended to understand the significance of genetic mutations and how best to approach further evaluation, treatment, and genetic counseling. **E**

Monogenic defects that cause β-cell dysfunction (e.g., neonatal diabetes and MODY) or insulin resistance syndromes (e.g., monogenic lipodystrophies) are present in a small fraction of people with diabetes (<5%) (152). **Table 2.7** describes the most common causes of monogenic diabetes. For a comprehensive list of causes, see *Genetic Diagnosis of Endocrine Disorders* (153) and ISPAD 2022 clinical practice consensus guidelines (152).

Diagnosis of Monogenic Diabetes

The diagnosis of monogenic diabetes should be considered in children and adults diagnosed with diabetes in early adulthood with the following findings:

- Diabetes diagnosed within the first 6 months of life (152,154)
- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, no obesity, and lacking other metabolic features, especially strong family history of diabetes)
- Stable, mild fasting hyperglycemia (100–150 mg/dL [5.6–8.5 mmol/L]), stable A1C between 5.6% and 7.6% (between 38 and 60 mmol/mol), especially if no obesity

Neonatal Diabetes

Diabetes occurring under 6 months of age is termed neonatal diabetes, and about 80–85% of cases can be found to have an underlying monogenic cause (36,154–157). Neonatal diabetes occurs much less often after 6 months of age, whereas autoimmune type 1 diabetes rarely occurs before 6 months of age. Neonatal diabetes can either be transient or permanent. Transient diabetes is most often due to overexpression of genes on chromosome 6q24, is recurrent in about half of cases, and may be treatable with medications other than insulin. Permanent neonatal diabetes is most commonly due to autosomal dominant mutations in the genes encoding the Kir6.2 subunit (*KCNJ11*) and SUR1 subunit (*ABCC8*) of the β-cell K_{ATP} channel.

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Table 2.7—Most common causes of monogenic diabetes

	Gene	Inheritance	Clinical features
MODY	*HNF1A*	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [>5 mmol/L]); low hs-CRP; sensitive to sulfonylureas
	HNF4A	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight (macrosomia) and transient neonatal hypoglycemia; sensitive to sulfonylureas
	HNF1B	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
	GCK	AD	GCK-MODY: higher glucose threshold (set point) for glucose-stimulated insulin secretion, causing stable, nonprogressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [<3 mmol/L])
Neonatal diabetes	*KCNJ11*	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	INS	AD	Permanent: IUGR; insulin requiring
	ABCC8	AD	Permanent or transient: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 (*PLAGL1*, *HYMA1*)	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication, or maternal methylation defect; may be treatable with medications other than insulin
	GATA6	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	EIF2AK3	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	EIF2B1	AD	Permanent diabetes: can be associated with fluctuating liver function (154)
	FOXP3	X-linked	Permanent: immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome: autoimmune diabetes, autoimmune thyroid disease, exfoliative dermatitis; insulin requiring

Adapted from Carmody et al. (153). AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction; OGTT, oral glucose tolerance test; UPD6, uniparental disomy of chromosome 6; 2-h PG, 2-h plasma glucose.

The ADA-European Association for the Study of Diabetes type 1 diabetes consensus report recommends that regardless of current age, individuals diagnosed under 6 months of age should have genetic testing (36). Correct diagnosis has critical implications, because 30–50% of people with K_{ATP}-related neonatal diabetes will exhibit improved blood glucose levels when treated with high-dose oral sulfonylureas instead of insulin. Insulin gene (*INS*) mutations are the second most common cause of permanent neonatal diabetes, with insulin therapy being the preferred treatment strategy.

Maturity-Onset Diabetes of the Young

MODY is frequently characterized by onset of hyperglycemia at an early age (classically before age 25 years, although diagnosis may occur at older ages). MODY is characterized by impaired insulin secretion with minimal or no defects in insulin action (in the absence of coexistent obesity). It is inherited in an autosomal dominant pattern with abnormalities in at least 14 genes on different chromosomes identified to date (152). The most commonly reported forms are GCK-MODY (MODY2), HNF1A-MODY (MODY3), and HNF4A-MODY (MODY1).

Correct diagnosis of monogenic forms of diabetes is critical because people who have them may be incorrectly diagnosed with type 1 or type 2 diabetes, leading to suboptimal, even potentially harmful, treatment plans and delays in diagnosing other family members (152). A diagnosis of MODY should be considered in individuals who have atypical diabetes and multiple family members with diabetes not characteristic of type 1 or type 2 diabetes (155–162) (**Fig. 2.1**). In most cases, the presence of autoantibodies for type 1 diabetes precludes further testing for monogenic diabetes, but the presence of autoantibodies in people with monogenic diabetes has been reported. Individuals in whom monogenic diabetes is suspected should have genetic testing. Genetic screening (i.e., next-generation sequencing) is increasingly available and cost-effective (152). Consultation with a center specializing in diabetes genetics is recommended to understand the significance of genetic mutations and how best to approach further evaluation, treatment, and genetic counseling. Genetic counseling is recommended to ensure that affected individuals understand the patterns of inheritance and the importance of a correct diagnosis and to address comprehensive cardiovascular risk.

A diagnosis of one of the three most common forms of MODY, HNF1A-MODY, GCK-MODY, and HNF4A-MODY, allows for more cost-effective personalized therapy (i.e., no therapy for GCK-MODY and sulfonylureas as first-line therapy for HNF1A-MODY and HNF4A-MODY). See Section 9, "Pharmacologic Approaches to Glycemic

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Treatment," for further information. Additionally, diagnosis can lead to identification of other affected family members and can indicate potential extrapancreatic complications in affected individuals.

GESTATIONAL DIABETES MELLITUS

Recommendations

2.25 In individuals who are planning pregnancy, screen those with risk factors (**Table 2.5**) **B** and consider testing all individuals of childbearing potential for undiagnosed prediabetes or diabetes. **E**

2.26a Before 15 weeks of gestation, test individuals with risk factors (**Table 2.5**) **B** and consider testing all individuals **E** for undiagnosed diabetes at the first prenatal visit using standard diagnostic criteria if not screened preconception.

2.26b Before 15 weeks of gestation, screen for abnormal glucose metabolism to identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes, are more likely to need insulin, and are at high risk of a later gestational diabetes mellitus (GDM) diagnosis. **B**

2.26c Screen for early abnormal glucose metabolism with dysglycemia using FPG 110–125 mg/dL (6.1–6.9 mmol/L) or A1C 5.9–6.4% (41–47 mmol/mol). **B**

2.27 Screen for GDM at 24–28 weeks of gestation in pregnant individuals not previously found to have diabetes or high-risk abnormal glucose metabolism detected earlier in the current pregnancy. **A**

2.28 Screen individuals with GDM for prediabetes or diabetes at 4–12 weeks postpartum, using the 75-g OGTT and clinically appropriate nonpregnancy diagnostic criteria. **B**

2.29 Individuals with a history of GDM should have lifelong screening for the development of prediabetes or diabetes every 1–3 years. **B**

Definition

For many years, gestational diabetes mellitus (GDM) was defined as any degree of glucose intolerance that was first recognized during pregnancy (86), regardless of the degree of hyperglycemia. This definition facilitated a uniform strategy for detection and classification of GDM, but this definition has limitations (163). First, the best evidence reveals that many cases of GDM represent preexisting hyperglycemia that is detected by routine screening in pregnancy, as routine screening is not widely performed in nonpregnant individuals of reproductive age. The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in people of reproductive age, with an increase in the number of pregnant individuals with undiagnosed type 2 diabetes in early pregnancy (164–166). Ideally, undiagnosed diabetes should be identified preconception in individuals with risk factors or in high-risk populations (167–172), as they are likely to benefit from preconception care. The preconception care of people with known preexisting diabetes results in lower A1C and reduced risk of birth defects, preterm delivery, perinatal mortality, small-for-gestational-age birth weight, and neonatal intensive care unit admission (173). If individuals are not screened prior to pregnancy, universal early screening at <15 weeks of gestation for undiagnosed diabetes may be considered over selective screening (**Table 2.5**), particularly in populations with high prevalence of risk factors and undiagnosed diabetes in people of childbearing age. Strong racial and ethnic disparities exist in the prevalence of undiagnosed diabetes. Therefore, early screening provides an initial step to identify these health disparities so that they can begin to address them (169–172). Diagnostic criteria for identifying undiagnosed diabetes in early pregnancy are the same as those used in nonpregnant individuals (**Table 2.1**). Individuals found to have diabetes should be classified as having diabetes complicating pregnancy (most often type 2 diabetes, rarely type 1 diabetes or monogenic diabetes) and managed accordingly.

Early abnormal glucose metabolism, defined as a fasting glucose threshold of 110 mg/dL (6.1 mmol/L) or an A1C of 5.9% (41 mmol/mol), may identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes (preeclampsia, macrosomia, shoulder dystocia, and perinatal death), are at high risk of a later GDM diagnosis, and are more likely to need insulin treatment (174–176). An A1C threshold of 5.7% (39 mmol/L) has not been shown to be associated with adverse perinatal outcomes (177,178).

If early screenings for undiagnosed diabetes or early abnormal glucose metabolism were negative, individuals should be rescreened for GDM between 24 and 28 weeks of gestation and individuals not previously screened should be screened for GDM at the same time point (see Section 15, "Management of Diabetes in Pregnancy"). The GDM diagnostic criteria for the 75-g OGTT from the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) and the GDM screening and diagnostic criteria with the two-step approach were not derived from data in the first half of pregnancy and should not be used for early screening (179). Most randomized controlled trials of treatment of early abnormal glucose metabolism have been underpowered for outcomes. One randomized controlled trial performed at 17 centers administered early screening (mean 15.6 ± 2.5 weeks) for GDM with a 75-g OGTT. Individuals who met World Health Organization criteria for GDM were randomized to receive early treatment or a repeat OGTT at 24–28 weeks (with deferred treatment if indicated). The first primary outcome measure was an adverse neonatal composite outcome including birth <37 weeks, birth weight ≥4.5 kg, birth trauma, neonatal respiratory distress within 24 h of birth, phototherapy, stillbirth neonatal death, or shoulder dystocia. Early GDM treatment resulted in a modest improvement in the composite adverse neonatal outcome (24.9% early treatment vs. 30.5% control treatment, relative risk 0.82 [0.68–0.98]), although this was driven primarily by differences in rates of neonatal respiratory distress between groups that included neonates requiring ≥4 h of supplemental oxygen who may not have required a higher level of respiratory care. There was also a suggestion of more benefit (per prespecified subgroup analyses) among individuals who had the OGTT at <14 weeks and among those with OGTT glycemic values in higher ranges (180). Therefore, the benefits of treatment of early abnormal glucose metabolism remain uncertain. Nutrition counseling and periodic testing of glucose levels weekly to identify individuals with high glucose levels are suggested. Testing frequency may proceed to daily, and treatment may be intensified, if the FPG is predominantly >110 mg/dL (>6.1 mmol/L) prior to 18 weeks of gestation.

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Both the FPG and A1C are low-cost tests. An advantage of the A1C test is its convenience, as it can be added to the prenatal laboratories and does not require an early-morning fasting appointment. Disadvantages include inaccuracies in the presence of increased red blood cell turnover and hemoglobinopathies (usually reads lower) and higher values with anemia and reduced red blood cell turnover (181). A1C is not reliable for screening for GDM or for preexisting diabetes at 15 weeks of gestation or later in part from the higher red blood cell turnover in pregnancy but also from the unknown diabetes status prior to pregnancy, which could help distinguish new-onset diabetes from preexisting diabetes.

GDM is often indicative of underlying β-cell dysfunction (182), which confers marked increased risk for later development of glucose intolerance and diabetes in the mother after delivery (183–185). As effective prevention interventions are available (186,187), individuals diagnosed with GDM should receive lifelong screening for prediabetes to allow interventions to reduce diabetes risk and for type 2 diabetes to allow treatment at the earliest possible time (188).

Table 2.8—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when an individual is fasting and at 1 and 2 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

If the plasma glucose level measured 1 h after the load is ≥130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L, respectively),* proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the individual is fasting.

The diagnosis of GDM is made when at least two† of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria [208]):

- Fasting: 95 mg/dL (5.3 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 155 mg/dL (8.6 mmol/L)
- 3 h: 140 mg/dL (7.8 mmol/L)

GDM, gestational diabetes mellitus; GLT, glucose load test; OGTT, oral glucose tolerance test. *American College of Obstetricians and Gynecologists (ACOG) recommends any of the commonly used thresholds of 130, 135, or 140 mg/dL for the 1-h 50-g GLT (204). †ACOG notes that one elevated value can be used for diagnosis (204).

Diagnosis

GDM carries risks for the mother, fetus, and neonate. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (189), a large-scale multinational cohort study completed by more than 23,000 pregnant individuals, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks of gestation, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk. These results have led to careful reconsideration of the diagnostic criteria for GDM.

GDM diagnosis (**Table 2.8**) can be accomplished with either of two strategies:

1. The "one-step" 75-g OGTT derived from the IADPSG criteria, or
2. The older "two-step" approach with a 50-g (nonfasting) screen followed by a 100-g OGTT for those who screen positive based on the work of Carpenter-Coustan's interpretation of the older O'Sullivan and Mahan (190) criteria.

Different diagnostic criteria will identify different degrees of maternal hyperglycemia and maternal/fetal risk, leading experts to debate optimal strategies for the diagnosis of GDM.

One-Step Strategy

The IADPSG examined data from the HAPO study and defined diagnostic cut points for GDM as the average fasting, 1-h, and 2-h PG values during a 75-g OGTT in individuals at 24–28 weeks of gestation, wherein the cut points were those at which odds for adverse outcomes reached 1.75 times the estimated odds. This one-step strategy was anticipated to significantly increase the incidence of GDM (from 5–6% to 15–20%), primarily because only one abnormal value, not two, became sufficient to make the diagnosis (191). Many regional studies have seen a roughly one- to threefold increase in GDM cases using the IADPSG criteria (192). A study of pregnancy OGTTs with glucose levels blinded to caregivers found that 11 years after their pregnancies, individuals who would have been diagnosed with GDM by the one-step approach, as compared with those without GDM, were at 3.4-fold higher risk of developing prediabetes and type 2 diabetes and had children with a higher risk of obesity and increased body fat, suggesting that the group identified as having GDM by the one-step approach would benefit from the increased screening for diabetes and prediabetes after pregnancy (193). The ADA recommends the IADPSG diagnostic criteria to optimize gestational outcomes, because these criteria are the only ones based on pregnancy outcomes rather than end points such as prediction of subsequent maternal diabetes.

Expected benefits of using IADPSG criteria for offspring are inferred from intervention trials focusing on individuals with lower levels of hyperglycemia than those identified using older GDM diagnostic criteria. Those trials found modest benefits, including reduced rates of large-for-gestational-age births and preeclampsia (194,195). Of note, 80–90% of participants being treated for mild GDM in these two randomized controlled trials could be managed with lifestyle therapy alone. The OGTT glucose cutoffs in these two trials overlapped the thresholds recommended by the IADPSG, and in one trial (195), the 2-h PG threshold (140 mg/dL [7.8 mmol/L]) was lower than the cutoff recommended by the IADPSG (153 mg/dL [8.5 mmol/L]).

No randomized controlled trials of treating versus not treating GDM diagnosed by

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different criteria have been published to date. However, a randomized trial of testing for GDM at 24–28 weeks of gestation by the one-step method using IADPSG criteria versus the two-step method by Carpenter-Coustan criteria identified twice as many individuals with GDM using the one-step method. Despite treating more individuals for GDM using the one-step method, there was no difference in pregnancy and perinatal complications (196), though concerns were raised about sample size estimates and unanticipated suboptimal engagement with the screening and treatment protocol. For example, in the two-step group, 165 participants not counted as having GDM were treated for isolated elevated FPG >95 mg/dL (>5.3 mmol/L) (197).

The one-step method identifies long-term risks of maternal prediabetes and diabetes as well as offspring glucose intolerance and adiposity. Post hoc GDM in individuals diagnosed with this method in the HAPO cohort was associated with higher prevalence of IGT; higher 30-min, 1-h, and 2-h glucose levels during the OGTT; and reduced insulin sensitivity and oral disposition index in their offspring at 10–14 years of age compared with offspring of mothers without GDM. Associations of mother's fasting, 1-h, and 2-h values on the 75-g OGTT were continuous with a comprehensive panel of offspring metabolic outcomes (198,199). HAPO Follow-up Study (HAPO FUS) data demonstrate that neonatal adiposity and fetal hyperinsulinemia (cord C-peptide), both higher across the continuum of maternal hyperglycemia, are mediators of childhood body fat (200).

Data are lacking on how the treatment of mother's hyperglycemia in pregnancy affects her offspring's risk for obesity, diabetes, and other metabolic disorders (201,202). Additional well-designed clinical studies are needed to determine the optimal intensity of monitoring and treatment of individuals with GDM diagnosed by the one-step strategy.

Two-Step Strategy

In 2013, the NIH convened a consensus development conference to consider diagnostic criteria for diagnosing GDM (203). The 15-member panel had representatives from obstetrics and gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other related fields. The panel recommended continuing a two-step approach to screening that used a 1-h 50-g glucose loading test (GLT) followed by a 3-h 100-g OGTT for those who screened positive. The American College of Obstetricians and Gynecologists (ACOG) recommends any of the commonly used thresholds of 130, 135, or 140 mg/dL for the 1-h 50-g GLT (204). A 2021 U.S. Preventive Services Task Force systematic review concluded that one-step versus two-step screening is associated with increased likelihood of GDM (11.5% vs. 4.9%) but without improved health outcomes (205). The use of A1C at 24–28 weeks of gestation as a screening test for GDM does not function as well as the GLT (206).

Importantly, the NIH panel noted the lack of clinical trial data demonstrating the benefits of the one-step strategy and the potential negative consequences of identifying a large group of individuals with GDM, including medicalization of pregnancy with increased health care utilization and costs. Moreover, screening with a 50-g GLT does not require fasting and therefore is easier to accomplish for many individuals. Treatment of higher-threshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, large-for-gestational-age births (207), and shoulder dystocia without increasing small-for-gestational-age births. ACOG currently supports the two-step approach but notes that one elevated value, as opposed to two, may be used for the diagnosis of GDM (204). If this approach is implemented, the incidence of GDM will likely increase markedly. ACOG recommends either of two sets of diagnostic thresholds for the 3-h 100-g OGTT Carpenter-Coustan or National Diabetes Data Group (208,209). Each is based on different mathematical conversions of the original recommended thresholds by O'Sullivan and Mahan (190), which used whole blood and nonenzymatic methods for glucose determination. A secondary analysis of data from a randomized clinical trial of identification and treatment of mild GDM (210) demonstrated that treatment was similarly beneficial in people meeting only the lower thresholds per Carpenter-Coustan (208) and in those meeting only the higher thresholds per National Diabetes Data Group (209). If the two-step approach is used, it would appear advantageous to use the Carpenter-Coustan lower diagnostic thresholds, as shown in step 2 in **Table 2.8**.

Future Considerations

Data exist to support each strategy, as demonstrated by conflicting recommendations by expert groups. A systematic review of economic evaluations of GDM screening found that the one-step method identified more cases of GDM and was more likely to be cost-effective than the two-step method (211). The decision of which strategy to implement must therefore be made based on the relative values placed on factors that have yet to be measured (e.g., willingness to change practice based on correlation studies rather than intervention trial results, available infrastructure, and importance of cost considerations).

The IADPSG criteria (one-step strategy) have been adopted internationally as the preferred approach. Data that compare population-wide outcomes with one-step versus two-step approaches have been inconsistent to date (196,212–214). Pregnancies complicated by GDM per the IADPSG criteria, but not recognized as such, have outcomes comparable to pregnancies with diagnosed GDM by the more stringent two-step criteria (215,216). There remains strong consensus that establishing a uniform approach to diagnosing GDM will benefit people with GDM, caregivers, and policymakers. Longer-term outcome studies are currently underway.

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3. Prevention or Delay of Diabetes and Associated Comorbidities: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For guidelines related to screening for increased risk for type 1 diabetes, prediabetes and type 2 diabetes, and other forms of diabetes, please refer to Section 2, "Diagnosis and Classification of Diabetes." For guidelines related to screening, diagnosis, and management of type 2 diabetes in youth, please refer to Section 14 "Children and Adolescents."

Recommendations

3.1 In people with prediabetes, monitor for the development of type 2 diabetes at least annually; modify frequency of testing based on individual risk assessment. **E**

3.2 In people with presymptomatic type 1 diabetes, monitor for disease progression using A1C approximately every 6 months and 75-g oral glucose tolerance test (i.e., fasting and 2-h plasma glucose) annually; modify frequency of monitoring based on individual risk assessment based on age, number and type of autoantibodies, and glycemic metrics. **E**

Screening for prediabetes and type 2 diabetes risk through an assessment of risk factors (**Table 2.5**) or with an assessment tool, such as the American Diabetes Association risk test, which can be used by either a layperson or a health care professional (**Fig. 2.2**), is recommended to guide whether to perform a diagnostic test for prediabetes (**Table 2.2**) and type 2 diabetes (**Table 2.1**) (see Section 2, "Diagnosis and Classification of Diabetes"). Testing high-risk adults for prediabetes is warranted because the laboratory assessment is safe and reasonable in cost. In addition, substantial time exists before the development of type 2 diabetes and its

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complications during which one can intervene. Once identified, several effective therapeutic approaches exist that can delay type 2 diabetes in those with prediabetes with an A1C 5.7–6.4% (39–47 mmol/mol), impaired glucose tolerance (IGT) on 75-g oral glucose tolerance test (OGTT), or impaired fasting glucose (IFG). The utility of screening with A1C for prediabetes and diabetes may be limited in the presence of certain hemoglobinopathies and conditions that affect red blood cell turnover (**Table 2.3**). See Section 2, "Diagnosis and Classification of Diabetes," and Section 6, "Glycemic Goals and Hypoglycemia," for additional details on the appropriate use and limitations of A1C testing.

Three distinct stages of type 1 diabetes have been defined, with symptomatic type 1 diabetes being stage 3 (**Table 2.4**). In individuals at risk for developing clinical type 1 diabetes, younger age of seroconversion (particularly under age 3 years), the total number of diabetes-related autoantibodies (1), and the development of autoantibodies against islet antigen 2 (IA-2) have been associated with a more rapid progression to clinical type 1 diabetes. While continuous glucose monitoring can predict progression to overt diabetes in children with autoantibodies (2), OGTT-based metrics appear to be better at predicting progression compared with continuous glucose monitoring (3). The decision to perform an OGTT may depend on such factors as eligibility and interest for stage-specific treatments, participation in clinical research, availability, and the burden of testing. A consensus guidance provides expert recommendations on what should be monitored and how often in people with presymptomatic type 1 diabetes (4).

LIFESTYLE BEHAVIOR CHANGE FOR TYPE 2 DIABETES PREVENTION

Recommendations

3.3 Refer adults with overweight or obesity at high risk of type 2 diabetes, as seen in the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 min/week of moderate-intensity physical activity. **A**

3.4 Prescribe an eating pattern known to be effective in preventing type 2 diabetes to individuals with prediabetes. A variety of eating patterns, such as Mediterranean style, intermittent fasting, and low carbohydrate, have shown benefit. **B**

3.5 Given the cost-effectiveness of lifestyle behavior modification programs for diabetes prevention, such diabetes prevention programs should be offered to adults at high risk of type 2 diabetes. **A** Diabetes prevention programs should be covered by third-party payors, and inconsistencies in access should be addressed. **E**

3.6 Based on individual preference, certified technology-assisted diabetes prevention programs may be effective in preventing type 2 diabetes and should be considered. **B**

The Diabetes Prevention Program

Several major randomized controlled trials, including the Diabetes Prevention Program (DPP) trial (5), the Finnish Diabetes Prevention Study (DPS) (6), and the Da Qing Diabetes Prevention Study (Da Qing study) (7), demonstrate that lifestyle/behavioral intervention with an individualized reduced-calorie meal plan is highly effective in preventing or delaying type 2 diabetes and improving other cardiometabolic risk factors (such as blood pressure, lipids, and inflammation) (8). The strongest evidence for diabetes prevention in the U.S. comes from the DPP trial (5). The DPP demonstrated that intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58% over 3 years. Follow-up of three large trials of lifestyle intervention for diabetes prevention showed sustained reduction in the risk of progression to type 2 diabetes: 39% reduction at 30 years in the Da Qing study (9), 43% reduction at 7 years in the Finnish DPS (6), and 34% reduction at 10 years (10) and 27% reduction at 15 years (11) in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS).

The DPP lifestyle intervention was a goal-based intervention. All participants were given the same weight loss and physical activity goals, but individualization was permitted to achieve the goals (12). The two major goals of the DPP intensive lifestyle intervention were to achieve and maintain a minimum of 7% weight loss and to partake in 150 min of moderate-intensity physical activity per week, such as brisk walking. Although weight loss was the most important factor in reducing the risk of incident diabetes, achieving the behavioral goal of at least 150 min of physical activity per week, even without achieving the weight loss goal, reduced the incidence of type 2 diabetes by 44% (13).

The 7% weight loss goal was selected because it was feasible to achieve and maintain and likely to lessen the risk of developing diabetes (as well as improve other cardiometabolic risk factors). Participants were encouraged to achieve the ≥7% weight loss during the first 6 months of the intervention. Further analysis suggests higher benefit for prevention of diabetes with at least 7–10% weight loss with lifestyle interventions (13). The recommended pace of weight loss was 1–2 lb/week. Calorie goals were calculated by estimating the daily calories needed to maintain the participant's initial weight and subtracting 500–1,000 calories/day (depending on initial body weight). The initial focus of the nutrition intervention was on reducing total fat rather than calories. After several weeks, the concepts of calorie balance and the need to restrict calories and fat were introduced (12).

The goal for physical activity was selected to approximate at least 700 kcal/week expenditure from physical activity. For ease of translation, this goal was described as at least 150 min of moderate-intensity physical activity per week, similar in intensity to brisk walking. Participants were encouraged to distribute their activity throughout the week with a minimum frequency of three times per week and at least 10 min per session. A maximum of 75 min of strength training could be applied toward the total 150 min/week physical activity goal (12).

To implement the weight loss and physical activity goals, the DPP used an individual model of treatment rather than a group-based approach. This choice was based on a desire to intervene before participants had the possibility of developing diabetes or losing interest in the program. The individual approach also allowed for the tailoring of interventions to reflect the diversity of the population (12).

The DPP intervention was administered as a structured core curriculum followed by a flexible maintenance program of individual counseling, group sessions,

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motivational campaigns, and restart opportunities. The 16-session core curriculum was completed within the first 24 weeks of the program. It included sessions on lowering calories, increasing physical activity, self-monitoring, maintaining healthy lifestyle behaviors (such as how to choose healthy food options when eating out), and guidance on managing psychological, social, and motivational challenges (12).

While the DPP interventions were successful in preventing or delaying the onset of type 2 diabetes, long-term effects on clinically meaningful events (microvascular and macrovascular disease) have not been established (14). However, there is potential benefit without the risk of harm with these interventions.

Nutrition

Nutrition counseling for weight loss in the DPP lifestyle intervention arm included a reduction of total fat and calories (5,12,13). However, evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people to prevent diabetes; therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals (15). Based on other trials, a variety of eating patterns (15,16) may also be appropriate for individuals with prediabetes (15), including Mediterranean-style and low-carbohydrate eating plans (17–19). Observational studies have also shown that vegetarian, plant-based (may include some animal products), and Dietary Approaches to Stop Hypertension (DASH) eating patterns are associated with a lower risk of developing type 2 diabetes (20–23). Evidence suggests that the overall quality of food consumed (as measured by the Healthy Eating Index, Alternative Healthy Eating Index, and DASH score), with an emphasis on whole grains, legumes, nuts, fruits, and vegetables and minimal refined and processed foods, is also associated with a lower risk of type 2 diabetes (22,24,25). As is the case for those with diabetes, individualized medical nutrition therapy (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more detailed information) is effective in lowering A1C in individuals diagnosed with prediabetes (26).

Physical Activity

Moderate-intensity physical activity, such as brisk walking for 150 min/week, has shown beneficial effects in those with prediabetes (5). Similarly, moderate-intensity physical activity has been shown to improve insulin sensitivity and reduce abdominal fat in children and young adults (27,28). Health care professionals are encouraged to promote a DPP-style program to all individuals who have been identified to be at an increased risk of type 2 diabetes. In addition to aerobic activity, a physical activity plan designed to prevent diabetes may include resistance training (12,29). Breaking up prolonged sedentary time may also be encouraged, as it lowers postprandial glucose levels (30). The effects of physical activity appear to extend to the prevention of gestational diabetes mellitus (GDM) (31).

Sleep Characteristics Associated With Increased Risk of Type 2 Diabetes

Sleep occupies approximately one-third of the day for most people and modulates a variety of metabolic, endocrine, and cardiovascular processes (32). The latest ADA-EASD consensus report on management of hyperglycemia highlights sleep as a central component in the management of prediabetes and type 2 diabetes, placing it, for the first time, on the same level as other lifestyle behaviors (e.g., physical activity and nutrition) (33). Sleep can be characterized using three key constructs: quantity, quality, and timing (i.e., chronotype). There is now established evidence for a U-shaped association between sleep duration and type 2 diabetes incidence, with the nadir typically occurring at 7 h per day, with short (typically defined as $<$6 h) and long (typically defined as $>$9 h) sleep duration having up to a 50% increase in the risk of type 2 diabetes, including progression from prediabetes (33). Sleep quality has recently been defined as "an individual's self-satisfaction with all aspects of the sleep experience" (34,35). Poor sleep quality was associated with a 40–84% increased risk of developing type 2 diabetes in a meta-analysis (36). Chronotype preference has been linked with many chronic diseases, including type 2 diabetes. For example, for those with a preference for evenings (i.e., going to bed late and getting up late), there was a 2.5-fold higher odds ratio for type 2 diabetes than for those with a preference for mornings (i.e., going to bed early and getting up early), independent of sleep duration and sleep sufficiency (37).

Delivery and Dissemination of Lifestyle Behavior Change for Diabetes Prevention

Because the intensive lifestyle intervention in the DPP was effective in preventing type 2 diabetes among those at high risk for the disease and lifestyle behavior change programs for diabetes prevention were shown to be cost-effective, broader efforts to disseminate scalable lifestyle behavior change programs for diabetes prevention with coverage by third-party payors ensued (38–42). Group delivery of DPP content in community or primary care settings has demonstrated the potential to reduce overall program costs while still producing weight loss and diabetes risk reduction (43,44).

The Centers for Disease Control and Prevention (CDC) developed the National Diabetes Prevention Program (National DPP), a resource designed to bring such evidence-based lifestyle change programs for preventing type 2 diabetes to communities (cdc.gov/diabetes-prevention). This online resource includes locations of CDC-recognized diabetes prevention lifestyle change programs (cdc.gov/diabetes/prevention/find-a-program.html). To be eligible for this program, individuals must have a BMI in the overweight range and be at risk for diabetes based on laboratory testing, a previous diagnosis of GDM, or a positive risk test (cdc.gov/prediabetes/risktest/). During the first 4 years of implementation of the CDC's National DPP, 36% achieved the 5% weight loss goal (45). The CDC has also developed the Diabetes Prevention Impact Tool Kit (nccd.cdc.gov/toolkit/diabetesimpact) to help organizations assess the economics of providing or covering the National DPP (46). To expand preventive services using a cost-effective model, the Centers for Medicare & Medicaid Services expanded Medicare reimbursement coverage for the National DPP to organizations recognized by the CDC that become Medicare suppliers for this service (innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program). The locations of Medicare DPPs are available online at innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program/mdpp-map. To qualify for Medicare coverage, individuals must have BMI

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>25 kg/m^2 (or BMI >23 kg/m^2 if self-identified as Asian) and glycemic testing consistent with prediabetes in the last year. Medicaid DPP is also expanding on a state-by-state basis.

While CDC-recognized behavioral counseling programs, including Medicare DPP services, have met minimum quality standards and are reimbursed by many payors, lower retention rates have been reported for younger adults and racial and ethnic minoritized populations (47). Therefore, other programs and modalities of behavioral counseling for diabetes prevention may also be appropriate and efficacious based on individual preferences and availability. The use of community health workers to support DPP-like interventions has been shown to be effective and cost-effective (48,49) (see Section 1, "Improving Care and Promoting Health in Populations," for more information). The use of community health workers may facilitate the adoption of behavior changes for diabetes prevention while bridging barriers related to social determinants of health. However, coverage by third-party payors remains limited. Counseling by a registered dietitian/nutritionist (RDN) has been shown to help individuals with prediabetes improve eating habits, increase physical activity, and achieve 7–10% weight loss (15,50–52). Individualized medical nutrition therapy (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more detailed information) is also effective in improving glycemia in individuals diagnosed with prediabetes (26,50). Furthermore, trials involving medical nutrition therapy for adults with prediabetes found significant reductions in weight, waist circumference, and glycemia (23,26). Individuals with prediabetes can benefit from referral to an RDN for individualized medical nutrition therapy upon diagnosis and at regular intervals throughout their treatment plan (51,53). Other health care professionals, such as pharmacists and diabetes care and education specialists, may also be considered for diabetes prevention efforts (53,54).

Technology-assisted programs may effectively deliver a DPP-like intervention (55–58). A digital diabetes prevention program improved cardiovascular risk at 4 months but not at 12 months (59). Such technology-assisted programs may deliver content through smartphones, web-based applications, and telehealth and may be an acceptable and efficacious option to bridge barriers, particularly for individuals with low income and/or in rural locations; however, not all technology-assisted programs are effective (55,60–62). The CDC Diabetes Prevention Recognition Program (DPRP) (cdc.gov/diabetes/prevention/requirements-recognition.htm) certifies technology-assisted modalities as effective vehicles for DPP-based interventions; such programs must use an approved curriculum, include interaction with a coach, and attain the DPP outcomes of participation, physical activity reporting, and weight loss. Health care professionals should consider referring adults with prediabetes to certified technology-assisted programs.

PHARMACOLOGIC INTERVENTIONS TO DELAY TYPE 2 DIABETES

Recommendations

3.7 Metformin for the prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25–59 years with BMI ≥35 kg/m^2, higher fasting plasma glucose (e.g., ≥110 mg/dL [≥6 mmol/L]), and higher A1C (e.g., ≥6.0% [≥42 mmol/mol]), and in individuals with prior gestational diabetes mellitus. **A**

3.8 Long-term use of metformin may be associated with vitamin B12 deficiency; consider periodic assessment of vitamin B12 level in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. **B**

Because weight loss through behavior changes in nutrition and physical activity may not be sufficient on their own and can be difficult to maintain long term (10), some people at high risk of type 2 diabetes may benefit from additional support and pharmacotherapeutic options. Various pharmacologic agents used to treat diabetes have been evaluated for diabetes prevention. Metformin, α-glucosidase inhibitors, incretin receptor agonists (e.g., liraglutide and semaglutide), thiazolidinediones, and insulin have been shown to lower the incidence of diabetes in specific populations (63–68), whereas diabetes prevention was not seen with nateglinide (69).

In the DPP, weight loss was an important factor in reducing the risk of progression, with every kilogram of weight loss conferring a 16% reduction in risk of progression over 3.2 years (13). In individuals with previous history of GDM, the risk of type 2 diabetes increased by 18% for every 1 unit BMI above the preconception baseline (70). Several medications evaluated for weight loss (e.g., orlistat, phentermine and topiramate, liraglutide, semaglutide, and tirzepatide) have been shown to decrease the incidence of type 2 diabetes in those with prediabetes (68,71–73).

Studies of other pharmacologic agents have shown some efficacy in diabetes prevention with valsartan or testosterone (74,75) but no efficacy in preventing diabetes with ramipril or anti-inflammatory drugs (75–78). Vitamin D therapy has recently been advocated by the U.S. Endocrine Society to prevent progression of high-risk prediabetes to type 2 diabetes in adults (79). Three randomized controlled trials have been designed and conducted to test whether vitamin D therapy in combination with lifestyle modification reduces the risk of developing diabetes in adults with high-risk prediabetes (i.e., IGT or meeting two or three ADA prediabetes glycemic criteria [fasting glucose, A1C, 2-h glucose after a 75-g OGTT]): the Tromsø study in Norway, with 511 participants; the Vitamin D and Type 2 Diabetes (D2d) study in the U.S., with 2,423 participants; and the Diabetes Prevention with Active Vitamin D (DPVD) study in Japan, with 1,256 participants (80–82). Although vitamin D therapy modestly reduced the risk of developing diabetes compared with the placebo to a nearly identical degree in all three trials, none of the results of the individual studies were statistically significant (reportedly due to insufficient power). Subsequently, several meta-analyses related to these (and other smaller) studies have suggested a modest potential benefit in specific populations (83,84). However, there are several concerns and uncertainties regarding recommending widespread vitamin D therapy for adults with high-risk prediabetes. *1*) The recommended vitamin D dose is unclear. The included trials used varying dosages of vitamin D that were higher than the recommended daily allowance for this population (i.e., 600 IU/day for those aged 18–70 years

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and 800 IU for those older than 70 years). Due to this variability, it is not possible to recommend a specific vitamin D dosage for diabetes prevention. *2*) The benefit-to-risk ratio of vitamin D therapy for high-risk prediabetes remains uncertain. Although there was no evidence of safety concerns with vitamin D therapy in study participants with prediabetes, the numbers of adults included in these studies are small compared with the potentially many millions of adults with prediabetes in the U.S. and globally who may have risk of adverse events if treated with unspecified doses of vitamin D without monitoring blood 25-hydroxy vitamin D levels. In light of these and other issues, further research is warranted to better define the population characteristics and determine the dose and clinical pathway of vitamin D therapy for diabetes prevention.

No pharmacologic agent has been approved by the U.S. Food and Drug Administration for prevention of type 2 diabetes. The risk versus benefit of each medication in support of person-centered goals must be weighed in addition to cost and burden of administration. Additionally, pharmacologic interventions must be long-term because of the waning of effect after stopping the medication.

Metformin

Metformin has the most safety data as a pharmacologic therapy for diabetes prevention (85). Metformin was overall less effective than lifestyle modification in the DPP, though group differences attenuated over time in the DPPOS (11), and metformin may be cost-saving over a 10-year period (40). In the DPP, metformin was as effective as lifestyle modification in participants with BMI $\geq$35 kg/m^2 and in younger participants aged 25–44 years (5). In individuals with a history of GDM in the DPP, metformin and intensive lifestyle modification led to an equivalent 50% reduction in diabetes risk (86). Both interventions remained highly effective during a 10-year follow-up period (87). By the time of the 15-year follow-up (DPPOS), exploratory analyses demonstrated that participants with a higher baseline fasting glucose ($\geq$110 mg/dL [$\geq$6 mmol/L] vs. 95–109 mg/dL [5.3–5.9 mmol/L]), those with a higher A1C (6.0–6.4% [42–46 mmol/mol] vs. $<$6.0% [$<$42 mmol/mol]), and individuals with a history of GDM (vs. individuals without a history of GDM) experienced higher risk reductions with metformin, identifying subgroups of participants that may benefit the most from metformin (88). In the Indian Diabetes Prevention Program (IDPP-1), metformin and lifestyle intervention reduced diabetes risk similarly at 30 months; however, the lifestyle intervention in IDPP-1 was less intensive than that in the DPP (89). Based on findings from the DPP, metformin should be recommended as an option for high-risk individuals (e.g., younger individuals, those with history of GDM, or those with BMI $\geq$35 kg/m^2).

Decreased vitamin B12 levels are a known consequence of long-term treatment with metformin (90). Periodic assessment of vitamin B12 level in those taking metformin chronically should be considered to check for possible deficiency, especially in those receiving a higher dose (e.g. $\geq$1,500 mg/day) (91) or longer treatment duration and in those with existing risk factors. Vitamin B12 serum levels should be tested if deficiency is suspected, such as in people with anemia or peripheral neuropathy (90,92) (see Section 9, "Pharmacologic Approaches to Glycemic Treatment," for more details). The effect of metformin on vitamin B12 increases with time (93), with a higher risk for vitamin B12 deficiency ($<$200 pg/mL [$<$150 pmol/L]) noted at 4–5 years of treatment. A person who has been taking metformin for more than 4 years or is at risk for vitamin B12 deficiency for other reasons (e.g., vegan dietary pattern, previous gastric/small bowel surgery) should be monitored for vitamin B12 deficiency annually (94).

PREVENTION OF VASCULAR DISEASE AND MORTALITY

Recommendations

3.9 Prediabetes is associated with heightened cardiovascular risk; therefore, screening for and treatment of modifiable risk factors for cardiovascular disease are suggested. **B**

3.10 Statin therapy may increase the risk of type 2 diabetes in people at high risk of developing type 2 diabetes. In such individuals, glucose status should be monitored regularly and diabetes prevention approaches reinforced. It is not recommended that statins be avoided or discontinued for this adverse effect. **B**

3.11 In people with a history of stroke and evidence of insulin resistance and prediabetes, pioglitazone may be considered to lower the risk of stroke or myocardial infarction. However, this benefit needs to be balanced with the increased risk of weight gain, edema, and fractures. **A** Lower doses may mitigate the risk of adverse effects but may be less effective. **C**

People with prediabetes often have other cardiovascular risk factors, including hypertension and dyslipidemia (95), and are at increased risk for cardiovascular disease (96,97). Evaluation for tobacco use and referral for tobacco cessation should be part of routine care for those at risk for diabetes. Of note, the years immediately following smoking cessation may represent a time of increased risk for diabetes (98,99), and individuals should be monitored for diabetes development and receive evidence-based lifestyle behavior change for diabetes prevention as described in this section. See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more detailed information. The lifestyle interventions for weight loss in study populations at risk for type 2 diabetes have shown a reduction in cardiovascular risk factors and the need for medications used to treat these cardiovascular risk factors (100,101). The lifestyle intervention in the Da Qing study was associated with lowering cardiovascular disease and mortality at 23 and 30 years of observational follow-up (7,9). Treatment goals and therapies for hypertension and dyslipidemia in the primary and secondary prevention of cardiovascular disease for people with prediabetes should be based on their level of cardiovascular risk. Increased vigilance is warranted to identify and treat these and other cardiovascular disease risk factors (102). Statin use increases risk of diabetes (103–105). In the DPP, statin use was associated with greater diabetes risk irrespective of the treatment group (pooled hazard ratio [HR] [95% CI] for incident diabetes 1.36 [1.17–1.58]) (104). In trials of primary and secondary prevention of cardiovascular disease, cardiovascular and mortality benefits of statin therapy exceed the risk of diabetes (106,107), suggesting a highly favorable benefit-to-harm balance with statin therapy. Hence, discontinuation of statins due to concerns

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of diabetes risk is not recommended in this population.

Cardiovascular outcome trials in people without diabetes also inform risk reduction potential in people without diabetes at increased cardiometabolic risk (see Section 10, "Cardiovascular Disease and Risk Management," for more details). The IRIS (Insulin Resistance Intervention after Stroke) trial of people with a recent (<6 months) stroke or transient ischemic attack, without diabetes but with insulin resistance (as defined by a HOMA of insulin resistance index of ≥3.0), evaluated pioglitazone (goal dose of 45 mg daily) compared with placebo. At 4.8 years, the risk of stroke or myocardial infarction, as well as the risk of diabetes, was lower in the pioglitazone group than in the placebo group; weight gain, edema, and fractures were higher in the pioglitazone treatment group (108–110). Lower doses may mitigate the adverse effects but may also be less effective (111).

PERSON-CENTERED CARE GOALS

Recommendations

3.12 In adults with overweight or obesity at high risk of type 2 diabetes, care goals should include weight loss and maintenance, minimizing the progression of hyperglycemia, and attention to cardiovascular risk. **B**

3.13 Pharmacotherapy (e.g., for weight management, minimizing the progression of hyperglycemia, and cardiovascular risk reduction) should be considered to support person-centered care goals. **B**

3.14 More intensive preventive approaches should be considered in individuals who are at particularly high risk of progression to diabetes, including individuals with BMI ≥35 kg/m^2, those at higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL [6.1–6.9 mmol/L], 2-h postchallenge glucose 173–199 mg/dL [9.6–11.0 mmol/L], and A1C ≥6.0% [≥42 mmol/mol]), and individuals with a history of gestational diabetes mellitus. **A**

Individualized risk-to-benefit ratio should be considered in screening, intervention, and monitoring to lower the risk of type 2 diabetes and associated comorbidities. Multiple factors, including age, BMI, and other comorbidities, may influence the risk of progression to diabetes and lifetime risk of complications (112,113). Prediabetes is associated with increased cardiovascular disease and mortality (97), which emphasizes the importance of attending to cardiovascular risk in this population. However, the new diagnosis of prediabetes in older adults (aged >70 years) is less relevant for progression to diabetes, because regression to normoglycemia or death was more frequent than progression to diabetes in the Atherosclerosis Risk in Communities (ARIC) study (113).

In the DPP, which enrolled high-risk individuals with IGT, elevated fasting glucose, and elevated BMI, the crude incidence of diabetes within the placebo group was 11 cases per 100 person-years, with a cumulative 3-year incidence of diabetes of 29% (5). Characteristics of individuals in the DPP/DPPOS who were at particularly high risk of progression to diabetes (crude incidence of diabetes 14–22 cases per 100 person-years) included BMI ≥35 kg/m^2, higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL [6.0–6.9 mmol/L], 2-h postchallenge glucose 173–199 mg/dL [9.6–11.0 mmol/L], A1C ≥6.0% [≥42 mmol/mol]), or a history of GDM (5,86,87). In contrast, in the community-based ARIC study, observational follow-up of adults with mean age 75 years with laboratory evidence of prediabetes (based on A1C 5.7–6.4% [39–47 mmol/mol] and/or fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L]), but not meeting specific BMI criteria, found lower progression to diabetes over 6 years: 9% of those with A1C-defined prediabetes and 8% of those with IFG (113).

Thus, it is important to individualize the risk-to-benefit ratio of intervention and consider person-centered goals. Risk models have generally found a higher benefit of the intervention in those at highest risk (13). Diabetes prevention trials and observational studies highlight key principles that may guide person-centered goals. In the DPP, which enrolled a high-risk population meeting criteria for overweight or obesity, weight loss was an important mediator of diabetes prevention or delay, with greater metabolic benefit seen with greater weight loss (13,114). In the DPP/DPPOS, progression to diabetes, duration of diabetes, and mean level of glycemia were important determinants of the development of microvascular complications (11). Achieving normal glucose regulation, even once, during the DPP was associated with a lower risk of diabetes and lower risk of microvascular complications irrespective of the treatment arm (115). Observational follow-up of the Da Qing study also showed that regression from IGT to normal glucose tolerance or remaining with IGT rather than progressing to type 2 diabetes at the end of the 6-year intervention trial resulted in significantly lower risk of cardiovascular disease and microvascular disease over 30 years (116).

Pharmacotherapy for weight management and cardiovascular risk reduction (see Section 10, "Cardiovascular Disease and Risk Management," for more details) can be considered to support individualized person-centered goals, with more intensive preventive approaches considered in individuals at high risk of progression.

PREVENTION OR DELAY OF SYMPTOMATIC TYPE 1 DIABETES

Lifestyle and Type 1 Diabetes Progression

Observational studies suggest that in those with islet autoantibodies, factors that may increase β-cell demand, including less physical activity (117), higher glycemic index (118), and total sugar intake (119), are associated with progression to clinical diabetes. Similar associations have not been seen in the development of autoantibodies. In The Environmental Determinants of Diabetes in the Young (TEDDY) longitudinal study, daily minutes spent in moderate to vigorous physical activity were associated with a reduced risk of progression to type 1 diabetes in children 5–15 years of age with multiple islet autoantibodies (HR 0.92 [95% CI 0.86–0.99] per 10-min increase; $P = 0.021$) (117). In the Diabetes Autoimmunity Study in the Young (DAISY), in children with islet autoantibodies, progression to type 1 diabetes was associated with higher glycemic index (HR 2.20 [95% CI 1.17–4.15]) and total sugar intake (HR 1.75 [95% CI 1.07–2.85]) (118,119). In nonobese diabetic mice, an animal model for the development of type 1 diabetes, sustained high-glucose drinking significantly aggravated islet inflammation and accelerated the onset of type 1 diabetes (120). Lifestyle interventions focusing on such factors in those with

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stage 1 or stage 2 type 1 diabetes have not yet been reported.

Pharmacologic Interventions to Delay Symptomatic Type 1 Diabetes

Recommendation

3.15 Teplizumab-mzwv infusion to delay the onset of symptomatic type 1 diabetes (stage 3) should be discussed with selected individuals aged ≥8 years with stage 2 type 1 diabetes. Treatment should be in a setting with appropriately trained personnel. **B**

Teplizumab, a CD3-directed humanized monoclonal antibody engineered to have decreased Fc receptor binding, has been approved to delay the onset of stage 3 type 1 diabetes in people 8 years of age and older with stage 2 type 1 diabetes based in part on the results of a single trial in relatives of people with type 1 diabetes (121). In this study, 44 individuals were randomized to a 14-day course of teplizumab and 32 to placebo. The median time to stage 3 type 1 diabetes diagnosis was 48.4 months in the teplizumab group and 24.4 months in the placebo group. Type 1 diabetes was diagnosed in 19 (43%) participants who received teplizumab and 23 (72%) participants who received placebo (HR 0.41 [95% CI 0.22–0.78]). In prespecified analyses, the presence of HLA-DR4, absence of HLA-DR3, and absence of anti-zinc transporter 8 antibody predicted response to teplizumab (HR 0.20 [95% CI 09.0.45], 0.18 [0.07–0.45], and 0.07 [0.02–0.26], respectively). The most common adverse reactions were transient lymphopenia (73%) followed by rash (36%).

Numerous clinical studies are being conducted to test methods for preventing or delaying the onset of stage 3 type 1 diabetes in those with evidence of autoimmunity without symptoms or for delaying loss of insulin secretory capacity after onset of stage 3, some with promising results (see ClinicalTrials.gov and TrialNet.org).

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4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

PERSON-CENTERED COLLABORATIVE CARE

Recommendations

4.1 A communication style that uses person-centered, culturally sensitive, and strength-based language and active listening; elicits individual preferences and beliefs; and assesses literacy, numeracy, and potential barriers to care should be used to optimize health outcomes and health-related quality of life. **B**

4.2 People with diabetes can benefit from a coordinated interprofessional team that may include but is not limited to diabetes care and education specialists, primary care and subspecialty clinicians, nurses, registered dietitian nutritionists, exercise specialists, pharmacists, dentists, podiatrists, and behavioral health professionals. **C**

A successful medical evaluation depends on beneficial interactions and care coordination between the person with diabetes and the care team (1). The Chronic Care Model (2–4) (see Section 1, "Improving Care and Promoting Health in Populations") is a person-centered approach to care that requires a close working relationship between the person with diabetes and clinicians involved in treatment planning. People with diabetes should receive health care from a coordinated interprofessional team that may include but is not limited to diabetes care and education specialists, primary care and subspecialty clinicians, nurses, registered dietitian nutritionists, exercise specialists, pharmacists, dentists, podiatrists, behavioral health professionals, and community partners such as community health workers and community paramedics. Individuals with diabetes and their care partners must assume an active role in their care. Based on the preferences and values of the person with diabetes, elicited by the care team, the person with diabetes, their family or support group, and the health care team together formulate the management plan, which includes lifestyle management (see Section 5,

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.*

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The BONE HEALTH subsection has received endorsement from the American Society for Bone and Mineral Research.

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"Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes") and pharmacotherapy, as appropriate.

The goals of treatment for diabetes are to prevent or delay complications and optimize quality of life (**Fig. 4.1**). Treatment goals and plans should be co-created by the care team and people with diabetes based on their individual preferences, values, and goals. This individualized management plan should take into account the person's age, cognitive abilities, school/work schedule and conditions, health beliefs, support systems, eating patterns, physical activity, social situation, financial concerns, cultural factors, literacy and numeracy (mathematical literacy), diabetes history (duration, complications, and current use of medications), comorbidities, disabilities, health priorities, other medical conditions, preferences for care, access to health care services, and life expectancy. People living with diabetes should be engaged in conversation about these aspects of their lives and diabetes management, with routine reassessment as necessary given their changing circumstances across the life span. Various strategies and techniques should be used to support the person's self-management efforts, including providing education on problem-solving and coping skills for all aspects of diabetes management.

Communication by health care professionals with people with diabetes and their families should acknowledge that multiple factors impact glycemic management but also emphasize that collaboratively developed treatment plans and a healthy lifestyle can significantly improve disease outcomes and well-being (5–10). Thus, the goal of communication between health care professionals and people with diabetes is to establish a collaborative relationship and to assess and address self-management barriers without blaming people with diabetes for "noncompliance" or "nonadherence" when the outcomes of self-management are not optimal (11). The familiar terms noncompliance and nonadherence denote a passive, obedient role for a person with diabetes in "following doctor's orders," which is at odds with the active role people with diabetes take in the day-to-day decision-making, planning, monitoring, evaluation, and problem-solving involved in diabetes self-management. Using a nonjudgmental approach that normalizes periodic lapses in management may help minimize the person's resistance to reporting problems with self-management. Empathizing and using active listening techniques, such as open-ended questions, reflective statements, and summarizing what the person said, can help facilitate communication. Perceptions of people with diabetes about their own ability, or self-efficacy, to self-manage diabetes constitute one important psychosocial factor related to improved diabetes self-management and treatment outcomes in diabetes (12–14) and should be a goal of ongoing assessment, education, and treatment planning.

Language has a strong impact on perceptions and behavior. Empowering language can help to inform and motivate, while shame and judgement can be

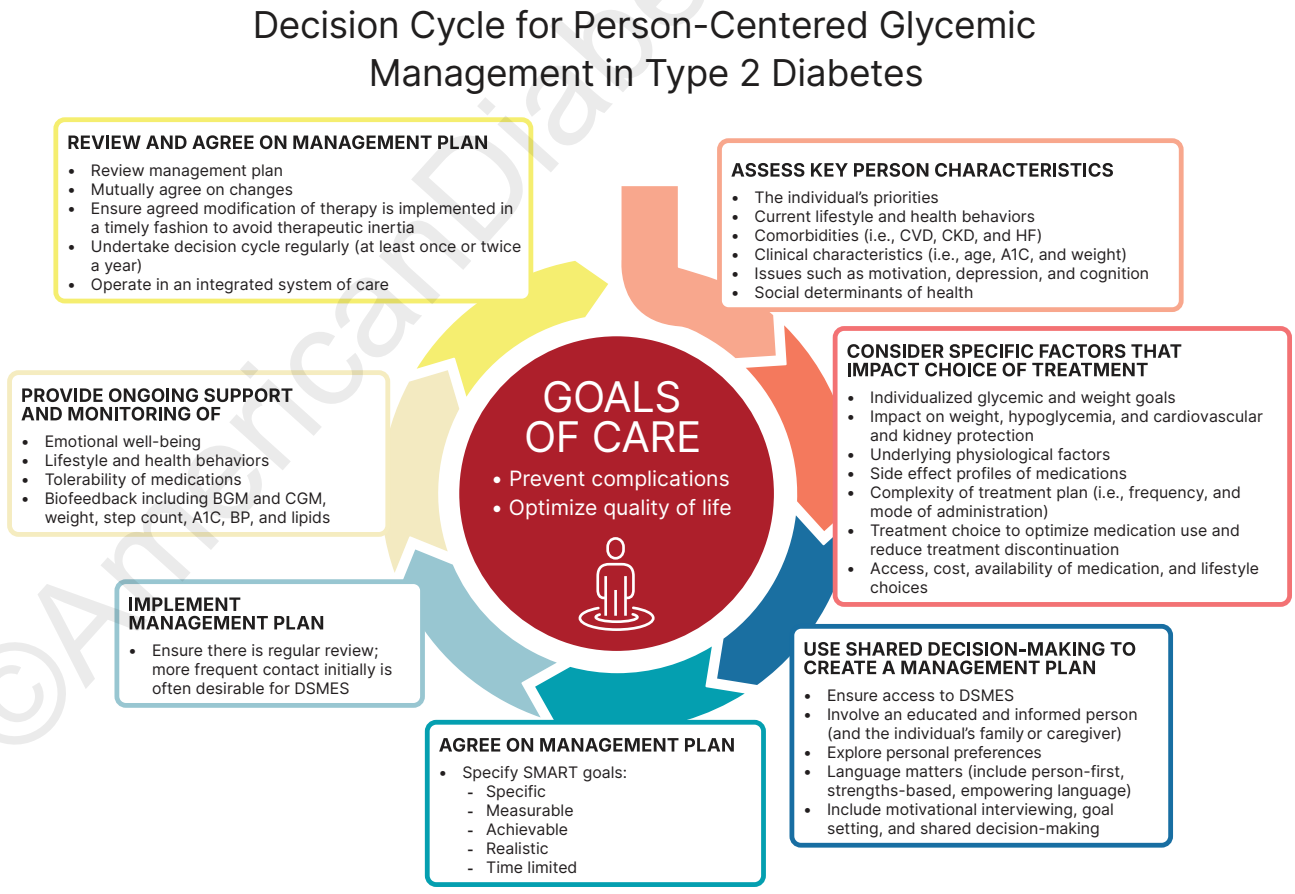

Figure 4.1—Decision cycle for person-centered glycemic management in type 2 diabetes. BGM, blood glucose monitoring; BP, blood pressure; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CVD, cardiovascular disease; DSMES, diabetes self-management education and support; HF, heart failure. Adapted from Davies et al. (324).

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discouraging. The American Diabetes Association (ADA) and the Association of Diabetes Care & Education Specialists (ADCES) (formerly called the American Association of Diabetes Educators) joint consensus report, "The Use of Language in Diabetes Care and Education," provides the authors' expert opinion regarding the use of language by health care professionals when speaking or writing about diabetes for people with diabetes or for professional audiences (15). Although further research is needed to address the impact of language on diabetes outcomes, the report includes five key consensus recommendations for language use:

- Use language that is neutral, nonjudgmental, and based on facts, actions, physiology, or biology.
- Use language free from stigma.
- Use language that is strength based, respectful, and inclusive and that imparts hope.
- Use language that fosters collaboration between people with diabetes and health care professionals.
- Use language that is person centered (e.g., "person with diabetes" is preferred over "diabetic").

COMPREHENSIVE MEDICAL EVALUATION

Recommendations

4.3 A complete medical evaluation should be performed at the initial visit and follow-up, as appropriate, to:

- Confirm the diagnosis and classify diabetes. **A**
- Assess glycemic status and previous treatment. **A**
- Evaluate for diabetes complications, potential comorbid conditions, and overall health status. **A**
- Identify care partners and support system. **E**
- Assess social determinants of health and structural barriers to optimal health and health care. **A**
- Review risk factor management in the person with diabetes. **A**
- Begin engagement with the person with diabetes in the formulation of a care management plan including initial goals of care. **A**
- Develop a plan for continuing care. **A**

4.4 Ongoing management should be guided by the assessment of overall health and functional status, diabetes complications, cardiovascular risk, hypoglycemia risk, and shared decision-making to set therapeutic goals. **B**

The comprehensive medical evaluation includes the initial and follow-up evaluations, which comprise assessment of complications, psychosocial assessment, management of comorbid conditions, overall health, functional and cognitive status, and engagement of the person with diabetes throughout the process. While a comprehensive list is provided in **Table 4.1**, in clinical practice the health care professional may need to prioritize the components of the medical evaluation given the available resources and time. Engaging other members of the health care team can also support comprehensive diabetes care. The goal of these recommendations is to provide the health care team information so it can optimally support people with diabetes and their care partners. In addition to the medical history, physical examination, and laboratory tests, health care professionals should assess diabetes self-management behaviors, nutrition, social determinants of health, and psychosocial health (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes") and give guidance on routine immunizations. The assessment of sleep pattern and duration should also be considered, as this may affect glycemic management. Interval follow-up visits should occur at least every 3–6 months individualized to the person and then at least annually.

Lifestyle management and behavioral health care are cornerstones of diabetes management. People with diabetes should be referred for diabetes self-management education and support, medical nutrition therapy, and assessment of behavioral health concerns as appropriate. People with diabetes should receive recommended preventive care services (e.g., immunizations and age- and sex-appropriate cancer screening); smoking cessation counseling; and ophthalmological, dental, podiatric, and other referrals, as needed.

The assessment of risk of acute and chronic diabetes complications and treatment planning are key components of initial and follow-up visits (**Table 4.2**). The risk of atherosclerotic cardiovascular disease and heart failure (see Section 10, "Cardiovascular Disease and Risk Management"), chronic kidney disease (CKD) staging (see Section 11, "Chronic Kidney Disease and Risk Management"), presence of retinopathy and neuropathy (see Section 12, "Retinopathy, Neuropathy, and Foot Care"), and risk of treatment-associated hypoglycemia should be used to individualize goals for glycemia (see Section 6, "Glycemic Goals and Hypoglycemia"), blood pressure, and lipids and to select specific glucose-lowering medication(s) (see Section 9, "Pharmacologic Approaches to Glycemic Treatment"), antihypertension medications, and lipid-lowering treatment intensity.

Additional referrals should be arranged as necessary (**Table 4.2**). Clinicians should ensure that people with diabetes are appropriately screened for complications, comorbidities, and treatment burden. Discussing and implementing an approach to glycemic management with the person is a part, not the sole goal, of the clinical encounter.

IMMUNIZATIONS

Recommendation

4.5 Provide routinely recommended vaccinations for children and adults with diabetes as indicated by age (see **Table 4.3**). **A**

Children and adults with diabetes should receive vaccinations according to age-appropriate recommendations (16,17). The Centers for Disease Control and Prevention (CDC) provides vaccination schedules specifically for children, adolescents, and adults with diabetes (cdc.gov/vaccines/). The CDC Advisory Committee on Immunization Practices (ACIP) makes recommendations based on its own review and rating of the evidence, provided in **Table 4.3** for selected vaccinations. The ACIP evidence review has evolved over time with the adoption of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) in 2010 and then the Evidence to Decision or Evidence to Recommendation frameworks in 2020 (18). Here, we discuss the particular importance of specific vaccines.

COVID-19

People with underlying medical conditions, including diabetes, are more likely to become severely ill with coronavirus

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Table 4.1—Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

	Visit		
	Initial	Every follow-up	Annual
Past medical and family history			
Diabetes history			
• Characteristics at onset (e.g., age and symptoms and/or signs)	✓		
• Review of previous treatment plans and response	✓		
• Assess frequency, cause, and severity of past hospitalizations	✓		
Family history			
• Family history of diabetes in a first-degree relative	✓		
• Family history of autoimmune disorders	✓		
Personal history of complications and common comorbidities			
• Common comorbidities (e.g., obesity, OSA, and MASLD)	✓		✓
• High blood pressure or abnormal lipids	✓		✓
• Macrovascular and microvascular complications	✓		✓
• Hypoglycemia: awareness, frequency, causes, and timing of episodes	✓	✓	✓
• Presence of hemoglobinopathies or anemias	✓		✓
• Last dental visit	✓		✓
• Last dilated eye exam	✓		✓
• Visits to specialists			✓
• Disability assessment and use of assistive devices (e.g., physical, cognitive, vision and auditory, history of fractures, and podiatry)	✓	✓	✓
• Personal history of autoimmune disease	✓		
Surgical and procedure history			
• Surgeries (e.g., metabolic surgery and transplantation)	✓	✓	✓
Interval history			
• Changes in medical or family history since last visit		✓	✓
Behavioral factors			
• Eating patterns and weight history	✓	✓	✓
• Assess familiarity with carbohydrate counting (e.g., type 1 diabetes or type 2 diabetes treated with MDI)	✓		✓
• Physical activity and sleep behaviors; screen for OSA	✓	✓	✓
• Tobacco, alcohol, and substance use	✓		✓
Medications and vaccinations			
• Current medication plan	✓	✓	✓
• Medication-taking behavior, including rationing of medications and/or medical equipment	✓	✓	✓
• Medication intolerance or side effects	✓	✓	✓
• Complementary and alternative medicine use	✓	✓	✓
• Vaccination history and needs	✓		✓
Technology use			
• Assess use of health apps, online education, patient portals, etc.	✓	✓	✓
• Glucose monitoring (meter/CGM): results and data use	✓	✓	✓

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disease 2019 (COVID-19). COVID-19 vaccination using an appropriate number of doses of updated vaccines is recommended for everyone aged 6 months and older in the U.S. (18).

Hepatitis B

Compared with the general population, people with type 1 or type 2 diabetes have higher rates of hepatitis. Because of the higher likelihood of transmission of the disease, hepatitis B vaccine is recommended for adults with diabetes aged <60 years. For adults aged ≥60 years, hepatitis B vaccine may be administered at the discretion of the treating clinician based on the person's likelihood of acquiring hepatitis B infection (19).

Influenza

Influenza is a common, preventable infectious disease associated with high mortality and morbidity in vulnerable populations, including youth, older adults, and people with chronic diseases. Influenza vaccination in people with diabetes has been found to significantly reduce influenza and diabetes-related hospital admissions (20). In people with diabetes, the influenza vaccine has been associated with lower risk of all-cause mortality, cardiovascular mortality, and cardiovascular events (21). Given the benefits of the annual influenza vaccination, it is recommended for all individuals ≥6 months of age who do not have a contraindication. The live attenuated influenza vaccine, which is delivered by nasal spray, is an option for people who are 2–49 years of age and are not pregnant, but people with chronic conditions such as diabetes are cautioned against taking the live attenuated influenza vaccine and are instead recommended to receive the inactive or recombinant influenza vaccination. As of the 2024–2025 season, all influenza vaccines offered in the U.S. are trivalent (22).

Pneumococcal Pneumonia

Like influenza, pneumococcal pneumonia is a common, preventable disease. People with diabetes are at increased risk for pneumococcal infection and have been reported to have a high risk of hospitalization and death, with a mortality rate as high as 50% (23). All people with diabetes should receive one of the CDC-recommended pneumococcal vaccines (24). See details in **Table 4.3**.

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Table 4.1—Continued

	Visit		
	Initial	Every follow-up	Annual
• Review insulin pump settings and use and connected pen and glucose data	✓	✓	✓
Social life assessment			
Social network			
• Identify existing social supports	✓		✓
• Identify surrogate decision maker and advanced care plan	✓		✓
• Identify social determinants of health (e.g., food security, housing stability and homelessness, transportation access, financial security, and community safety)	✓		✓
• Assess daily routine and environment, including school or work schedules and ability to engage in diabetes self-management	✓	✓	✓
Physical examination			
• Height, weight, and BMI; growth and pubertal development in children and adolescents	✓	✓	✓
• Blood pressure determination	✓	✓	✓
• Orthostatic blood pressure measures (when indicated)	✓		✓
• Fundoscopic examination (refer to eye specialist)	✓		✓
• Thyroid palpation	✓		✓
• Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, and lipodystrophy)	✓	✓	✓
• Comprehensive foot examination	✓		✓
• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, and toenails)*	✓	✓	✓
• Check pedal pulses and screen for PAD with ABI testing if a PAD diagnosis would change management	✓		✓
• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓
• Screen for depression, anxiety, diabetes distress, fear of hypoglycemia, and disordered eating	✓		✓
• Assessment for cognitive performance if indicated†	✓		✓
• Assessment for functional performance if indicated†	✓		✓
• Consider assessment for bone health (e.g., loss of height and kyphosis)	✓		✓
Laboratory evaluation			
• A1C, if the results are not available within the past 3 months	✓	✓	✓
• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides‡	✓		✓^
• Liver function tests (i.e., FIB-4)‡	✓		✓
• Spot urinary albumin-to-creatinine ratio	✓		✓
• Serum creatinine and estimated glomerular filtration rate§	✓		✓
• Thyroid-stimulating hormone in people with type 1 diabetes‡	✓		✓
• Celiac disease in people with type 1 diabetes‖	✓		

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Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is a cause of respiratory illness in some individuals, including older adults. People with chronic conditions such as diabetes have a higher risk of severe illness. The U.S. Food and Drug Administration (FDA) approved the first vaccines for prevention of RSV-associated lower respiratory tract disease in adults aged ≥60 years. On 26 June 2024, ACIP voted to recommend that all adults aged ≥75 years and adults aged 60–74 years who are at increased risk for severe RSV should receive a single dose of RSV vaccine (25).

ASSESSMENT OF COMORBIDITIES

Besides assessing diabetes-related complications, clinicians and people with diabetes need to be aware of common comorbidities that affect people with diabetes and that may complicate management (26–28). Diabetes comorbidities are conditions that affect people with diabetes more often than age-matched people without diabetes. This section discusses many of the common comorbidities observed in people with diabetes but is not necessarily inclusive of all the conditions that have been reported.

Autoimmune Diseases

Recommendations

4.6 Screen people with type 1 diabetes for autoimmune thyroid disease soon after diagnosis and thereafter at repeated intervals if clinically indicated. **B**

4.7 Adults with type 1 diabetes should be screened for celiac disease in the presence of gastrointestinal symptoms, signs, laboratory manifestations, or clinical suspicion suggestive of celiac disease. **B**

People with type 1 diabetes are at increased risk for other autoimmune diseases, with thyroid disease, celiac disease, and pernicious anemia (vitamin B12 deficiency) being among the most common (29). Other autoimmune conditions associated with type 1 diabetes include autoimmune liver disease, primary adrenal insufficiency (Addison disease), vitiligo, collagen vascular diseases, and myasthenia gravis (30–33). Type 1 diabetes may also occur with other autoimmune diseases in the context of specific genetic

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Table 4.1—Continued

	Visit		
	Initial	Every follow-up	Annual
• Vitamin B12 if taking metformin for >5 years	✓		✓
• CBC with platelets	✓		✓
• Serum potassium levels in people with diabetes on ACE inhibitors, ARBs, or diuretics§	✓		✓
• Calcium, vitamin D, and phosphorous for appropriate people with diabetes	✓		✓

ABI, ankle brachial index; ARBs, angiotensin receptor blockers; CBC, complete blood count; CGM, continuous glucose monitor; FIB-4: fibrosis-4 index; MASLD, metabolic-associated steatotic liver disease; MDI, multiple daily injections; OSA, obstructive sleep apnea; PAD, peripheral arterial disease. *Should be performed at every visit in people with diabetes with sensory loss, previous foot ulcers, or amputations. †At 65 years of age or older. ‡May also need to be checked after initiation or dose changes of medications that affect these laboratory values (i.e., diabetes medications, blood pressure medications, cholesterol medications, or thyroid medications). ^In people without dyslipidemia and not on cholesterol-lowering therapy, testing may be less frequent. §May be needed more frequently in people with diabetes with known chronic kidney disease or with changes in medications that affect kidney function and serum potassium (see **Table 11.2**). ||In people with presence of gastrointestinal symptoms, signs, laboratory manifestations, or clinical suspicion suggestive of celiac disease.

disorders such as polyglandular autoimmune syndromes (34). Given the high prevalence, nonspecific symptoms, and insidious onset of primary hypothyroidism, routine screening for thyroid dysfunction is recommended for all people with type 1 diabetes. Screening for celiac disease should be considered in adults with diabetes with suggestive symptoms (e.g., diarrhea, malabsorption, and abdominal pain) or signs (e.g., osteoporosis, vitamin deficiencies, and iron deficiency anemia) (35,36). Measurement of vitamin B12 levels should be considered for people with type 1 diabetes and peripheral neuropathy or unexplained anemia.

Bone Health

Recommendations

4.8 Assess fracture risk in older adults with diabetes as a part of routine care in diabetes clinical practice, according to risk factors and comorbidities. **A**

4.9 Monitor bone mineral density using dual-energy X-ray absorptiometry in older adults with diabetes (aged ≥65 years) and younger individuals with diabetes and multiple risk factors every 2–3 years (**Table 4.4**). **A**

4.10 Consider the potential adverse impact on skeletal health when selecting pharmacological options to lower glucose levels in people with diabetes. Avoiding medications with a known association with higher fracture risk (e.g., thiazolidinediones and sulfonylureas) is recommended, particularly for those at elevated risk for fractures. **B**

4.11 To reduce the risk of falls and fractures, glycemic management goals should be individualized for people with diabetes at a higher risk of fracture. **C** Prioritize use of glucose-lowering medications that are associated with low risk for hypoglycemia to avoid falls. **B**

4.12 Advise people with diabetes on their intake of calcium (1,000–1,200 mg/day) and vitamin D to ensure it meets the recommended daily allowance for those at risk for fracture, either through their diet or supplemental means. **B**

4.13 Antiresorptive medications and osteoanabolic agents should be recommended for older adults with diabetes who are at higher risk of fracture, including those with low bone mineral density with a T-score ≤−2.0, history of fragility fracture, or elevated Fracture Risk Assessment Tool score (≥3% for hip fracture or ≥20% for major osteoporotic fracture). **B**

Determination of fracture risk traditionally has relied on measurements of bone mineral density (BMD) and the World Health Organization–defined T-score of ≤–2.5 SD. However, it is now established that the consideration of other risk factors improves the categorization of fracture risk (**Table 4.4**). There are factors beyond BMD that contribute to bone strength in people with diabetes.

A low-trauma hip/pelvis, vertebral, or forearm fracture in people aged ≥65 years is diagnostic for osteoporosis independent of BMD and is one of the strongest risk factors for subsequent fractures, especially in the first 1–2 years after a fracture (37,38). Osteoporotic hip fractures are associated with significant morbidity, mortality, and societal costs (39). It is estimated that 20% of individuals do not survive to 1 year after hip fracture, while 60% do not regain their prior functionality, living with permanent disability (40).

Hip fractures in people with diabetes are associated with higher risk of mortality (28% in women and 57% in men), longer recovery, and delayed healing (41) compared with individuals without diabetes.

Epidemiology and Risk Factors

Age-specific fracture risk is significantly increased in people with type 1 or type 2 diabetes in both sexes, with a 34% increase in fracture risk compared with those without diabetes (42).

Type 1 Diabetes. Fracture risk in people with type 1 diabetes is increased by 4.35 times for hip fractures, 1.83 times for upper limb fractures, and 1.97 times for ankle fractures (43). Fractures occur even at young ages, 10–15 years earlier than they do in people without diabetes, and are less frequent at the vertebral level. Type 1 diabetes is often associated with low bone mass, although BMD underestimates the high risk of fracture observed in young individuals (43). Risk of fracture is increased in people with type 1 diabetes with microvascular complications or neuropathy (41). Moreover, average A1C >7.9% (risk ratio [RR] 3.57 [CI 1.08–11.78]), duration of diabetes >26 years (RR 7.6 [CI 1.67–34.6]), and family history of fractures (RR 2.64 [CI 1.15–6.09]) have been independently associated with high risk of nonvertebral fractures (44).

Type 2 Diabetes. In people with type 2 diabetes, even with normal or higher BMD, hip fracture risk is increased by 1.79 times, and risk throughout life is 40–70%

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Table 4.2—Essential components for assessment, planning, and referral

Assessing risk of diabetes complications
• ASCVD and heart failure history
• ASCVD risk factors and 10-year ASCVD risk assessment
• Staging of chronic kidney disease (see **Table 11.2**)
• Hypoglycemia risk (see Section 6, "Glycemic Targets and Hypoglycemia Prevention")
• Assessment for retinopathy
• Assessment for neuropathy
• Assessment for MASLD and MASH
Goal setting
• Set A1C, blood glucose, and time in range goals
• Set lipid goal
• If hypertension is present, establish blood pressure goal
• Weight management and physical activity goals
• Diabetes self-management goals
Therapeutic treatment plans
• Lifestyle management (e.g., registered dietitian nutritionist)
• Pharmacologic therapy: glucose lowering
• Pharmacologic therapy: cardiovascular and kidney disease risk factors
• Weight management with pharmacotherapy or metabolic surgery, as appropriate
• Use of glucose monitoring and insulin delivery devices
• Referral to diabetes education and medical specialists (as needed)
Referrals for initial care management
• Eye care professional for annual dilated eye exam
• Family planning for individuals of childbearing potential
• Registered dietitian nutritionist for medical nutrition therapy
• Diabetes self-management education and support
• Dentist for comprehensive dental and periodontal examination
• Behavioral health professional, if indicated
• Audiology, if indicated
• Social worker and community resources, if indicated
• Rehabilitation medicine or another relevant health care professional for physical and cognitive disability evaluation, if indicated
• Other appropriate health care professionals

Assessment and treatment planning are essential components of initial and all follow-up visits. ASCVD, atherosclerotic cardiovascular disease; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease.

higher than in it is in individuals without diabetes (42,45–47). According to a meta-analysis that included 15 studies, people with type 2 diabetes had a 35% higher incidence of vertebral fractures, causing increased risk of mortality (HR 2.11 [95% CI 1.72–2.59]) (48). Fracture risk is also increased in the upper limbs and ankle. However, bone loss is accelerated, and low BMD remains an independent risk factor for fractures (49,50).

Glycemic management significantly impacts fracture risk in people with diabetes. A meta-analysis revealed an 8% increased fracture risk per 1% rise in A1C level (RR 1.08 [95% CI 1.03–1.14]) (51). Poor glycemic management (A1C >9%) over 2 years in individuals with type 2 diabetes correlated with a 29% heightened fracture risk (52). Notably, this risk was higher among White individuals than in other racial groups. Hypoglycemia also escalated the risk of fractures at the hip and other skeletal sites (RR 1.52 [95% CI 1.23–1.88]) (51). A Japanese study echoed these findings, showing a fracture risk increase (hazard ratio [HR] 2.24 [95% CI 1.56–3.21]) with severe hypoglycemia episodes (53).

Longer disease duration further elevates fracture risk (54); data indicate individuals who have had type 2 diabetes for >10 years face significantly higher fracture risks, which are largely attributed to ensuing microvascular and macrovascular damage affecting the skeleton. Additionally, high fracture risk is seen in people with cardiovascular disease (CVD), nephropathy, retinopathy, neuropathy, poor physical function, and frequent falls (55–57).

Certain glucose-lowering medications also factor into fracture risk. Studies have reported increased fracture incidences in women using thiazolidinediones (TZD), with the risk doubling with 1–2 years of TZD use compared with placebo or other glucose-lowering medications (HR 2.23 [95% CI 1.65–3.01]) (58,59). According to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, reduced risk is noted in women who had discontinued TZD use for 1–2 years (HR 0.57 [95% CI 0.35–0.92]) or >2 years (HR 0.42 [95% CI 0.24–0.74]) compared with current users (60). Furthermore, individuals with type 2 diabetes on insulin (RR 1.49 [95% CI 1.29–1.73]) or sulfonylurea (RR 1.30 [95% CI 1.18–1.43]) treatment exhibit a heightened fracture risk (61).

Screening

Most evidence on screening in individuals at risk for fracture is available from people with type 2 diabetes; fracture risk prediction using BMD in type 1 diabetes has not been extensively studied. Health care professionals should assess fracture history and risk factors in people with diabetes and recommend measurement of BMD if appropriate according to the individual's age and sex.

Type 2 Diabetes. People with type 2 diabetes have 5–10% higher BMD than people without diabetes, although they present with lower bone strength, impaired bone microarchitecture, and accelerated bone loss (49,62–64). A T-score adjustment of −0.5 has been proposed to improve fracture prediction by dual-energy X-ray absorptiometry (DXA). For example, a T-score ≤–2.0 should be interpreted as equivalent to –2.5 in a person without diabetes (50). Notably, the Fracture Risk Assessment Tool (FRAX), although useful, does not factor in type 2 diabetes; an inclusion of the condition is estimated to mirror the effect of either a 10-year age increase or a 0.5 SD reduction in BMD T-score (65). Fracture risk was higher in large observational studies in participants with diabetes compared with those without diabetes for a given T-score and age or for a given FRAX score (50). One method to potentially improve fracture risk prediction for people with type 2 diabetes involves using the FRAX "rheumatoid arthritis" input as a proxy for diabetes risk (66,67). Additionally, performance of FRAX can be improved by using *1*) trabecular bone score adjustment, *2*) lowering femoral neck T-score input by 0.5 SD, or *3*) increasing the age by 10 years (66). Growing evidence suggests that fracture risk prediction is enhanced by use of trabecular bone score (65,66), although such studies are not available for

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Table 4.3—Highly recommended immunizations for adults with diabetes (from the Advisory Committee on Immunization Practices and Centers for Disease Control and Prevention)

Vaccine	Recommended ages	Schedule	GRADE evidence type*	References
COVID-19	All people 6 months of age and older	Current initial vaccination and boosters		Centers for Disease Control and Prevention, Interim Clinical Considerations for Use of COVID-19 Vaccines in the United States (318)
Hepatitis B	Adults with diabetes aged <60 years; for adults aged ≥60 years, hepatitis B vaccine may be administered at the discretion of the treating clinician based on the person's likelihood of acquiring hepatitis B infection			Weng et al., Universal Hepatitis B Vaccination in Adults Aged 19–59 Years: Updated Recommendations of the Advisory Committee on Immunization Practices—United States, 2022 (19)
Influenza	All people with diabetes advised to receive a trivalent influenza vaccine and not to receive live attenuated influenza vaccine	Annual		Centers for Disease Control and Prevention, Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2024–25 Influenza Season (22)
Pneumonia (PPSV23 [Pneumovax])	19–64 years of age, vaccinate with Pneumovax	One dose is recommended for those who previously received PCV13; if PCV15 was used, follow with PPSV23 ≥1 year later; PPSV23 is not indicated after PCV20; adults who received only PPSV23 may receive PCV15 or PCV20 ≥1 year after their last dose	2	Centers for Disease Control and Prevention, Updated Recommendations for Prevention of Invasive Pneumococcal Disease Among Adults Using the 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23) (24,319)
	≥65 years of age	One dose is recommended for those who previously received PCV13; if PCV15 was used, follow with PPSV23 ≥1 year later; PPSV23 is not indicated after PCV20; adults who received only PPSV23 may receive PCV15 or PCV20 ≥1 year after their last dose	2	Falkenhorst et al., Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) Against Pneumococcal Disease in the Elderly: Systematic Review and Meta-analysis (24,320)
PCV20 or PCV15	Adults 19–64 years of age with an immunocompromising condition (e.g., chronic renal failure), cochlear implant, or cerebrospinal fluid leak	One dose of PCV15 or PCV20 is recommended by the Centers for Disease Control and Prevention		Kobayashi et al., Use of 15-Valent Pneumococcal Conjugate Vaccine and 20-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Updated Recommendations of the Advisory Committee on Immunization Practices—United States, 2022 (24, 321)
	Adults 19–64 years of age, immunocompetent	For those who have never received any pneumococcal vaccine, the Centers for Disease Control and Prevention recommends one dose of PCV15 or PCV20		
	≥65 years of age, immunocompetent, have shared decision-making discussion with health care professionals	One dose of PCV15 or PCV20; PCSV23 may be given ≥8 weeks after PCV15; PPSV23 is not indicated after PCV20		
RSV	Older adults ≥60 years of age with diabetes appear to be a risk group	Adults aged ≥75 years and those aged ≥60 years and at high risk may receive a single dose of an RSV vaccine		Centers for Disease Control and Prevention, CDC Recommends RSV Vaccine for Older Adults (25)
Tetanus, diphtheria, pertussis (Tdap)	All adults; pregnant individuals should have an extra dose	Booster every 10 years	2 for effectiveness, 3 for safety	Havers et al., Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccines: Updated Recommendations of the Advisory Committee on Immunization Practices—United States, 2019 (322)

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Table 4.3—Continued

Vaccine	Recommended ages	Schedule	GRADE evidence type*	References
Zoster	≥50 years of age	Two-dose Shingrix, even if previously vaccinated	1	Dooling et al., Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines (323)

For a comprehensive list of vaccines, refer to the Centers for Disease Control and Prevention web site at cdc.gov/vaccines/. Advisory Committee on Immunization Practices recommendations can be found at cdc.gov/vaccines/acip/recommendations. GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV 20, 20-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine. *Evidence type: 1, randomized controlled trials (RCTs) or overwhelming evidence from observational studies; 2, RCTs with important limitations or exceptionally strong evidence from observational studies; 3, observational studies or RCTs with notable limitations; 4, clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations.

individuals with type 1 diabetes and are based on data from the U.S. or Canada.

In people with type 2 diabetes, BMD should be monitored by DXA scan in older adults (aged ≥65 years) in the absence of other comorbidities and in younger individuals (>50 years of age) with bone or diabetes-related risk factors, such as insulin use or diabetes duration >10 years (**Table 4.4**). Reassessment is recommended every 2–3 years (65), depending on the screening evaluation and the presence of additional risk factors, although the evidence on how frequently DXA should be repeated is less robust. According to the European Association for the Study of Obesity (EASO), DXA should be performed every 2 years in subjects undergoing bariatric-metabolic surgery.

DXA-assisted vertebral fracture assessment is a convenient and low-cost method to assess vertebral fractures, although traditional lateral thoracic/lumbar spine X-ray is still considered the gold standard (68). MRI or computed tomography imaging studies performed for other purposes should be analyzed for presence of vertebral fractures as well as chest X-rays in hospitalized individuals. Bone turnover markers are commonly used in clinical practice to monitor bone formation and bone resorption, although they are suppressed in people with diabetes and have not been shown to predict fracture risk (69).

Type 1 Diabetes. Because hip fracture risk in type 1 diabetes starts to increase after the age of 50, clinicians may consider assessing BMD after the 5th decade of life (43). In people with type 1 diabetes, BMD underestimates fracture risk, but studies do not address the extent of underestimation of fracture risk.

According to the International Society for Pediatric and Adolescent Diabetes (ISPAD), regular assessment of bone health using bone densitometry in youth with type 1 diabetes is still controversial and not recommended, but it may be considered in association with celiac disease (70).

Management

Appropriate glycemic management and minimizing hypoglycemic episodes are crucial for bone health in people with diabetes. Individuals with prolonged disease, microvascular and macrovascular complications, or frequent hypoglycemic episodes face higher fracture risks and fall risks due to factors like poor vision, neuropathy, sarcopenia, and impaired gait. Health care professionals should advocate moderate physical activity to enhance muscle health, gait coordination, and balance as part of fracture preventive strategies (56,57,71).

Aerobic and weight-bearing exercise should be recommended to counteract the potential negative effect of weight loss on bone; specific guidelines have been published for older adults with type 2 diabetes (72).

Osteoporosis and fracture prevention are first based on measures applied to the general population. All people with diabetes should receive an adequate daily intake of proteins, calcium, and vitamin D, stop smoking, and have regular physical activity (73–75).

Intake of calcium should reflect the age-specific recommendations for the general population and should be obtained through diet and/or oral supplements (76).

The optimal level of 25-hydroxyvitamin D is a matter of controversy (77), although serum levels 20–30 ng/mL are generally thought to be sufficient (78).

The safe upper limit is also a matter of debate, and there is substantial disagreement over whether to treat to a specified serum level. In the U.S., the recommended daily allowance of vitamin D is 600 IU for people aged 51–70 years and 800 IU for people aged >70 years (78). In clinical practice, this dose of supplement may not be sufficient to reach recommended serum levels of vitamin D, particularly in those at risk for vitamin D deficiency, and therefore supplementation should be individualized.

Fractures are important determinants of frailty, a predisability condition that should be mitigated with individualized

Table 4.4—Diagnostic assessment

Individuals who should receive BMD testing
People aged ≥65 years
Postmenopausal women and men aged ≥50 years with history of adult-age fracture or with diabetes–specific risk factors: • Frequent hypoglycemic events • Diabetes duration >10 years • Diabetes medications: insulin, thiazolidinediones, sulfonylureas • A1C >8% • Peripheral or autonomic neuropathy, retinopathy, nephropathy • Frequent falls • Glucocorticoid use

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interventions to prevent falls, maintain mobility, and delay disability (72). In many circumstances, conservative management (calcium, vitamin D, and lifestyle measures) are not enough to reduce fracture risk. When pharmacological treatment is needed, treatment initiation strategies are the same as those used for the general population. Antiosteoporosis medications reduce bone resorption (bisphosphonates, selective estrogen receptor modulators, and denosumab), stimulate bone formation (teriparatide and abaloparatide), or have dual actions by stimulating bone formation and reducing bone resorption (romosozumab). These agents improve bone density and reduce the risk of vertebral and nonvertebral fractures. Although there are no studies specifically designed for people with diabetes, data on antiresorptive and osteoanabolic agents suggest efficacy in type 2 diabetes is similar to that for individuals without diabetes (79–81). Using individual participant data from randomized trials, antiresorptive therapies show similar effects in people with and without type 2 diabetes for vertebral, hip, and nonvertebral fractures (79). No similar studies of efficacy of antiosteoporosis treatment in people with type 1 diabetes have been published.

Primary Prevention of Fragility Fractures in People With Diabetes. In the general population, a T-score ≤–2.5 is the threshold to consider pharmacological treatment for osteoporosis. In type 2 diabetes, since T-score underestimates fracture risk (as discussed above), a T-score ≤–2.0 may be more appropriate for considering initiation of a first-line drug, including bisphosphonates (alendronate, risedronate, and zoledronic acid) or denosumab.

Denosumab is preferred in individuals with estimated glomerular filtration rate <30–35 mL/min/1.73 m^2, although the FDA has recently issued a boxed warning for increased risk of severe hypocalcemia in individuals with advanced chronic kidney disease. Self-management abilities of the person with diabetes should be considered in medication selection, recommending strict medication-taking behavior, as there can be rebound bone loss causing multiple vertebral fractures with missed doses of denosumab or delays in care. Bisphosphonate therapy (oral or intravenous) may be more appropriate in individuals with poor medication-taking behavior or gaps in access to medical care.

There are some additional considerations related to medication selection in people with diabetes. Data from a phase 3 trial, Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM), and its 10-year extension have shown that people with diabetes treated with denosumab experienced positive effects on fasting glucose (82) and significant improvements in BMD and lower vertebral fracture risk (67). However, according to a post hoc subgroup analysis, a higher risk of nonvertebral fractures was observed in people with diabetes treated with denosumab (67). Romosozumab received FDA approval with a box warning because it may increase risk of myocardial infarction, stroke, or cardiovascular death and should not be prescribed in women who experienced a myocardial infarction or a stroke within the past year (83,84).

Secondary Prevention of Fragility Fractures. The risk of subsequent fracture in individuals with hip or vertebral fracture is high, especially in the first 1–2 years after a fracture. Antiosteoporosis treatment reduces the risk of fracture in older individuals with prior hip or vertebral fracture.

As in the general population, people with diabetes who experience fragility fracture should *1*) be given the diagnosis of osteoporosis regardless of DXA data and *2*) receive the appropriate work-up and therapy to prevent future fractures (85). Individuals on long-term treatment with antiosteoporosis medications, with multiple fragility fractures, or with multiple comorbidities should be referred to a bone metabolic specialist. In these more complicated cases, a bone specialist may choose to initiate an osteoanabolic agent to optimize bone formation and reduce immediate fracture risk (86). It is strongly recommended that all individuals with a fragility fracture be started on antiosteoporosis therapy and adequate calcium and vitamin D supplementation (if required) as soon as possible. In the appropriate individual, therapy may even be initiated during an inpatient stay to reduce care delays (85).

Glucose-Lowering Medications and Bone Health

Care plans for type 2 diabetes treatment should consider individual fracture risk and the potential effect of medications on bone metabolism. Medications other than TZDs are advisable for postmenopausal women or older men with type 2 diabetes due to their safer bone health profiles. While several studies have shown metformin to have a safe profile, special attention should be paid to the wide use of sulfonylureas because of the high risk of hypoglycemic events leading to falls and fractures (87). Dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have been used in clinical practice for more than 15 years, and both clinical trials and postmarketing data suggest a neutral impact on bone health (88,89). Tirzepatide may play a positive effect through glucose-dependent insulinotropic polypeptide (GIP) receptor agonism, preventing bone loss associated with weight loss (90), although bone outcomes have not yet been reported in clinical data.

Use of sodium–glucose cotransporter 2 (SGLT2) inhibitors has raised some concerns. The Canagliflozin Cardiovascular Assessment Study (CANVAS) study showed that the proportion of subjects with fracture was higher in the canagliflozin groups than the noncanagliflozin groups (2.7% vs. 1.9%, respectively). Further analyses from the same trial and from the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study found a neutral effect on fracture risk (91–94). Although few data are available, use of empagliflozin, ertugliflozin, or dapagliflozin has not been associated with negative effects on bone health (93–95). Use of insulin has been shown to be associated with a doubling of the risk of hip fractures (87), likely because of higher risk of hypoglycemia, longer duration of the disease, and comorbidities that may contribute to diminished bone strength.

In conclusion, glucose-lowering medications with a good bone safety profile are preferred. This is especially true in older adults, in people with longer duration of disease, or in people with complications. Aggressive therapeutic approaches should be avoided in those who are frail and in older adults to prevent hypoglycemic events and falls.

Cancer

Diabetes is associated with increased risk of cancers of the liver, pancreas, endometrium, colon and rectum, breast,

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and bladder (96). The association may result from shared risk factors between type 2 diabetes and cancer (older age, obesity, and physical inactivity) but may also be due to diabetes-related factors (97), such as underlying disease physiology or diabetes treatments, although evidence for these links is scarce. People with diabetes should be encouraged to undergo recommended age-and sex-appropriate cancer screenings, coordinated with their primary health care professional, and to reduce their modifiable cancer risk factors (obesity, physical inactivity, and smoking). New onset of atypical diabetes (lean body habitus and negative family history) in a middle-aged or older person may precede the diagnosis of pancreatic adenocarcinoma (98). Additionally, in a nationwide cancer registry in New Zealand, postpancreatitis diabetes mellitus was associated with significantly higher risk (2.4-fold) of pancreatic cancer compared with pancreatitis after type 2 diabetes (99). However, in the absence of other symptoms (e.g., weight loss and abdominal pain), routine screening for pancreatic cancer is not currently recommended. Metformin and sulfonylureas may have anticancer properties. Data for pioglitazone are mixed, with a previous concern for bladder cancer association. Recommendations cannot be made at this time (100–102). Thus far, the use of GLP-1 RAs has not been shown to be associated with the incidence of thyroid cancer, pancreatic cancer, or any other type of cancer in humans (103).

Cognitive Impairment/Dementia

Recommendation

4.14 In the presence of cognitive impairment, diabetes treatment plans should be simplified as much as possible and tailored to minimize the risk of hypoglycemia. **B**

Diabetes is associated with a significantly increased risk and rate of cognitive decline and an increased risk of dementia (104). A meta-analysis of prospective observational studies found that individuals with diabetes had a 43% higher risk of all types of dementia, a 43% higher risk of Alzheimer dementia, and a 91% higher risk of vascular dementia compared with individuals without diabetes (104). The reverse is also true: people with Alzheimer dementia are more likely to develop diabetes than people without Alzheimer dementia. In a 15-year prospective study of community-dwelling people >60 years of age, the presence of diabetes at baseline significantly increased the age-and sex-adjusted incidence of all-cause dementia, Alzheimer dementia, and vascular dementia compared with rates in those with normal glucose tolerance (105). A new clinical entity of diabetes-related dementia is being recognized as distinct from Alzheimer dementia or vascular dementia. It is characterized by slow progression of dementia, absence of typical neuroimaging findings seen in Alzheimer or vascular dementia, old age, high A1C levels, long duration of diabetes, high frequency of insulin use, frailty, and sarcopenia or dynapenia (106). See Section 13, "Older Adults," for a more detailed discussion regarding assessment of cognitive impairment.

Glycemic Status and Cognition

In individuals with diabetes, higher A1C level is associated with lower cognitive function (107). A meta-analysis of randomized trials found that intensive glycemic management, compared with higher A1C goals, was associated with a slightly lower rate of cognitive decline (108). However, these findings were driven by an older study with an A1C goal of <7.0% in the intensive treatment arm. Analyses within the ACCORD, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) studies found that intensive glycemic management (A1C goal of <6.0–6.5%) resulted in no differences in cognitive outcomes compared with standard control (108–110). Therefore, intensive glycemic management should not be advised for the improvement of cognitive function in individuals with type 2 diabetes. Additionally, people with type 2 diabetes and dementia are at heightened risk for experiencing hyperglycemic crises (diabetic ketoacidosis and hyperglycemic hyperosmolar state) compared with people without dementia (111), underscoring the importance of supporting diabetes management for individuals experiencing cognitive decline and diminished capacity for self-care. In addition, these individuals have increased difficulty with complex treatment and monitoring plans and are at risk of frailty, hypoglycemia, and disability (112).

In type 2 diabetes, severe hypoglycemia is associated with reduced cognitive function, and those with poor cognitive function have more severe or repeated episodes of hypoglycemia. Multiple observational studies of adults with diabetes have found an association between severe hypoglycemic episodes and cognitive decline or incident dementia (113–116). Decreased cognitive function also increases the risk for severe hypoglycemia, likely through impaired ability to recognize and respond appropriately to hypoglycemic symptoms (113,117,118). Additionally, long-term follow-up of Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) showed recurrent severe hypoglycemia was associated with the highest risk of long-term psychomotor and mental function decline (119). Simplifying or deintensifying glycemic therapy and/or liberalizing A1C goals may prevent hypoglycemia in individuals with cognitive dysfunction. See Section 13, "Older Adults," for more detailed discussion of hypoglycemia in older people with type 1 and type 2 diabetes.

Dental Care

Recommendations

4.15 People with diabetes should be referred for a dental exam at least once per year. **E**

4.16 Coordinate efforts between the medical and dental teams to appropriately adjust glucose-lowering medication and treatment plans prior to and in the post–dental procedure period as needed. **B**

Periodontal disease is more severe, and may be more prevalent, in people with diabetes than in those without and has been associated with higher A1C levels (120–122). Longitudinal studies suggest that people with periodontal disease have higher rates of incident diabetes. Current evidence suggests that periodontal disease adversely affects diabetes outcomes, and periodontal treatment using subgingival instrumentation may improve glycemic outcomes (123,124). In a randomized controlled trial (RCT), intensive periodontal treatment was associated with better glycemic outcomes (A1C 8.3% vs. 7.8% in control subjects and the intensive-treatment group, respectively) and

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reduction in inflammatory markers after 12 months of follow-up (125).

Dental health professionals should be included in the diabetes care team (126). Early detection of oral health problems by clinicians may be helpful to promote prompt referral to dental care and mitigate the expensive and extensive procedures needed to treat advanced oral disease (127,128). Clinical assessment of people with diabetes should include a dental history, and dental professionals should be informed about key aspects of the person's health and diabetes treatment plan, including glycemic goals, medications, and comorbid conditions (127,128). It is important for dental professionals to know when people with diabetes have high A1C levels, as this population may have lower oral healing capacity (129,130). Hepatic, renal, and pulmonary conditions should also be known by dental professionals to assist in appropriate dosing of antibiotics and other medications. Coordination between dental professionals and the diabetes care team will be especially important for people treated with insulin, sulfonylureas, or meglitinides who are at risk of hypoglycemia during dental procedures, especially if fasting. The risk of hypoglycemia can be mitigated by coordination between the dentist and treating clinician prior to the procedure to make a hypoglycemia prevention plan, which may include medication adjustment, blood glucose monitoring before and during the procedure, and treatment of hypoglycemia if appropriate. Therefore, dental professionals caring for people with diabetes should have access to blood glucose monitors during procedures as well as carbohydrates and glucagon to treat any hypoglycemia that occurs.

Disability

Recommendation

4.17 Assess for disability at the initial visit and for decline in function at each subsequent visit in people with diabetes. If a disability is impacting functional ability or capacity to manage their diabetes, a referral should be made to an appropriate health care professional specializing in disability (e.g., physical medicine and rehabilitation specialist, physical therapist, occupational therapist, or speech-language pathologist). **C**

A disability is defined as a physical or mental impairment that substantially limits one or more major life activities of an individual (131,132). Activities of daily living (ADLs) and instrumental activities of daily living (IADLs) comprise basic and complex life care tasks, respectively. The capacity to accomplish such tasks serves as an important measure of function. Diabetes is associated with an increase in the risk of work and physical disability, with estimates of 50–80% increased risk of disability for people with diabetes compared with people without diabetes (133). Reviews have shown that lower-body functional limitation was the most prevalent disability (47–84%) among people with diabetes (134,135). In a systematic review and meta-analysis, the presence of diabetes increased the risk of mobility disability (15 studies; odds ratio [OR] 1.71 [95% CI 1.53–1.91]; RR 1.51 [95% CI 1.38–1.64]), of IADL disability (10 studies; OR 1.65 [95% CI 1.55–1.74]), and of ADL disability (16 studies; OR 1.82 [95% CI 1.63–2.04]; RR 1.82 [95% CI 1.40–2.36]) (133). The mechanisms underlying disability are multifactorial and include obesity, coronary artery disease, stroke, lower extremity complications, and physiological factors such as hyperglycemia, sarcopenia, inflammation, and insulin resistance (136).

Diabetic peripheral neuropathy (DPN) is a common complication of both type 1 and 2 diabetes and may cause impaired postural balance and gait kinematics (137), leading to functional disability. DPN can be found in up to half of people with type 1 or type 2 diabetes, resulting in physical disability, and neuropathic pain, resulting in a diminished quality of life (138). Glycemic management prevents DPN development in type 1 diabetes; in contrast, glycemic management has modest or no benefit in individuals with type 2 diabetes, possibly due to the combined effect of coexisting comorbidities (138). People with lower-extremity involvement due to DPN have 3 times more risk of restricted mobility, resulting in people with DPN experiencing more physical dysfunctions and impairments than people who have diabetes but not neuropathy (139). Furthermore, DPN may progress to nontraumatic lower-limb amputation, which significantly impacts quality of life (140).

In addition to complications of diabetes from microvascular conditions such as CKD, retinopathy, autonomic neuropathy, and peripheral neuropathy, it is important to recognize the disabilities caused by macrovascular complications of diabetes. These macrovascular complications, which include coronary heart disease, stroke, and peripheral arterial disease, can lead to further impairments (134).

An assessment of disability should be performed as necessary with referrals made to appropriate health care professionals specializing in disability (e.g., physical medicine and rehabilitation physician, physical therapist, occupational therapist, or speech-language pathologist) (133,141,142). Customized rehabilitation interventions for individuals with a disability from diabetes can recover function, allowing for safe physical activity (143), and improve quality of life (144). Additionally, frailty is commonly associated with diabetes, with progression to disability, morbidity, and mortality in older adults. People with diabetes as well as frailty or disability may contend with comorbid conditions such as hypoglycemia, sarcopenia, falls, and cognitive dysfunction. A thorough medical evaluation is imperative to identify the best approaches to preventative and therapeutic interventions for frailty and diabetes management (145).

To assess the impact of diabetes on an individual's daily functioning, clinicians should consider evaluating their ability to perform ADLs and IADLs, ensuring they can manage basic self-care and more complex tasks necessary for specific living situations, services, and supports. A psychosocial assessment should be conducted to screen for behavioral health conditions like depression and anxiety and to understand the individual's social support and coping mechanisms. Functional capacity evaluations, involving tests for physical endurance and strength, are used to gauge the ability of the person with diabetes to work and carry out daily activities. Additionally, standardized disability questionnaires and scales, such as the Diabetes Distress Scale (DDS) and the World Health Organization Disability Assessment Schedule (WHODAS 2.0), are employed to measure the emotional burden of diabetes and overall disability (146,147). These suggested structured assessments are particularly relevant if individuals have fallen, had emergency department visits, missed appointments, made significant errors in the treatment plan, or exhibit apathy and depressed mood.

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Moreover, when treating people with an acquired disability from diabetes, it is vital to consider social determinants of health, race and ethnicity, and socioeconomic status (148). Rates of diabetes-related major amputations are higher in individuals who are from racial and ethnic minoritized groups (149), live in rural areas, and are from regions with the lowest socioeconomic levels (150). Addressing the complex challenges faced by individuals with acquired disabilities from diabetes requires a multifaceted approach involving solutions from both within and outside the health care system. By focusing on social determinants of health, health care professionals can develop appropriate interventions, provide advocacy, and establish support systems that cater to the specific needs of this population. See Section 1, "Improving Care and Promoting Health in Populations."

Hepatitis C

Infection with hepatitis C virus (HCV) is associated with a higher prevalence of type 2 diabetes, which is present in up to one-third of individuals with chronic HCV infection. HCV may impair glucose metabolism by several mechanisms, including directly via viral proteins and indirectly by altering proinflammatory cytokine levels (151). The use of newer direct-acting antiviral drugs produces a sustained virological response (cure) in nearly all cases and has been reported to improve glucose metabolism in individuals with diabetes (152). A meta-analysis of mostly observational studies found a mean reduction in A1C levels of 0.45% (95% CI –0.60 to –0.30) and reduced requirement for glucose-lowering medication use following successful eradication of HCV infection (153).

Low Testosterone in Men

Recommendation

4.18 In men with diabetes or prediabetes, inquire about sexual health (e.g., low libido and erectile dysfunction [ED]). If symptoms and/or signs of hypogonadism are detected (e.g., low libido, ED, and depression), screen with a morning serum total testosterone level. **B**

Mean levels of testosterone are lower in men with diabetes than in age-matched men without diabetes, but obesity is a major confounder (154,155). Testosterone replacement in men with symptomatic hypogonadism may have benefits, including improved sexual function, well-being, muscle mass and strength, and bone density (156). In men with diabetes who have symptoms or signs of low testosterone (hypogonadism), a morning total testosterone level should be measured using an accurate and reliable assay (157). In men who have total testosterone levels close to the lower limit, it is reasonable to determine free testosterone concentrations either directly from equilibrium dialysis assays or by calculations that use total testosterone, sex hormone binding globulin, and albumin concentrations (157). Further tests (such as luteinizing hormone and follicle-stimulating hormone levels) may be needed to further evaluate the individual. Testosterone replacement in older men with hypogonadism has been associated with increased coronary artery plaque volume, with no conclusive evidence that testosterone supplementation is associated with increased cardiovascular risk in all men with hypogonadism (157). Furthermore, erectile dysfunction (ED) is also common in people with diabetes (158), and it is reasonable to measure and correct testosterone levels close to the lower limit to address the desire component that contributes to erectile difficulties (159) (see ERECTILE DYSFUNCTION, below, for more information on evaluation and further discussion).

Erectile Dysfunction

Recommendation

4.19 In men with diabetes or prediabetes, screen for ED, particularly in those with high cardiovascular risk, retinopathy, cardiovascular disease, chronic kidney disease, peripheral or autonomic neuropathy, longer duration of diabetes, depression, and hypogonadism, and in those who are not meeting glycemic goals. **B**

The most common sexual dysfunction in men is ED, with an estimated prevalence of 52.5% in men with diabetes (160). The best predictors of ED are age (>40 years), CVD, diabetes, hypertension, obesity, dyslipidemia, metabolic syndrome, hypogonadism, smoking, depression, and use of medications such as antidepressants and opioids (161,162). Because diabetes, poor nutrition, obesity, lack of exercise, and CVD are often interrelated, it may be challenging to identify the primary risk factor (159), although the most likely primary underlying risk factor is vascular disease (159).

Men with diabetes are at increased risk for both CVD and ED, and ED is a predictor of cardiovascular events in men with diabetes (163,164) as well as in men without diabetes. The significant factors associated with ED in men with diabetes are age, peripheral or autonomic neuropathy, presence of microvascular disease including retinopathy, CVD, duration of diabetes, poor glycemic management, hypogonadism, and diuretic therapy (165). Physical activity may be protective. Men with diabetes and ED report a significant decline in quality-of-life measures and an increase in depressive symptoms (166), and depression is a well-recognized risk factor for ED. Given the bidirectional relationship between ED and depression, treatment of either one can result in improvement in the other condition. CKD is also a risk factor for CVD and ED, with prevalence rates of ED >75% in men on hemodialysis (167).

Awareness and identification of these characteristics, factors, and behaviors can guide clinicians in early screening, treatment, prevention, and counseling in all men with diabetes and particularly those at higher risk for ED (165). Given the evidence that ED is strongly associated with diabetes and CVD, men with ED should be evaluated and managed for cardiovascular and endocrine risk factors. Glycemic assessment in men not previously diagnosed with diabetes, lipid profile, and morning total testosterone should be considered mandatory in all men newly presenting with ED (168).

In a recent meta-analysis, testosterone was superior to placebo in improving erectile function in men with testosterone deficiency; however, the magnitude of the effect was lower in the presence of diabetes and obesity (169).

Meta-analyses show that all phosphodiesterase type 5 inhibitors (PDE5Is) are superior to placebo in treating ED, lower dosages had effects comparable with those of higher dosages, and various PDE5Is show comparable efficacy (159). PDE5Is are associated with an increased risk of headaches, flushing, and dyspepsia (159). First-line therapy for ED in men with diabetes is PDE5Is, but men with diabetes may be less responsive than men without diabetes (160). Strategies to improve response to PDE5Is include daily therapy and

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optimization of comorbidities. In men with diabetes not responding to PDEIs, other potentially effective treatments may include intracavernosal injections, intraurethral prostaglandin, vacuum erection devices, and penile prosthetic surgery (160).

Female Sexual Dysfunction

Recommendations

4.20 In women with diabetes or prediabetes, inquire about sexual health by screening for desire (libido), arousal, and orgasm difficulties, particularly in those who experience depression and/or anxiety and those with recurrent urinary tract infections. **B**

4.21 In postmenopausal women with diabetes or prediabetes, screen for symptoms and/or signs of genitourinary syndrome of menopause, including vaginal dryness and dyspareunia. **B**

Female sexual dysfunction (FSD) is common in women with diabetes. In an epidemiologic cross-sectional study of community-residing middle-aged and older adults (57–85 years), women with diagnosed diabetes were less likely than men with diagnosed diabetes (adjusted OR 0.28 [95% CI 0.16–0.49]) and women without diabetes (0.63 [0.45–0.87]) to be sexually active (170). Older women with diabetes are as likely as men to have sexual problems but are significantly less likely to have discussed sex with a physician (170).

While studies showing the association between diabetes and FSD are less conclusive than those in men, most have reported a higher prevalence of FSD in women with diabetes compared with women without diabetes (171). A meta-analysis found that sexual dysfunctions are more common in women with type 1 and type 2 diabetes (OR 2.27 and 2.49, respectively) than in women without diabetes (172).

Reviews report a wide range of prevalence rates of sexual dysfunctions in women with diabetes. In women with type 1 diabetes, 16–85% (vs. 0–66% in women without diabetes) report problems with desire, 11–76% (vs. 0–41%) report problems with arousal, and 9–66% (vs. 0–39%) report problems with orgasm; 9–57% (vs. 0–28%) report problems with lubrication, and 7–61% (vs. 5–39%) report problems with pain. In women with type 2 diabetes, 70–82% (vs. 10–66% in women without diabetes) report problems with desire, 54–68% (vs. 3–41%) report problems with arousal, and 33–84% (vs. 2–39%) report problems with orgasm; 33–66% (vs. 4–28%) report problems with lubrication, and 33–46% (vs. 8–39%) report problems with pain (173).

The Diabetes MILES (Management and Impact for Long-term Empowerment and Success) study examined the prevalence of sexual dysfunction in sexually active women with type 1 or type 2 diabetes and the associations between sexual dysfunction and clinical and psychological variables. Overall, 33% of women reported sexual dysfunction (type 1, 36.0%; type 2, 26.2%). The prevalence of specific FSDs according to diabetes type was decreased desire (type 1, 22%; type 2, 15%), decreased arousal (type 1, 9%; type 2, 11%), lubrication problems (type 1, 19%; type 2, 14%), and orgasmic dysfunction (type 1, 16%; type 2, 15%) (173).

Medical comorbidities that are risk factors for FSD include hypertension, obesity, metabolic syndrome, smoking, and hyperlipidemia. Clinical factors for consideration include longer duration of diabetic retinopathy and neuropathy and individuals not meeting glycemic goals. The prevalence of FSD in women with end-stage kidney disease is 74% (174).

In women with diabetes, social and psychological components play a major role in FSD. Depression, anxiety, and emotional adjustments to diabetes have been found to be associated with sexual dysfunctions in women with diabetes. A study from Norway reported that women with type 1 diabetes with scores on the Female Sexual Function Index (FSFI) (a validated instrument) indicating sexual dysfunction were more likely than women without sexual dysfunction to have diabetes distress, depression, and menopausal symptoms. They were also older and more likely to be single and postmenopausal (175). Another study also showed that women with sexual dysfunction were significantly more likely to report impaired well-being, have elevated diabetes distress, have poor adjustment to diabetes, and have more moderate to severe anxiety than women without sexual dysfunctions (173).

In a qualitative study exploring the experiences of sexual health and sexual challenges, women with type 1 diabetes reported that diabetes affected their relationship, including sex life, and had an impact on their partner. Challenges included reduced sexual desire, decline in frequency, less spontaneous desire resulting in lack of initiation, and physical challenges such as pain, vaginal dryness, and impaired sensitivity. Several women explained that vaginal dryness was an obstacle during sexual intercourse, leading to pain or even refraining from sexual activity. Sexual challenges were perceived to become a source of disappointment to the partners and consequential guilt for the women. Women also reported fear of hypoglycemia during sex, and some reported trying to maintain mild hyperglycemia. Technology devices, such as glucose monitors and insulin pumps, could be perceived as both a physical and mental obstacle during sexual activity (176).

Women with type 2 (25%) or type 1 (17%) diabetes would like their health care professional to initiate a discussion on how diabetes is affecting their sex life (177). Women with type 1 diabetes almost unanimously endorsed that sexual health should be addressed, that they would find it a relief that they were not alone, that they should be provided with information when they are young, and that it would be difficult to address the topic themselves (176). Unfortunately, many health care professionals do not actively discuss sexual functioning in consultations, meaning that when the topic is discussed it is mostly the person with diabetes who initiates the conversation (170). This leads to a marked underdiagnosis and undertreatment of sexual dysfunctions in people with diabetes.

While no specific guidelines are available for the treatment of FSD in this population, women with type 1 or type 2 diabetes should be encouraged to engage in lifestyle interventions and, in the absence of contraindications, may benefit from already-approved treatments for FSD (178). The Look AHEAD (Action for Health in Diabetes) study on intervention demonstrated statistical improvements in the FSFI total score and all domains of sexual dysfunction (179). Lifestyle factors that enhance desire and sexual function include nutrition (such as the Mediterranean eating pattern), exercise (such as walking), and smoking cessation. Other interventions include improving glycemic management and prevention of diabetes complications; diagnosis and treatment of menopausal symptoms with hormonal therapies; addressing vaginal dryness and dyspareunia as well as urinary tract and mycotic genital infections; screening and addressing depression, anxiety, diabetes distress, and

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related psychosocial issues; and considering FDA-approved centrally acting medications for hypoactive sexual desire disorder, including flibanserin and bremelanotide.

Metabolic Dysfunction–Associated Steatotic Liver Disease and Metabolic Dysfunction–Associated Steatohepatitis

Screening

Recommendations

4.22a Screen adults with type 2 diabetes or with prediabetes, particularly those with obesity or other cardiometabolic risk factors or established cardiovascular disease, for their risk of having or developing cirrhosis related to metabolic dysfunction–associated steatohepatitis (MASH) using a calculated fibrosis-4 index (FIB-4) (derived from age, ALT, AST, and platelets [mdcalc.com/calc/2200/fibrosis4-fib-4-index-liver-fibrosis]), even if they have normal liver enzymes. **B**

4.22b Adults with diabetes or prediabetes with persistently elevated plasma aminotransferase levels for >6 months and low FIB-4 should be evaluated for other causes of liver disease. **B**

4.23 Adults with type 2 diabetes or prediabetes with a FIB-4 ≥1.3 should have additional risk stratification by liver stiffness measurement with transient elastography, or, if unavailable, the enhanced liver fibrosis (ELF) test. **B**

4.24 Refer adults with type 2 diabetes or prediabetes at higher risk for significant liver fibrosis (i.e., as indicated by FIB-4, liver stiffness measurement, or ELF) to a gastroenterologist or hepatologist for further evaluation and management. **B**

Metabolic dysfunction–associated steatotic liver disease (MASLD) has replaced the term nonalcoholic fatty liver disease (NAFLD) to identify steatotic liver disease. The definition includes the presence of steatotic liver disease and at least one cardiometabolic risk factor associated with insulin resistance (e.g., prediabetes, diabetes, atherogenic dyslipidemia, or hypertension) without other identifiable causes of steatosis (180). This is in the absence of ongoing or recent consumption of significant amounts of alcohol (defined as ingestion of >21 standard drinks per week in men and >14 standard drinks per week in women over a 2-year period preceding evaluation) or other secondary causes of hepatic steatosis (181). It is estimated that in adults in the U.S., the prevalence of MASLD is >70% of people with type 2 diabetes (182–184). This is consistent with studies from other countries (185,186). The new definition of MASLD aims to remove potential stigma from the term "fatty" when referring to steatosis, highlights the role of prediabetes and type 2 diabetes in MASLD, and provides a positive diagnosis by using cardiometabolic risk factors as surrogates for insulin resistance, the main driver for the development of steatosis. The new definition correlates well with the past definition of MASLD for people with prediabetes or type 2 diabetes (who already have, by definition, one cardiometabolic risk factor) (187,188). A separate category outside of MASLD, named metabolic dysfunction and alcoholic liver disease, was created for circumstances in which alcohol intake is greater than that allowed for MASLD but less than that attributed to alcoholic liver disease. More research is needed to better characterize the predictive value for metabolic dysfunction–associated steatohepatitis (MASH) of different cardiometabolic risk factors and the natural history of metabolic dysfunction and alcoholic liver disease or steatosis in young adults without cardiometabolic risk factors.

Diabetes is a major risk factor for developing MASH (formerly nonalcoholic steatohepatitis, or NASH) and worse liver outcomes (185,186). MASH is defined histologically as having ≥5% hepatic steatosis with inflammation and hepatocyte injury (hepatocyte ballooning), with or without evidence of liver fibrosis (181). Steatohepatitis is estimated to affect more than half of people with type 2 diabetes with MASLD (189,190). Fibrosis stages are classified histologically as the following: F0, no fibrosis; F1, mild; F2, moderate (significant); F3, severe (advanced); and F4, cirrhosis. In the U.S., between 12% and 20% of people with type 2 diabetes have "at-risk" MASH (i.e., steatohepatitis with clinically significant fibrosis [≥F2] and at risk for cirrhosis) (182,183,189). A similar or higher prevalence has been observed worldwide (185,186,190). People with type 2 diabetes and at-risk MASH are at an increased risk of future cirrhosis, hepatocellular carcinoma (HCC) (191,192), and liver transplantation (193). The prevalence of MASLD in people with type 1 diabetes is ∼20% and is driven by obesity, which is becoming more common in this population (194), with a large variability across studies using different steatosis measurement methods (195). The prevalence of liver steatosis in a population with type 1 diabetes by MRI (i.e., the gold standard) with low prevalence of obesity was only 8.8% compared with 68% in people with type 2 diabetes (196). The prevalence of clinically significant fibrosis (≥F2) is estimated to be ∼5% (197), which is much lower than the prevalence in type 2 diabetes (182,183,189). Therefore, screening for fibrosis in people with type 1 diabetes should only be considered in the presence of additional risk factors for MASLD, such as obesity, incidental hepatic steatosis on imaging, or elevated plasma aminotransferases.

Clinicians underestimate the prevalence of at-risk MASH and do not consistently implement appropriate screening strategies in people with prediabetes or type 2 diabetes, thus missing a chance to establish an early diagnosis (198). This pattern of underdiagnosis is compounded by sparse referral to specialists and inadequate prescription of medications with potential efficacy in MASH (199,200). The goal of screening for MASLD is to identify people with at-risk MASH to prevent future cirrhosis, HCC, liver transplantation, and all-cause mortality (201–204). This risk is higher in people who have central obesity and cardiometabolic risk factors or insulin resistance, are >50 years of age, and/or have persistently elevated plasma aminotransferases (AST and/or ALT >30 units/L for >6 months) (205,206). Some genetic variants that alter hepatocyte triglyceride metabolism may also increase the risk of MASH progression and cirrhosis (207,208), amplifying the impact of obesity, but the role of genetic testing in clinical practice remains to be established. Individuals with MASLD also are at a greater risk of developing extrahepatic cancer (192), type 2 diabetes (209), and CVD (210,211). Emerging evidence suggests that MASLD increases the risk of CKD in people with type 2 diabetes, particularly when liver fibrosis is present (212,213), although the association of MASLD with diabetic retinopathy is less clear (214).

The fibrosis-4 index (FIB-4) is the most cost-effective strategy for the initial screening of people with prediabetes and cardiometabolic risk factors or with type 2 diabetes for at-risk MASH in

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primary care and diabetes clinical settings (186,200,205,206,215–217). The diagnostic algorithm for the screening and liver fibrosis risk stratification of people with prediabetes or type 2 diabetes is shown in **Fig. 4.2**. A screening strategy relying on elevated plasma aminotransferases >40 units/L would miss most individuals with MASH in these settings, as at-risk MASH with clinically significant fibrosis (≥F2) is frequently observed with plasma aminotransferases below the commonly used cutoff of 40 units/L (182–184,189,218,219). The American College of Gastroenterology considers the upper limit of normal ALT levels to be 29–33 units/L for male individuals and 19–25 units/L for female individuals (220), as higher levels are associated with increased liver-related mortality. The FIB-4 estimates the risk of hepatic cirrhosis and is calculated from the computation of age, plasma aminotransferases (AST and ALT), and platelet count (mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis). A value of <1.3 is considered low risk of having advanced fibrosis (F3–F4) and for developing adverse liver outcomes, while ≥1.3 is considered as having a higher probability of at-risk MASH clinically significant fibrosis (≥F2) and increased risk of adverse liver outcomes. A value of >2.67 confers a high risk of having advanced fibrosis (F3–F4), and referral to the liver specialist is warranted without additional testing. FIB-4 predicts changes over time in hepatic fibrosis (221,222) and allows risk stratification of individuals in terms of future liver-related morbidity and mortality (223). FIB-4 has reasonable specificity but low sensitivity, hence a negative result rules out fibrosis while a positive result requires confirmatory testing (222,224,225). Its low cost, simplicity, and good specificity make it the initial test of choice (**Fig. 4.2**). FIB-4 has not been validated in pediatric populations or in adults aged <35 years. In people with diabetes ≥65 years of age, higher cutoffs for FIB-4 have been recommended (1.9–2.0 rather than ≥1.3) (226).

In people with a FIB-4 ≥1.3, there is need for additional risk stratification with a liver stiffness measurement (LSM) by transient elastography (**Fig. 4.2**). Use of a second nonproprietary diagnostic panel is not recommended (e.g., MASLD fibrosis score and others), as they generally do not perform better than FIB-4 (181,184,224). Transient elastography (LSM) is the best-validated imaging technique for fibrosis risk stratification, and it predicts future cirrhosis and all-cause mortality in MASLD (205,206,227). An LSM value of <8.0 kPa has a good negative predictive value to exclude advanced fibrosis (≥F3–F4) (228–230) and indicates lower risk for clinically significant fibrosis. Such individuals with prediabetes or type 2 diabetes can be followed in nonspecialty clinics with repeat surveillance testing every ≥2 years, although the precise time interval remains to be established. If the LSM is ≥8.0 kPa, the risk for advanced fibrosis (≥F3–F4) is higher and such individuals should be referred to the hepatologist (181,189,205,206) within the framework of an interprofessional team (231–233). FIB-4 followed by LSM helps stratify people with diabetes by risk level and minimize specialty referrals (227,234–237) (**Fig. 4.2**). Given the lack of widespread availability of LSM, the ELF test is a good alternative (238). Individuals with ELF <9.8 are considered at low risk for adverse liver outcomes. Individuals with ELF ≥9.8 are considered at high risk of having MASH with advanced liver fibrosis (≥F3–F4) and

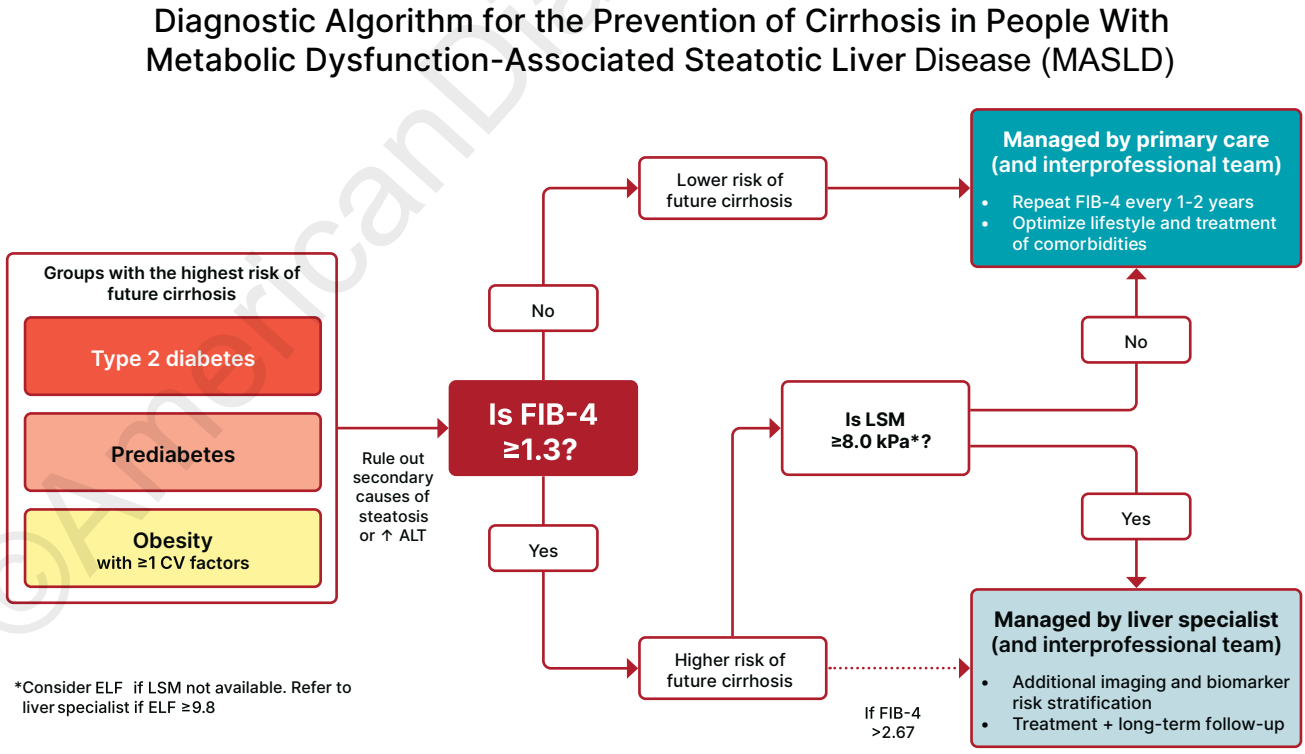

Figure 4.2—Diagnostic algorithm for risk stratification and the prevention of cirrhosis in individuals with metabolic dysfunction–associated steatotic liver disease (MASLD). CV, cardiovascular; ELF, enhanced liver fibrosis test; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement, as measured by vibration-controlled transient elastography. *In the absence of LSM, consider ELF a diagnostic alternative. If ELF ≥9.8, an individual is at high risk of metabolic dysfunction–associated steatohepatitis with advanced liver fibrosis (≥F3–F4) and should be referred to a liver specialist.

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therefore are at risk for adverse liver outcomes (181,217). They should be referred to a gastroenterologist or hepatologist. The optimal cutoff for clinical use of ELF in primary care and endocrinology settings is evolving (239–242). An ELF <9.8 suggests an individual is at low risk of advanced liver fibrosis and may be followed in the nonspecialty clinic with repeat testing in ≥2 years but may need repeat testing more often if ELF is between 9.2 and 9.7.

Specialists may order additional tests for fibrosis risk stratification in MASH (180,205,206,217), including magnetic resonance elastography (MRE) (best overall performance, particularly for early fibrosis stages) or multiparametric iron-corrected T1 MRI (cT1) (243) and patented blood-based fibrosis biomarkers. While liver biopsy remains the gold standard for the diagnosis of MASH, its indication is reserved to the discretion of the specialist within an interprofessional team approach due to high costs and potential for morbidity associated with this procedure.

Management

Recommendations

4.25 Adults with type 2 diabetes or prediabetes, particularly with overweight or obesity, who have metabolic dysfunction–associated steatotic liver disease (MASLD) should be recommended lifestyle changes using an interprofessional approach that promotes weight loss, ideally within a structured nutrition plan and physical activity program for cardiometabolic benefits **B** and histological improvement. **C**

4.26 In adults with type 2 diabetes, MASLD, and overweight or obesity, consider using a glucagon-like peptide 1 (GLP-1) receptor agonist (RA) or a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA for the treatment of obesity with potential benefits in MASH as an adjunctive therapy to lifestyle interventions for weight loss. **B**

4.27a In adults with type 2 diabetes and biopsy-proven MASH or those at high risk for liver fibrosis (based on noninvasive tests), pioglitazone, a GLP-1 RA, or a dual GIP and GLP-1 RA is preferred for glycemic management because of potential beneficial effects on MASH. **B**

4.27b Combination therapy with pioglitazone plus GLP-1 RA can be considered for the treatment of hyperglycemia in adults with type 2 diabetes with biopsy-proven MASH or those at high risk of liver fibrosis (identified with noninvasive tests) because of potential beneficial effects on MASH.**B**

4.28 For consideration of treatment with a thyroid hormone receptor-β agonist in adults with type 2 diabetes or prediabetes with MASLD with moderate (F2) or advanced (F3) liver fibrosis on liver histology, or by a validated imaging-based or blood-based test, refer to a gastroenterologist or hepatologist with expertise in MASLD management. **A**

4.29 Treatment initiation and monitoring should be individualized and within the context of an interprofessional team that includes a gastroenterologist or hepatologist, consideration of individual preferences, and a careful shared-decision cost-benefit discussion. **B**

4.30a In adults with type 2 diabetes and MASLD, use of glucose-lowering therapies other than pioglitazone or GLP-1 RAs may be continued as clinically indicated, but these therapies lack evidence of benefit in MASH. **B**

4.30b Insulin therapy is the preferred agent for the treatment of hyperglycemia in adults with type 2 diabetes with decompensated cirrhosis. **C**

4.31a Adults with type 2 diabetes and MASLD are at increased cardiovascular risk; therefore, comprehensive management of cardiovascular risk factors is recommended. **B**

4.31b Statin therapy is safe in adults with type 2 diabetes and compensated cirrhosis from MASLD and should be initiated or continued for cardiovascular risk reduction as clinically indicated. **B** In people with decompensated cirrhosis, statin therapy should be used with caution, and close monitoring is needed, given limited safety and efficacy data. **B**

4.32a Consider metabolic surgery in appropriate candidates as an option to treat MASH in adults with type 2 diabetes **B** and to improve cardiovascular outcomes. **B**

4.32b Metabolic surgery should be used with caution in adults with type 2 diabetes with compensated cirrhosis from MASLD **B** and is not recommended in decompensated cirrhosis. **B**

While steatohepatitis and cirrhosis occur in lean people with diabetes and are believed to be linked to genetic predisposition, insulin resistance, and environmental factors (244,245), ample evidence implicates excess visceral fat and overall adiposity in people with overweight and obesity in the pathogenesis of the disease (246,247). Obesity in the setting of type 2 diabetes worsens insulin resistance and steatohepatitis, promoting the development of cirrhosis (248). Therefore, clinicians should enact evidence-based interventions (as discussed in Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes") to promote healthy lifestyle change and weight loss for people with overweight or obesity and MASLD. There is consensus that a minimum weight loss goal of 5%, preferably ≥10%, is needed to improve liver histology (181,205,206,217), with fibrosis requiring the larger weight reduction to promote change (249,250). However, there is significant individual variability in histological outcomes with weight loss. Individualized, structured weight loss and exercise programs offer greater benefit than standard counseling in people with MASLD (251).

Dietary recommendations to induce an energy deficit are not different from those for people with diabetes with obesity without MASLD and should include a reduction of macronutrient content, limiting saturated fat, starch, and added sugar, with adoption of healthier eating patterns. The Mediterranean eating pattern has the best evidence for improving liver and cardiometabolic health (205,215–217,251). Both aerobic and resistance training improve MASLD in proportion to treatment engagement and intensity of the program (252). Obesity pharmacotherapy may assist with weight loss in the context of lifestyle modification if not achieved by lifestyle modification alone (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes").

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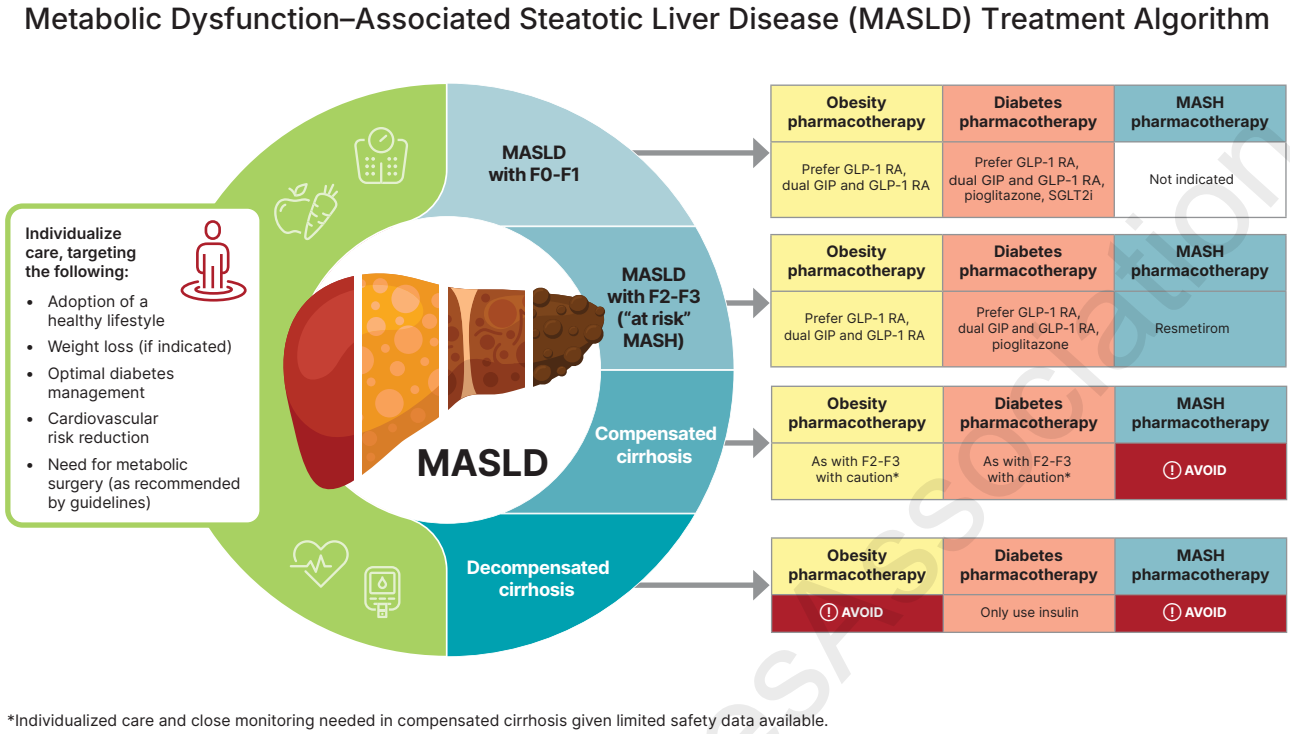

*Individualized care and close monitoring needed in compensated cirrhosis given limited safety data available.

Figure 4.3—Metabolic dysfunction–associated steatotic liver disease (MASLD) treatment algorithm. F0-F1, no to minimal fibrosis; F2-F3, moderate fibrosis; F4, cirrhosis; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MASH, metabolic dysfunction–associated steatohepatitis; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Given the high prevalence of at-risk MASH (~12–20%) (182–184,186,189), higher risk of disease progression and liver-related mortality (185,204,253), and the lack of pharmacological treatments once cirrhosis is established (254,255), optimizing the pharmacological management of hyperglycemia and obesity in people with type 2 diabetes and MASH could serve the dual purpose of addressing these comorbidities while treating the liver disease (**Fig. 4.3**). Therefore, early diagnosis and treatment of MASLD offers the best opportunity for cirrhosis prevention. In phase 2 clinical trials, pioglitazone and some GLP-1 RAs have been shown to be potentially effective to treat steatohepatitis (205,256–259) and to slow fibrosis progression (260–262). They may also decrease CVD (257), which is the number one cause of death in people with type 2 diabetes and MASLD (210). Evidence from phase 3 clinical trials still are not fully published (e.g., a phase 3 study on semaglutide, The Effect of Semaglutide in Subjects With Non-cirrhotic Non- alcoholic Steatohepatitis [ESSENSE] trial, is predicted to be published in 2025) (263), and no glucose-lowering or weight management medication is FDA approved for the treatment of MASH. The recommendation to treat hyperglycemia with GLP-1 RAs and/or pioglitazone in people with type 2 diabetes and MASLD is based on consistent histological benefit for steatohepatitis in several phase 2 RCTs with GLP-1 RAs and with pioglitazone (264–268) compared with no benefit with metformin or other glucose-lowering medications in MASH (181,205,206).

Pioglitazone improves glucose and lipid metabolism and reverses steatohepatitis in people with prediabetes or type 2 diabetes (261,264,265) and even in individuals without diabetes (266–268) (**Fig. 4.3**). Fibrosis also improved in some trials (265,267). A meta-analysis (260) concluded that pioglitazone treatment results in resolution of MASH and may improve fibrosis. Furthermore, combination therapy with pioglitazone plus a GLP-1 RA has been reported safe and effective for the treatment of hyperglycemia in adults with type 2 diabetes (269–272) as well as in reducing hepatic steatosis (269,271), suggesting additive benefit in individuals with MASLD. It is important to note that these studies are based on phase 2 clinical trials and await further phase 3 evidence. However, these plans are attractive because they offer potential benefit compared with lack of histological benefit (or clinical trial data) from other oral glucose-lowering therapies in MASLD. In the context of treating hyperglycemia in people with type 2 diabetes with MASLD, where the low cost of pioglitazone and any liver improvement would be an added benefit to glycemic management, these plans would be potentially cost-effective for the treatment of MASLD (273,274). Vitamin E may be beneficial for the treatment of MASH in people without diabetes (266). However, in people with type 2 diabetes, vitamin E monotherapy was found to be ineffective in a small RCT (261), and it did not seem to enhance pioglitazone's efficacy when used in combination, as reported in an earlier trial in this population (265). Pioglitazone causes dose-dependent weight gain (15 mg/day, mean weight gain of 1–2%; 45 mg/day, mean weight gain of 3–5%), which can be blunted or reversed if combined with SGLT2 inhibitors or GLP-1 RAs (257,271,272,275). Pioglitazone increases fracture risk, may promote heart failure if used in individuals with preexisting congestive heart failure, and may increase the risk of bladder cancer, although this remains controversial (181,205,206,257,258).

GLP-1 RAs are effective at inducing weight loss and ameliorating elevated

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plasma aminotransferases and steatosis (256) (**Fig. 4.3**). However, there are few phase 2 RCTs of GLP-1 RAs in individuals with MASH proven by biopsy. A small RCT reported that liraglutide improved some features of MASH and may delay fibrosis progression (276). Subcutaneous semaglutide treatment in 320 people with MASH (62% having type 2 diabetes) led to resolution of steatohepatitis without worsening of fibrosis in 59% of individuals at the higher dose (equivalent to 2.4 mg/week semaglutide) compared with 17% in the placebo group ($P < 0.001$) (262). Cumulatively, semaglutide did not significantly affect the stage of liver fibrosis in this group of people but, over 72 weeks, slowed the progression of liver fibrosis (4.9% with the GLP-1 RA at the highest dose compared with 18.8% on placebo). Tirzepatide is a dual GIP and GLP-1 RA known to reduce liver steatosis in MASLD (277), and a phase 2 paired-biopsy study of 190 adults with overweight or obesity with MASH (50–60% of whom had type 2 diabetes) recently reported that doses of 5, 10, and 15 mg/day resulted in resolution of steatohepatitis without worsening of fibrosis in 44%, 56%, and 62% of participants, respectively, compared with 10% of participants receiving placebo ($P < 0.001$ for all three comparisons) (278). Improvement of at least one fibrosis stage without worsening of MASH occurred in 55%, 51%, and 61% of participants, respectively, compared with 30% of participants receiving placebo. Survodutide is a dual GLP-1 and glucagon RA that is in development, and a phase 2 paired-biopsy trial recently reported benefit in MASH (279). In summary, GLP-1–based therapies and/or pioglitazone is recommended to treat type 2 diabetes in adults with MASH based on histological benefit for steatohepatitis in several phase 2 RCTs (278,279) compared with no benefit with metformin or other glucose-lowering or weight loss medications. Within the context of their approved indication (e.g., obesity or type 2 diabetes), these medications are cost-effective to treat the comorbidity, while potentially improving MASH, which becomes an added benefit.

SGLT2 inhibitors (280–282) and insulin (258) reduce hepatic steatosis, but their effects on steatohepatitis remain unknown. The use of glucose-lowering agents other than pioglitazone or GLP-1 RAs may be continued in individuals with type 2 diabetes and MASLD for glycemic management, as clinically indicated. However, these agents have either failed to improve steatohepatitis in paired-biopsy studies (metformin) or have no RCTs with liver histological end points (i.e., sulfonylureas, glitinides, dipeptidyl peptidase 4 inhibitors, or acarbose).

Resmetirom is a thyroid hormone receptor-β agonist approved by the FDA for the treatment of adults with MASLD with moderate (F2) or advanced (F3) liver fibrosis on liver histology or a validated imaging- or blood-based test. In a phase 3 RCT, resmetirom for 52 weeks in 966 adults at the highest dose of 100 mg (or placebo) met the primary end point of MASH resolution without worsening of fibrosis in 29.9% of participants compared with 9.7% on placebo ($P < 0.001$) (283). Fibrosis improved in up to 25.9% and 14.2%, respectively ($P < 0.001$). Nausea, vomiting, and diarrhea occurred more often with resmetirom. The gastrointestinal side effects are dose dependent and improve with continued treatment. Resmetirom decreased free thyroxine (T4) levels by ∼20% and increased sex hormone-binding protein levels two- to threefold. Although a recent review of the data concluded that there is little concern about these changes, long-term postmarketing data must be collected (284,285). Guidance by the American Association for the Study of Liver Diseases (AASLD) about optimal individual identification for treatment, safety, and long-term monitoring has recently been published (286). This is especially relevant because hypothyroidism and hypogonadism are more prevalent in people with MASLD than in the general population (181,205), and clinicians should monitor all individuals with MASLD for symptoms of endocrine deficiency and manage according to clinical practice guidelines. Per its label, candidates for resmetirom treatment are those with MASLD and moderate (F2) to advanced (F3) liver fibrosis but not with cirrhosis or other active liver disease (i.e., alcohol-related liver disease, autoimmune hepatitis, or primary biliary cholangitis) or unmanaged hypothyroidism or hyperthyroidism. Given complexities associated with selection of an individual for therapy, drug cost, and treatment monitoring, therapy should be individualized and initiated by a hepatologist or gastroenterologist with expertise in MASH within an interprofessional team.

Insulin is the preferred glucose-lowering agent for the treatment of hyperglycemia in adults with type 2 diabetes with decompensated cirrhosis given the lack of robust evidence about the safety and efficacy of oral agents and noninsulin injectables (i.e., GLP-1 RAs and dual GIP and GLP-1 RAs) (255), although a recent 48-week study suggested that GLP-1 RAs are safe in individuals with MASH and compensated cirrhosis (287).

Metabolic surgery leading to sustained weight loss and improvement of type 2 diabetes can improve MASH and cardiometabolic health, altering the natural history of the disease (288). Meta-analyses report that 70–80% of people have improvement in hepatic steatosis, 50–75% of people have improvement in inflammation and hepatocyte ballooning (necrosis), and 30–40% of people have improvement in fibrosis (289,290). It may also reduce the risk of HCC (290). It is important to note that currently metabolic surgery is not indicated solely for treatment of MASH. Given that many individuals with MASH have metabolic risks (type 2 diabetes and obesity) that are indications for metabolic surgery, the improvement in liver health is expected, but surgical indication should follow current practice guidelines. Metabolic surgery should be used with caution in individuals with compensated cirrhosis (i.e., asymptomatic stage of cirrhosis without associated liver complications), but with experienced surgeons the risk of hepatic decompensation is similar to that for individuals with less advanced liver disease. Because of the paucity of safety and outcome data, metabolic surgery is not recommended in individuals with decompensated cirrhosis (i.e., cirrhosis stage with complications such as variceal hemorrhage, ascites, hepatic encephalopathy, or jaundice) who also have a much higher risk of postoperative development of these liver-related complications (181,205,206).

Adults with type 2 diabetes and MASLD are at an increased risk of CVD and require comprehensive management of cardiovascular risk factors (181,205,206). Within an interprofessional approach, statin therapy should be initiated or continued for cardiovascular risk reduction as clinically indicated. Overall, its use appears to be safe in adults with type 2 diabetes and MASH, including in the presence of compensated cirrhosis (Child-Pugh class A or B cirrhosis) from MASLD. Some studies

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even suggest that statin use in people with chronic liver disease may reduce episodes of hepatic decompensation and/or overall mortality (291,292). Statin therapy is not recommended in decompensated cirrhosis given limited safety and efficacy data (181,205,206).

Obstructive Sleep Apnea

Age-adjusted rates of obstructive sleep apnea, a risk factor for CVD, are significantly higher (4- to 10-fold) with obesity, especially with central obesity (293) (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes"). The prevalence of obstructive sleep apnea in the population with type 2 diabetes may be as high as 23%, and the prevalence of any sleep-disordered breathing may be as high as 58% (294,295). In participants with obesity enrolled in the Look AHEAD trial, the prevalence exceeded 80% (296). Obstructive sleep apnea should be evaluated in individuals with suggestive symptoms (e.g., excessive daytime sleepiness, snoring, and witnessed apnea) (297). Sleep apnea treatment (lifestyle modification, continuous positive airway pressure, oral appliances, and surgery) significantly improves quality of life and blood pressure management. Recently, two phase 3 randomized trials found that among adults with obesity and moderate-to-severe obstructive sleep apnea but without diabetes, treatment with the dual GIP and GLP-1 RA tirzepatide substantially reduced sleep apnea severity (298). More research is needed to determine the effects of GLP-1 and dual GIP and GLP-1 RAs on sleep apnea in people with diabetes.

Pancreatitis

Diabetes is linked to diseases of the exocrine pancreas, such as pancreatitis, which may disrupt the global architecture or physiology of the pancreas, often resulting in both exocrine and endocrine dysfunction. Up to half of individuals with diabetes may have some degree of impaired exocrine pancreas function (299). People with diabetes are at an approximately twofold higher risk of developing acute pancreatitis (300).

Conversely, prediabetes and/or diabetes has been found to develop in approximately one-third of individuals after an episode of acute pancreatitis (301); thus, the relationship is likely bidirectional. Postpancreatitis diabetes may include either new-onset disease or previously unrecognized diabetes (302). Studies of individuals treated with incretin-based therapies for diabetes have also reported that pancreatitis may occur more frequently with these medications, but results have been mixed and causality has not been established (303–306).

Islet autotransplantation should be considered for individuals requiring total pancreatectomy for medically refractory chronic pancreatitis to prevent postsurgical diabetes. Approximately one-third of individuals undergoing total pancreatectomy with islet autotransplantation are insulin free 1 year postoperatively, and observational studies from different centers have demonstrated islet graft function up to a decade after the surgery in some individuals (307–311). Both personal factors for the individual with diabetes and disease factors should be carefully considered when deciding the indications and timing of this surgery. Surgeries should be performed in skilled facilities that have demonstrated expertise in islet autotransplantation.

Sensory Impairment

Hearing impairment, both in high-frequency and low- to midfrequency ranges, is more common in people with diabetes than in those without, with stronger associations found in studies of younger people (312). Proposed pathophysiologic mechanisms include the combined contributions of hyperglycemia and oxidative stress with cochlear microangiopathy and auditory neuropathy (313). In a National Health and Nutrition Examination Survey (NHANES) analysis, hearing impairment was about twice as prevalent in people with diabetes as in those without, after adjusting for age and other risk factors for hearing impairment (314). Low HDL cholesterol, coronary heart disease, peripheral neuropathy, and general poor health have been reported as risk factors for hearing impairment for people with diabetes, but an association of hearing loss with glycemia has not been consistently observed (315). In the DCCT/EDIC cohort, increases in the time-weighted mean A1C was associated with increased risk of hearing impairment when tested after long-term (>20 years) follow-up, with every 10% increase in A1C leading to 19% high-frequency impairment (316). Impairment in smell, but not taste, has also been reported in individuals with diabetes (317).

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5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Building positive health behaviors and maintaining psychological well-being are foundational for achieving diabetes management goals and maximizing quality of life (1,2). Essential to achieving these goals are diabetes self-management education and support (DSMES), medical nutrition therapy (MNT), routine physical activity, adequate quality sleep, support for cessation of tobacco products and vaping, health behavior counseling, and psychosocial care. Following an initial comprehensive health evaluation (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities"), health care professionals should engage in person-centered collaborative care with people with diabetes (3–6). Person-centered collaborative care is guided by shared decision-making in treatment plan selection; facilitating access to medical, behavioral, psychosocial, and technological resources and support; and shared monitoring of agreed-upon diabetes care plans and behavioral goals (7,8). Routine care evaluations should include assessments of medical and behavioral health outcomes, particularly during periods of changes in health and well-being.

DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

Recommendations

5.1 All people with diabetes should be advised to participate in developmentally and culturally appropriate diabetes self-management education and support (DSMES) to facilitate informed decision-making, self-care behaviors, problem-solving, and active collaboration with the health care team. **A**

5.2 Provide DSMES at diagnosis, annually and/or when not meeting treatment goals, when complicating factors develop (e.g., medical, functional, and psychosocial), and when transitions in life and care occur. **E**

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.*

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5.3 Routinely assess clinical outcomes, health status, and well-being as key goals of DSMES. **C**

5.4 Screen for behavioral health concerns at the same critical times as evaluating the need for DSMES and refer to a qualified behavioral health professional if indicated to increase engagement in DSMES. **E**

5.5 DSMES should be culturally appropriate and responsive to individual preferences, needs, and values and may be offered in group or individual settings. **A** Such education and support should be documented and made available to members of the entire diabetes care team. **E**

5.6 Consider offering DSMES via telehealth and/or digital interventions as needed to meet individual preferences, address barriers to access, and improve satisfaction. **B**

5.7 DSMES can improve outcomes and reduce costs, so reimbursement by third-party payors is recommended. **B**

5.8 Identify and address barriers to DSMES that exist at the payor, health system, clinic, health care professional, and individual levels. **E**

5.9 Screen for and include social determinants of health in guiding design and delivery of DSMES **C** with the ultimate goal of health equity across all populations.

The overall objectives of DSMES are to support informed decision-making, self-care behaviors, problem-solving, and active collaboration with the health care team to improve clinical outcomes, health status, and well-being in a cost-effective manner (2). DSMES services facilitate the knowledge, decision-making, and skills mastery necessary for optimal diabetes self-care and incorporate the needs, goals, and life experiences of the person with diabetes (9). When providing DSMES, health care professionals should consider the individual's burden of treatment, level of self-efficacy for self-care behaviors, and degree of social and family support. Engagement in self-management behaviors and subsequent clinical outcomes, health status, and quality of life, in addition to psychosocial factors affecting the person's ability to self-manage, should be monitored routinely. A randomized controlled trial (RCT) that evaluated a decision-making education and skill-building program (10) showed that addressing these aims improved health outcomes in a population in need of health care resources. Furthermore, following a DSMES curriculum improves quality of care (11).

Use of judgmental words is associated with increased feelings of shame and guilt; therefore, health care professionals should consider the impact language has on building therapeutic and productive relationships. Health care professionals should use positive, strength-based words and phrases putting people first (4). Please see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," for more on use of language.

In accordance with the "2022 National Standards for Diabetes Self-Management Education and Support" (here referred to as the National Standards for DSMES) (9), all people with diabetes should participate in developmentally appropriate and culturally sensitive DSMES, as it helps people with diabetes identify and implement effective self-management strategies and coping skills (2). DSMES includes collaborative goal setting that improves empowerment, self-management, and quality of life as the person with diabetes encounters new challenges and as advances in treatment become available (12–14). Moreover, DSMES should be thought of as an ongoing process—not a one-time occurrence. The National Standards for DSMES (9) include delivery of content addressing:

- Pathophysiology of diabetes and treatment options
- Healthy coping
- Healthy eating
- Being active
- Taking medication
- Monitoring
- Reducing risk (treating acute and chronic complications)
- Problem solving and behavior change strategies

In addition to providing DSMES upon diagnosis, there are additional critical time points when the need for DSMES should be evaluated by the health care professional and/or interprofessional team, with referrals made as needed (2):

- Annually and/or when not meeting treatment goals, whichever is more frequent
- When complicating factors (e.g., health conditions, physical or functional limitations, emotional factors, and basic living needs) that influence self-management develop
- When transitions in life and care occur

DSMES empowers individuals with diabetes by providing them with tools to make informed self-management decisions (4). DSMES should be person-centered—placing the person with diabetes and their family and/or support system at the center of the care model as they work in collaboration with health care professionals. Person-centered care is respectful of and responsive to individual and cultural preferences, needs, and values. It ensures the values of the person with diabetes guide all decision-making (15).

Evidence for the Benefits

DSMES is associated with improved diabetes knowledge and self-care behaviors (16,17), lower A1C (16–21), lower self-reported weight (22), improved quality of life (23,24), reduced all-cause mortality risk (25), positive coping behaviors (5,26), and lower health care costs (27–29). DSMES is also associated with an increased use of primary care and preventive services (27,30) and less frequent use of acute care and inpatient hospital services (22). People with diabetes who participate in DSMES are more likely to follow best practice treatment recommendations, particularly those with Medicare, and have lower Medicare and insurance claim costs (28,30). Better outcomes were reported for DSMES interventions that were >10 h over the course of 6–12 months (19), included ongoing support (12,13,31), were culturally (30,32–34) and age appropriate (35,36), were tailored to individual needs and preferences, addressed psychosocial issues, and incorporated behavioral strategies (4,26, 37,38). Individual and group approaches are effective (22,39,40), with a slight benefit realized by those who engage in both (19).

Strong evidence now exists for the benefits of telehealth, telemedicine, and telephone-based or internet-based (i.e., virtual) DSMES for diabetes prevention and management in a wide variety of populations and age-groups (9,41–44). When feasible, the best choice for delivery of DSMES is that which will align with individual preferences. A 2023 systematic

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review and meta-analysis of RCTs reported moderate evidence indicating digital health technologies (e.g., mobile apps, websites, digital coaching, and SMS [i.e., texting]) can be effective modes of intervention delivery for DSMES. In fact, telehealth-based interventions have been found to produce a greater reduction in A1C (−0.30 percentage points; 95% CI −0.42 to −0.19) compared with control (43,45). These digital methods provide outcomes that are comparable to or even better than those seen with traditional in-person care (46). Greater A1C reductions are demonstrated with increased engagement (47), although data from trials are heterogeneous.

Diabetes care and education specialists (DCES) are effective providers of DSMES. Members of the DSMES team can include a variety of health care professionals such as nurses (registered nurses and nurse practitioners), registered dietitian nutritionists (RDNs), pharmacists, social workers, certified health education specialists, exercise physiologists, care coordinators or navigators, and others who can tailor curricula to individual needs (48–50). Team members acting in the DCES capacity should have specialized clinical knowledge of diabetes and behavior change principles. In addition, a DCES needs to be knowledgeable about technology-enabled services and may serve as a technology champion within their practice (51). Credentialing such as certified diabetes care and education specialists (CDCES) (cbdce.org/) and/or board certification in advanced diabetes management (BC-ADM) (diabeteseducator.org/education/certification/bc_adm) demonstrates an individual's specialized training in and understanding of diabetes management and support (9), and engagement with qualified professionals has been shown to improve diabetes-related outcomes (52). There is also continued and growing evidence for the role of community health workers, peer educators, peer support, and lay leaders in providing ongoing diabetes self-management support (53,54).

Social determinants of health (SDOH) are an important aspect of diabetes care and should always be weighed in guiding the design and delivery of DSMES. The DSMES team should consider demographic characteristics such as racial identity, ethnic and cultural background, biological sex and gender identity, age, geographic location, technology access, education, literacy, and numeracy (4). For example, a systematic review and meta-analysis of telehealth DSMES interventions with Black and Hispanic adults with diabetes showed a 0.465% decrease in A1C, demonstrating the importance of considering demographic factors in relation to DSMES interventions (44). Barriers to equitable DSMES access can be mitigated by keeping in mind the SDOH and leveraging creative delivery options (e.g., telehealth and online) that will work best for the population in need of DSMES (9).

Despite the recognized benefits of DSMES, only about half of individuals eligible for DSMES through their health insurance receive it (55). Barriers to DSMES exist at multiple levels including the health system, payor, clinic, health care professional, and individual for a myriad of reasons from lack of administrative leadership support to ineffective DSMES referral processes and transportation challenges. Low participation can be due to lack of referrals, logistical issues (e.g., accessibility, timing, and costs), and lack of a perceived benefit (56). Thus, in addition to educating referring health care professionals about the benefits of DSMES and the critical times to refer, efforts to identify and address potential barriers at all levels need to be made (2). This was illustrated in a multilevel diabetes care intervention that combined clinical outreach, standardized protocols, and DSMES with SDOH screening and referrals to social needs support; a 15% increase in receipt of DSMES, including among people on Medicaid, was documented (57). Support from institutional leadership is foundational for DSMES success. Expert stakeholders, including those external to an organization, should also support DSMES by advocating for it and for people with diabetes (9).

Diabetes Technologies

Technology-enabled diabetes self-management solutions (e.g., continuous glucose monitors [CGM], closed-loop pump systems, and connected glucose meters) improve A1C most effectively when there is two-way communication between the person with diabetes and the health care team, individualized feedback, use of person-generated health data, and education (58). Alternative and innovative models of DSMES delivery (59), including integration of technology-enabled diabetes and cardiometabolic health services (8), need to be continually explored and evaluated. Technology can facilitate self-management decisions and improve access to DSMES (58). Additionally, use of diabetes technologies warrants broader adoption because they can reduce therapeutic inertia (60). One potential model is virtual environments, which allow people with diabetes to self-represent as avatars and interact in a world with embedded informational resources that can be accessed using principles of gamification. An RCT that tested DSMES in a virtual environment demonstrated greater weight loss but similar decreases in A1C, blood pressure, cholesterol, and triglycerides compared with DSMES via a standard website (61). These versions may not always be reimbursed; however, adoption of reimbursement policies that increase DSMES access and use will positively affect beneficiaries' clinical outcomes, quality of life, health care use, and costs (9,62,63).

Of all the newer diabetes technologies, CGM might be the most widely adopted. When combined with individualized DSMES or behavioral interventions, CGM demonstrated greater improvement of glycemic and psychosocial outcomes than CGM alone (47,64). Similarly, DSMES plus intermittently scanned CGM (isCGM) demonstrated increased time in range (70–180 mg/dL [3.9–10.0 mmol/L]), less time above range, and greater reduction in A1C compared with DSMES alone (65). Incorporating a systematic approach for technology assessment, adoption, and integration into the diabetes care plan could help ensure equity in access and standardized application of technology-enabled solutions (8,51,66–68).

Reimbursement

Medicare reimburses DSMES (referred to as diabetes self-management training [DSMT] by Medicare) when the service is in accordance with the National Standards for DSMES (2,9) and is recognized by the American Diabetes Association (ADA) through the Education Recognition Program (professional.diabetes.org/diabetes-education) or by the Association of Diabetes Care & Education Specialists (www.adces.org/store/online-education/unlisted-detail/becoming-an-accredited-dsmes-program).

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DSMES is also covered by most other health insurance plans. Ongoing support has been shown to be instrumental for improving outcomes when it is implemented after the completion of formal DSMES. For comprehensive information about Medicare reimbursement, readers may find the following website useful: www.cdc.gov/diabetes-toolkit/php/reimbursement/medicare-reimbursement-guidelines.html. In brief, the Medicare Part B initial DSMT is a "once-in-a-lifetime" benefit. Individual encounters are reimbursable for the first 10 h (1 h of individual training and 9 h of group training). Two hours of follow-up DSMT are allowed each year after the initial DSMT. If a person has special needs that would interfere with effective group participation, these should be identified on the referral order. For Medicaid, DSMES coverage varies by state, but further guidance can be found at www.cdc.gov/diabetes-toolkit/php/reimbursement/medicare-reimbursement-guidelines.html. Additional information addressing implementation of a successful DSMES program can be found in the Centers for Disease Control and Prevention DSMES toolkit at www.cdc.gov/diabetes-toolkit/php/index.html.

Programs recognized by the ADA and accredited by the Association of Diabetes Care & Education Specialists are currently included on the list of telehealth professionals approved by Centers for Medicare & Medicaid Services (CMS), via the Consolidated Appropriations Act of 2023 (69). Continuation of reimbursement for DSMES telehealth services is expected through the end of 2025, after which CMS is likely to reinstate limitations on the number of times certain services in high-acuity settings may be performed via telehealth. During this time, CMS will continue to evaluate whether the removal of these frequency limitations should be made permanent (70).

DSMES uses an evidence-based curriculum designed to educate people with diabetes about all elements from the National Standards for DSMES, as described above, that can be delivered and billed by a variety of health care professionals on the diabetes care team. While the overarching healthy eating concepts used in DSMES can be taught by all members of the team, MNT, which is more in-depth and individualized and derived from the evidence-based Nutrition Care Process, can only be delivered and billed by RDNs. For Medicare Part B, the MNT benefit includes individual encounters reimbursable for 3 h. Each subsequent year is reimbursed for 2 h. However, additional hours are available if a subsequent referral identifies a change in treatment. For further information on Medicare coverage of MNT, readers are encouraged to review www.cdc.gov/diabetes-toolkit/php/reimbursement/medical-nutrition-therapy.html and www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=53.

MEDICAL NUTRITION THERAPY

When the first ADA Standards of Care guidelines were published in 1989, nutrition was only mentioned in two sentences of the entire 4-page document (71). Even today, the science of nutrition for diabetes continues to evolve. There has also been a change in how we talk about nutrition. We are moving away from emphasizing macronutrients, which include carbohydrates, proteins, and fats, and micronutrients, which include vitamins and minerals, and instead focusing on foods. More broadly, we are encouraging people to think in terms of eating patterns, also known as dietary patterns or food patterns, or the totality of the foods and beverages a person consumes. Additionally, promoting nutrient-dense food choices, defined as foods high in micronutrients while being relatively low in calories (e.g., vegetables, fruits, and legumes), is useful. This integrative food-based approach aligns with the 2021 American Heart Association dietary guidance to improve cardiovascular health (72), the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (73), the European Association for the Study of Diabetes and ADA type 1 consensus report (74) and type 2 consensus report (75), and the *Dietary Guidelines for Americans, 2020–2025* (76). Simply put, people eat food, not nutrients, and nutrition recommendations need to be applicable to what people actually eat. Additionally, macronutrients are not interchangeable entities and vary by nutrient type and quality. As an example, carbohydrates include legumes, whole grains, and fruits, which are in the same category as refined grains, but their health effects are quite different (77).

MNT is effective and beneficial to people with diabetes. When delivered by an RDN, MNT is associated with A1C absolute decreases of 1.0–1.9% for people with type 1 diabetes and 0.3–2.0% for people with type 2 diabetes (78). Because type 2 diabetes is progressive, behavior modification alone may not be adequate to maintain euglycemia over time. However, after pharmacotherapy is initiated, nutrition therapy continues to be an important component of ongoing diabetes self-management, and RDNs providing diabetes-specific MNT should assess and monitor medication changes in relation to the nutrition care plan (50,79). All members of the health care team should also be empowered to reiterate the general and evidence-based nutrition advice to limit processed foods and foods high in added salt, sugars, and fats and, when possible, choose whole foods.

For more detailed information on nutrition therapy, please refer to the ADA consensus report on nutrition therapy (50). Contained in the report is an important and often repeated tenet, i.e., there is no one-size-fits-all eating pattern for individuals with diabetes, and meal planning should be individualized. Nutrition therapy plays an integral role in overall diabetes management, and each person with diabetes should actively engage in education, self-management, and treatment planning with the health care team and participate in collaborative development of an individualized eating plan (50,79).

All health care professionals should refer people with diabetes for individualized MNT provided by an RDN who is experienced and skilled in providing diabetes-specific MNT (80–82), at diagnosis and as needed throughout the life span, similar to DSMES. Referrals to RDNs are particularly warranted when a person with diabetes is dealing with additional health conditions such as hypertension, dyslipidemia, heart failure, gastrointestinal disorders, chronic kidney disease, pregnancy-related nutrition concerns, pediatric growth issues, or obesity (83). See **Table 5.1** for general nutrition recommendations, **Table 5.2** for macronutrient-specific recommendations, and **Table 5.3** for nutrition behaviors that should be encouraged.

Eating Patterns and Meal Planning

For an understanding of the role of nutrition in diabetes, it is important to clarify the terminology. Food patterns,

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Table 5.1—Nutrition therapy recommendations

	Recommendations
Provide medical nutrition therapy	**5.10** An individualized medical nutrition therapy program, as needed to achieve treatment goals and provided by a registered dietitian nutritionist, preferably one who has comprehensive knowledge and experience in diabetes care, is recommended for all people with type 1 or type 2 diabetes, prediabetes, and gestational diabetes mellitus. **A** **5.11** Because diabetes medical nutrition therapy can result in cost savings **B** and improved cardiometabolic outcomes, **A** medical nutrition therapy should be adequately reimbursed by insurance. **E**
Promote energy balance	**5.12** Provide weight management treatment based on nutrition, physical activity, and behavioral therapy for all people with overweight or obesity, aiming for at least 3–7% weight loss. **A**
Encourage healthy, evidence-based eating patterns	**5.13** For diabetes prevention and management of people with prediabetes or diabetes, recommend individualized meal plans that keep nutrient quality, total calories, and metabolic goals in mind, **B** as data do not support a specific macronutrient pattern. **5.14** Eating patterns should emphasize key nutrition principles (inclusion of nonstarchy vegetables, whole fruits, legumes, lean proteins, whole grains, nuts and seeds, and low-fat dairy or nondairy alternatives) and minimize consumption of red meat, sugar-sweetened beverages, sweets, refined grains, processed and ultraprocessed foods in people with prediabetes and diabetes. **B** **5.15** Consider reducing overall carbohydrate intake for adults with diabetes to improve glycemia, as this approach may be applied to a variety of eating patterns that meet individual needs and preferences. **B**
Do not promote the use of micronutrient, herbal, and other supplements to aid in glycemic management	**5.16** Health care professionals should inquire about intake of dietary supplements and counsel as necessary. Supplementation with micronutrients (e.g., vitamins and minerals, such as magnesium or chromium) or herbs or spices (e.g., cinnamon and aloe vera) for glycemic benefits is not recommended. **C** **5.17** Counsel against β-carotene supplementation, as there is evidence of harm for certain individuals and it confers no benefit. **B**
Avoid excess alcohol intake	**5.18** Advise adults with diabetes and those at risk for diabetes who consume alcohol to not exceed the recommended daily limits. **B** Advise abstainers to not start drinking alcohol, even in moderation. **5.19** Educate people with diabetes about the signs, symptoms, and self-management of delayed hypoglycemia after drinking alcohol, especially when using insulin or insulin secretagogues. The importance of monitoring glucose after drinking alcoholic beverages to reduce hypoglycemia risk should be emphasized. **B**
Limit sodium and foods high in salt	**5.20** Counsel people with diabetes to limit sodium consumption to <2,300 mg/day, as clinically appropriate, **B** and that the best way to achieve this is through limiting consumption of processed foods. **B**
Recommend water over other beverages	**5.21** Counsel people with prediabetes and diabetes that water is recommended over nutritive and nonnutritive sweetened beverages. **A** **5.22** Counsel people with diabetes and those at risk for diabetes that nonnutritive sweeteners can be used instead of sugar-sweetened products if consumed in moderation and for the short term to reduce overall calorie and carbohydrate intake. **B**
Screen for malnutrition	**5.23** Screen people with diabetes and those at risk for diabetes for malnutrition, especially those who have undergone metabolic surgery **A** and those being treated with weight loss pharmacologic therapies. **B**

eating plans, and approaches are terms that are often used interchangeably, but they are different and relevant in individualizing nutrition care plans (84).

- **Eating pattern, dietary pattern, or food pattern.** The totality of all foods and beverages consumed over a given period of time. An eating pattern can be ascribed to an individual, but it is also the term used in prospective cohort and observational nutrition studies to classify and study nutrition patterns. Examples of eating patterns include Mediterranean style, Dietary Approaches to Stop Hypertension (DASH), low carbohydrate, vegetarian, and plant based (84).
- **Eating/meal plan (historically referred to as a diet).** An individualized guide to plan when, what, and how much to eat on a daily basis, completed by the person with diabetes and the RDN. The eating plan could incorporate an eating pattern combined with a strategy or method to direct some of the choices. Eating plans are based on the individual's usual eating style and food preferences.
- **Eating/meal plan approach.** Method or strategy to individualize a desired eating pattern and provide practical tools for developing healthy eating patterns. Examples of dietary approaches include the plate method, carbohydrate choice, carbohydrate counting, and highly individualized behavioral approaches (85).

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Table 5.2—Macronutrient-specific nutrition recommendations

	Recommendations
Carbohydrates	**5.24** Emphasize minimally processed, nutrient-dense, high-fiber sources of carbohydrate (at least 14 g fiber per 1,000 kcal). **B** **5.25** Advise people with diabetes and those at risk to replace sugar-sweetened beverages (including fruit juices) with water or low-calorie or no-calorie beverages as much as possible to manage glycemia and reduce risk for cardiometabolic disease **B** and minimize consumption of foods with added sugar that have the capacity to displace healthier, more nutrient-dense food choices. **A** **5.26** Regardless of diabetes classification, individuals treated with sodium–glucose cotransporter 2 inhibitors should avoid a ketogenic eating pattern, be educated on the signs of ketoacidosis and methods of risk mitigation and provided with appropriate tools for accurate ketone measurement (i.e., serum β-hydroxybutyrate), and be instructed to avoid fasting and maintain appropriate insulin therapy. **E** **5.27** Provide education on the glycemic impact of carbohydrate, **A** fat, and protein **B** tailored to an individual's needs, insulin plan, and preferences to optimize mealtime insulin dosing. **5.28** When using fixed insulin doses, individuals should be provided with education about consistent patterns of carbohydrate intake with respect to time and amount while considering the insulin action time, as it can result in improved glycemia and reduce the risk for hypoglycemia. **B**
Proteins	**5.29** People with diabetes and those at risk for diabetes are advised to incorporate more plant-based protein sources (e.g., nuts, seeds, and legumes) as part of an overall diverse eating pattern to reduce cardiovascular disease risk. **B** **5.30** Counsel people with diabetes to consider an eating plan emphasizing elements of a Mediterranean eating pattern, which is rich in monounsaturated and polyunsaturated fats and long-chain fatty acids such as fatty fish, nuts, and seeds, to reduce cardiovascular disease risk **A** and improve glucose metabolism. **B**
Fats	**5.31** Counsel people with diabetes and those at risk for diabetes to limit intake of foods high in saturated fat (e.g., red meat, full-fat dairy, butter, and coconut oil) to help reduce cardiovascular disease risk. **A**

Meal Planning

There is no ideal percentage of calories from carbohydrate, protein, or fat for people with diabetes. Therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals. Members of the health care team should complement and reinforce MNT by providing evidence-based guidance that helps people with diabetes make healthy food choices that meet their individualized needs and improve overall health. Ultimately, ongoing diabetes and nutrition education paired with appropriate support to implement and sustain health behaviors are recommended (82).

Research confirms that a variety of eating patterns are acceptable for the management of diabetes (50,78,86,87). Evidence for eating patterns has been informed by RCTs, prospective cohort studies, systematic reviews, and network meta-analyses. Those most frequently recommended based on the evidence include Mediterranean, DASH, low-fat, carbohydrate-restricted, vegetarian, and vegan eating patterns. Until evidence around benefits of different eating patterns is strengthened, health care professionals should focus on the core dimensions common among healthful patterns: inclusion of nonstarchy vegetables, whole fruits, legumes, whole grains, nuts, seeds, and low-fat dairy products and minimizing consumption of red meat, sugar-sweetened beverages, sweets, refined grains, and processed and ultraprocessed foods (88,89).

Referral to and ongoing support from an RDN is essential to assess the overall nutrition status of, and to work collaboratively with, the person with diabetes to create a personalized meal plan that coordinates and aligns with the overall lifestyle treatment plan, including physical activity and medication use. Using shared decision-making to collaboratively select a method for how to execute the plan may be part of the nutrition care process.

Eating/Meal Plan Approaches and Methods

Few head-to-head studies have compared different eating approaches. In a systematic review and meta-analysis of carbohydrate counting versus other forms of meal planning advice (e.g., standard education, low glycemic index, and fixed carbohydrate quantities), no significant differences were seen in A1C levels compared with standard education (90). In another RCT, a simplified carbohydrate counting tool based on individual glycemic response was noninferior to conventional carbohydrate counting in 85 adults with type 1 diabetes (91). In a randomized crossover trial, carbohydrate counting and qualitative meal size (i.e., low, medium, and high carbohydrate) were compared. Time in range was 74% for carbohydrate counting and 70.5% for the quantitative meal size estimates. Noninferiority was not confirmed for the qualitative method (92). Newer technologies (e.g., smart phone apps and CGM) and automated insulin delivery may decrease the need for precise carbohydrate counting and allow for personalized nutrition approaches (93,94).

One RCT found that two meal-planning approaches (diabetes plate method and carbohydrate counting) were effective in helping achieve improved A1C (95). The diabetes plate method (96) is a commonly used visual approach for providing basic meal planning guidance for individuals with type 1 and type 2 diabetes. This simple graphic (featuring a 9-in plate) shows how to portion foods (one-half of the plate for nonstarchy vegetables, one-quarter of the plate for protein, and one-quarter of the plate for carbohydrates). Carbohydrate counting is a more advanced skill that helps plan for and track how much carbohydrate is consumed at meals and snacks. Meal planning approaches should be customized to the individual, including their numeracy (95) and

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Table 5.3—Nutrition behaviors to encourage

• Vegetables—especially nonstarchy vegetables that are dark green, red, and orange in color; fresh, frozen, or low-sodium canned are all acceptable vegetable options.
• Legumes—dried beans, peas, and lentils.
• Fruits—especially whole fruit—fresh, frozen, or canned in own juice (or no added sugar) are all acceptable fruit options.
• Whole-grain foods—where culturally appropriate, whole-grain versions of commonly consumed foods such as 100% whole-wheat breads or pastas, and brown rice. When not culturally appropriate, focus more on portion control.
• Foods with at least 3 g of fiber per serving, which generally indicates a food higher in fiber.
• Water should be the primary beverage of choice.
• For individuals who do not prefer plain water, no-calorie alternatives are the next best choice. Options include adding lemon, lime, or cucumber slices to water; sparkling no-calorie water or flavored no-calorie waters; no-calorie carbonated beverages, etc.
• Plant-based proteins can include legumes (e.g., soybeans, pinto beans, black beans, garbanzo beans, dried peas, and lentils), nuts, and seeds.
• Meats and poultry should be from fresh, frozen, or low-sodium canned and in lean forms (e.g., chicken breast and ground turkey).
• Heart-healthy wild-caught fatty fish such as salmon, tuna, sardines, and mackerel. Fresh, frozen, or low-sodium canned are all acceptable options.
• Use herbs (e.g., basil, fennel, mint, parsley, rosemary, and thyme) and spices (e.g., cinnamon, garam masala, ginger, pepper, and turmeric) to season foods instead of salt or salt-containing preparations.
• Incorporate onions, garlic, celery, carrots, and other vegetables as a base for preparing various homemade foods.
• Cook with vegetable oil (e.g., canola and olive) in place of fats high in saturated fat (e.g., butter, shortening, lard, and coconut oil).
• Meal prep by planning out meals for the week, grocery shopping with a list, and cooking on a day off so there are ready-to-eat and ready-to-reheat homemade meals waiting in the fridge or freezer.
• Include family or roommates in meal preparation; share the responsibilities of grocery shopping and cooking.

food literacy level. Health numeracy refers to understanding and using numbers and numerical concepts in relation to health and self-management. Food literacy generally describes proficiency in food-related knowledge and skills that ultimately affect health, although specific definitions vary across initiatives (97,98).

Nutrition Therapy Goals for All People With Diabetes

1. To promote and support healthful eating patterns, emphasizing a variety of nutrient-dense foods in appropriate portion sizes, contributing to improved overall health, and to:
   - achieve and maintain body weight goals
   - attain individualized glycemic, blood pressure, and lipid goals
   - delay or prevent the complications of diabetes
2. To address individual nutrition needs based on personal and cultural preferences, health literacy and numeracy, access to healthful foods, willingness and ability to make behavioral changes, and existing barriers to change
3. To maintain the pleasure of eating by providing nonjudgmental messages about food choices while also reducing or limiting certain foods only when indicated by scientific evidence
4. To provide an individual with diabetes the practical tools for developing healthy eating patterns rather than focusing on individual macronutrients, micronutrients, or single foods

Carbohydrates

Studies examining the optimal amount of carbohydrate intake for people with diabetes are inconclusive, although monitoring carbohydrate intake is a key strategy in reaching glucose goals in people with type 1 and type 2 diabetes (99,100).

For people with type 2 diabetes, low-carbohydrate and very-low-carbohydrate eating patterns have been found to reduce A1C and the need for glucose-lowering medications (84,101–103). Systematic reviews and meta-analyses of RCTs found carbohydrate-restricted eating patterns, particularly those considered very low carbohydrate (<26% total energy), were effective in reducing A1C in the short term (<6 months), with less difference in eating patterns beyond 1 year (84,104,105). However, in a 2022 carefully designed 12-week RCT feeding study among adults with prediabetes and type 2 diabetes, a well-formulated ketogenic diet (20–50 g/day and keeping protein to ∼1.5 g/kg ideal body weight/day, with the remainder of energy from fat) did not significantly improve A1C and increased LDL cholesterol compared with a low-carbohydrate Mediterranean diet (105). Therefore, questions still remain about the optimal degree of carbohydrate restriction and long-term effects of those meal patterns on cardiovascular disease (CVD).

The effects of changes in body weight and the wide range of definitions for a low-carbohydrate eating plan are important challenges in interpreting carbohydrate-restricted research studies (106). Weight reduction is often a goal in many studies on low-carbohydrate eating plans, which complicates evaluating the distinct contribution of the eating pattern (107–109). As studies on low-carbohydrate eating plans generally indicate challenges with long-term sustainability (101), it is important to reassess and individualize meal plan guidance regularly for those interested in this approach.

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Health care professionals should maintain consistent medical oversight of individuals following very-low-carbohydrate eating plans and recognize that insulin and other diabetes medications may need to be adjusted to prevent hypoglycemia, and blood pressure will need to be monitored. In addition, very-low-carbohydrate eating plans are not currently recommended for individuals who are pregnant or lactating, children, people who have kidney disease, or people with or at risk for disordered eating.

Very-low-carbohydrate eating plans should also be used with caution in those taking sodium–glucose cotransporter 2 (SGLT2) inhibitors because of the potential risk of ketoacidosis (110,111). Numerous case reports have now been published illustrating that diabetic ketoacidosis (DKA) or euglycemic DKA can occur in people with type 1 and type 2 diabetes using SGLT2 inhibitors in combination with very-low-carbohydrate or ketogenic eating patterns. Additionally, excessive alcohol intake should be avoided when taking SGLT2 inhibitors (110).

Regardless of the amount of carbohydrate in the meal plan, focus should be placed on high-quality, minimally processed, nutrient-dense carbohydrate sources high in fiber. Dietary fiber modulates gut microbiota composition and increases gut microbial diversity. Although there is still much to be elucidated about the gut microbiome and chronic disease, higher-fiber diets are advantageous (112). Both children and adults with diabetes are encouraged to minimize intake of refined carbohydrates with added sugars, fat, and sodium and instead focus on carbohydrates from vegetables, legumes, fruits, dairy (milk and yogurt) or fortified nondairy alternatives, and whole grains. People with diabetes and those at risk for diabetes are encouraged to consume a minimum of 14 g of fiber/1,000 kcal, with at least half of grain consumption being whole, intact grains, according to the *Dietary Guidelines for Americans, 2020–2025* (76). Regular intake of sufficient dietary fiber is associated with lower all-cause mortality in people with diabetes, and prospective cohort studies have found dietary fiber intake is inversely associated with risk for type 2 diabetes (113,114). The consumption of sugar-sweetened beverages and processed food products with large amounts of refined grains and added sugars is strongly discouraged (76), as these have the capacity to displace healthier, more nutrient-dense food choices and increase inflammation (115).

The literature concerning glycemic index and glycemic load in individuals with diabetes is complex, often with varying definitions of low– and high–glycemic index foods (116–118). The glycemic index ranks carbohydrate foods on their postprandial glycemic response, and glycemic load considers both the glycemic index of foods and the amount of carbohydrate eaten. Studies have found mixed results regarding the effect of glycemic index and glycemic load on fasting glucose levels and A1C, with one systematic review finding no significant effect on A1C (117) while others demonstrated A1C reductions of 0.15% (116) to 0.5% (106,119). More recently, however, a meta-analysis of large cohorts (≥100,000 participants) reported that when people had larger intakes of high glycemic index foods, there was increased incidence of type 2 diabetes (risk ratio 1.27 [95% CI 1.21–1.34]; $P < 0.0001$), total CVD (1.15 [1.11–1.19]; $P < 0.0001$), diabetes-related cancer (1.05 [1.02–1.08]; $P = 0.0010$), and all-cause mortality (1.08 [1.05–1.12]; $P < 0.0001$) (118). It is important to note that "low glycemic index" or "low glycemic load" is synonymous with high-fiber eating patterns.

Individuals with type 1 or type 2 diabetes taking insulin at mealtime should be offered comprehensive and ongoing education about nutrition content and the need to couple insulin administration with carbohydrate intake. For people whose meal schedule or carbohydrate consumption is variable, regular education to increase understanding of the relationship between carbohydrate intake and insulin needs is important. In addition, education on using insulin-to-carbohydrate ratios for meal planning can assist individuals with effectively modifying insulin dosing from meal to meal to improve glycemic management (78,99). Consumption of fat and protein can affect early and delayed postprandial glycemia (120), and it appears to have a dose-dependent response (121,122). Results from high-fat, high-protein feeding studies highlight the need for additional insulin to cover these meals; however, more research is needed to determine the optimal insulin dose and delivery strategy. Results from these studies also point to individual differences in postprandial glycemic response; therefore, a cautious approach to increasing insulin doses for high-fat and/or high-protein mixed meals is recommended to address delayed hyperglycemia that may occur after eating (50,123). For individuals using an insulin pump, a split bolus feature (part of the bolus delivered immediately and the remainder over a programmed duration of time) may provide better insulin coverage for high-fat and/or high-protein mixed meals (124,125).

Insulin dosing decisions should be confirmed with a structured approach to blood glucose monitoring or CGM to evaluate individual responses and guide insulin dose adjustments. Checking glucose 3 h after eating may help determine if additional insulin adjustments are required (i.e., increasing or stopping bolus) (124,125). Adjusting insulin doses to account for high-fat and/or high-protein meals requires determination of anticipated nutrient intake to calculate the mealtime dose. Food literacy, numeracy, interest, and capability should be evaluated. For individuals on a fixed daily insulin schedule, meal planning should emphasize a relatively fixed carbohydrate consumption pattern with respect to both time and amount while considering insulin action. Attention to hunger and satiety cues will also help with nutrient modifications throughout the day (50). Most commercially available automated insulin delivery systems still require basic diabetes management skills, including carbohydrate counting and understanding of the effect of protein and fat on postprandial glucose response (126).

Protein

There is no evidence that adjusting the daily protein intake above or below the recommended amount for the general public (typically 0.8–1.5 g/kg body weight/day or 15–20% of total calories) will improve health, and research is inconclusive regarding the ideal amount of dietary protein to optimize either glycemic management or CVD risk (76,127). Therefore, protein intake goals should be individualized based on current eating patterns. Some research has found successful management of type 2 diabetes with meal plans including slightly higher levels of protein (20–30%), which may contribute to increased satiety (128).

Historically, low-protein eating plans were advised for individuals with diabetes-

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related chronic kidney disease (CKD) (with albuminuria and/or reduced estimated glomerular filtration rate [eGFR]); however, current evidence does not suggest that people with CKD need to restrict protein to less than the generally recommended protein intake (129). Reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the rate at which eGFR declines and may increase risk for malnutrition (129).

Growing evidence suggests higher plant protein intake and replacement of animal protein with plant protein is associated with lower risk of all-cause and cardiovascular mortality. A meta-analysis of 13 RCTs showed that replacing animal proteins with plant proteins leads to small improvements in A1C and fasting glucose in adults with type 2 diabetes (130). A 2023 systematic review and meta-analysis of 13 RCTs and 7 cohort studies concluded that there is limited-suggestive evidence to support replacing animal protein with plant-based protein based on a moderate degree of bias in cohort studies (131). However, a prospective observational study of more than 11,000 community-dwelling adults over 22 years of follow-up reported that those with higher intakes of plant foods and lower intakes of animal foods had lower diabetes risk (132). Plant proteins are lower in saturated fat, higher in fiber, and also support planetary health (133).

Fats

There is no optimal percentage of calories from fat for people with or at risk for diabetes, and macronutrient distribution should be individualized according to the individual's eating patterns, preferences, and metabolic goals (50). The type of fats consumed is more important than total amount of fat when looking at metabolic goals and CVD risk, and the percentage of total calories from saturated fats should be limited (76,134–136). Multiple RCTs including people with type 2 diabetes have reported that a Mediterranean eating pattern can improve both glycemic management and blood lipids (137–139). The Mediterranean eating pattern is based on the traditional eating habits in the countries bordering the Mediterranean Sea. Although eating styles vary by country and culture, they share a number of common features, including consumption of fresh fruits and vegetables, whole grains, beans, and nuts/seeds; olive oil as the primary fat source; low to moderate amounts of fish, eggs, and poultry; and limited added sugars, sugary beverages, sodium, highly processed foods, refined carbohydrates, saturated fats, and fatty or processed meats.

People with diabetes should be advised to follow the guidelines for the general population for the recommended intakes of saturated fat, cholesterol, and *trans* fat (76). In a 12-week double-blinded randomized controlled feeding study among 61 adults with overweight and obesity, without diabetes, higher intakes of saturated fat, compared with polyunsaturated fat, were found to increase liver fat deposition (140). A 2021 systematic review and meta-analysis including over 22,500 prospective study participants followed for 9.8 years reported that replacing saturated fats with other macronutrients, such as polyunsaturated fats, was associated with reduced CVD occurrence (141). *Trans* fats should be avoided. In addition, as foods high in saturated fats are progressively decreased, they should be replaced with foods high in unsaturated fats and not with refined carbohydrate foods (142).

Evidence does not conclusively support recommending n-3 (eicosapentaenoic acid and docosahexaenoic acid) supplements for all people with diabetes for the prevention or treatment of cardiovascular events (50,143). In individuals with type 2 diabetes, two systematic reviews with n-3 and n-6 fatty acids concluded that the dietary supplements did not improve glycemic management (144,145). In the ASCEND (A Study of Cardiovascular Events iN Diabetes) trial, when compared with placebo, supplementation with n-3 fatty acids at a dose of 1 g/day did not lead to cardiovascular benefit in people with diabetes without evidence of CVD (146). However, results from the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) found that supplementation with 4 g/day of pure eicosapentaenoic acid significantly lowered the risk of adverse cardiovascular events. REDUCE-IT included 8,179 participants, of whom over 50% had diabetes, and found a 5% absolute reduction in cardiovascular events for individuals with established atherosclerotic CVD already treated with a statin with residual hypertriglyceridemia (135–499 mg/dL [1.52–5.63 mmol/L]) (147). See Section 10, "Cardiovascular Disease and Risk Management," for more information.

Sodium

As for the general population, people with diabetes are advised to limit their sodium consumption to <2,300 mg/day (50,148). Sodium intake has been shown to mediate glucose metabolism in a number of studies and affect eGFR, so limiting sodium intake is a valuable strategy for people with diabetes with or without kidney disease (148,149). In their post hoc analysis of the DASH-sodium RCT, Morales-Alvarez et al. reported that participants randomized to the low-sodium DASH eating pattern (containing ~1,150 mg sodium/day [50 mmol sodium/day]) had change in eGFR of −3.10 mL/min/1.73 m^2 (95% CI −5.46 to −0.73) after 4 weeks compared with 3,450 mg sodium/day (150 mmol sodium/day) (150).

Limiting sodium intake is most easily achieved through reducing consumption of processed and ultraprocessed foods, which are major contributors of sodium intake. Encouraging people to avoid adding salt to foods and during cooking can also help. Sodium recommendations should consider palatability, availability, affordability, clinical appropriateness, and the difficulty of achieving low-sodium recommendations in a nutritionally adequate eating plan.

Micronutrients and Other Supplements

Despite lack of evidence of benefit from dietary supplements, consumers continue to take them. Estimates show that up to 59% of people with diabetes in the U.S. use supplements (151). Without underlying deficiency, there is no benefit from herbal or other (i.e., vitamin or mineral) supplementation for people with diabetes (50,152).

Federal law in the U.S. broadly defines dietary supplements as products having one or more dietary ingredients, including vitamins, minerals, herbs or other botanicals, amino acids, enzymes, tissues from organs or glands, or extracts of these (153). It should also be noted that dietary supplements are not regulated like other over-the-counter medications or prescription drugs in the U.S. (154). In combination with the strong

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views on dietary supplements (both positive and negative), this can contribute to consumer confusion (155). Consumers can also consult the U.S. Food and Drug Administration (FDA) Dietary Supplement Ingredient Directory to locate information about ingredients used in dietary supplements and any action taken by the agency with regard to that ingredient (156). Routine antioxidant supplementation (such as vitamins E and C) is not recommended due to lack of evidence of efficacy and concern related to long-term safety. Based on the 2022 U.S. Preventative Services Task Force statement, the harms of β-carotene outweigh the benefits for the prevention of CVD or cancer. β-Carotene was associated with increased lung cancer and cardiovascular mortality risk (157).

Vitamin D in the context of diabetes has generated much research, but universal vitamin D supplementation for people with type 1 or type 2 diabetes without deficiency is not recommended at this time. Although post hoc analyses of the Vitamin D and Type 2 Diabetes Study (D2d) prospective RCT and Diabetes Prevention and Active Vitamin D (DPVD) and some meta-analyses suggest a potential benefit in specific populations (158–160), other studies have found no benefit or mixed results (161–163). Furthermore, adopting healthy lifestyle habits, including the eating patterns recommended herein, are strongly advised. Additional research is needed to define individual characteristics, clinical indicators, and appropriate dosages if and when vitamin D supplementation might benefit people with type 1 or type 2 diabetes.

There is insufficient evidence to support the routine use of herbal supplements and micronutrients, such as cinnamon (164), curcumin (e.g., turmeric), aloe vera, or chromium, to improve glycemia in people with type 1 or type 2 diabetes (50).

Metformin is associated with vitamin B12 deficiency per a report from the Diabetes Prevention Program Outcomes Study (DPPOS), which suggests that periodic testing of vitamin B12 levels should be considered in people taking metformin, particularly in those with anemia or peripheral neuropathy (165) (see Section 9, "Pharmacologic Approaches to Glycemic Treatment").

For special populations, including pregnant or lactating individuals, older adults, vegetarians, and people following very-low-calorie or low-carbohydrate diets, a multivitamin may be necessary (166).

Alcohol

The long-term effects of alcohol consumption for people with diabetes are unknown. The World Health Organization declared that there is no safe amount of alcohol intake (167,168). Risks associated with alcohol consumption include hypoglycemia and/or delayed hypoglycemia (particularly for those using insulin or insulin secretagogue therapies), weight gain, and hyperglycemia (for those consuming excessive amounts) (50,169). People with diabetes should be educated about these risks and encouraged to monitor glucose frequently before and after drinking alcohol to minimize such risks. People with diabetes who consume alcohol can follow the same guidelines as those without diabetes consistent with *Dietary Guidelines for Americans, 2020–2025* (76), which does not promote alcohol consumption in people who do not currently drink. To reduce risk of alcohol-related harms, adults can choose not to drink or to drink in moderation by limiting intake to ≤2 drinks a day for men or ≤1 drink a day for women (one drink is equal to a 12-oz beer, a 5-oz glass of wine, or 1.5 oz of distilled spirits) (76). Recent meta-analyses have reported the previously recognized J-shaped relationship between alcohol intake and health risks likely varies by sex, obesity status, genetics, and alcohol intake behaviors (170,171). A YMCA-based psychoeducational intervention tailored to those with chronic conditions, including 14- to 18-year-olds with type 1 diabetes, reported improvements in perceived risks of alcohol intake. Importantly, they also reported reduced alcohol consumption (172).

Nonnutritive Sweeteners and Water

The FDA has approved many nonnutritive sweeteners (NNS) (containing few or no calories; commonly referred to as artificial sweeteners) for consumption by the general public, including people with diabetes (50,173). However, the safety and role of NNS continue to be sources of concern and confusion for the public.

For some people with diabetes who are accustomed to regularly consuming sugar-sweetened foods or beverages (e.g., regular soda pop, juice drinks, and other items sweetened with cane sugar or high-fructose corn syrup), NNS may be an acceptable substitute for nutritive sweeteners (those containing calories, such as sugar, honey, and agave syrup) when consumed in moderation (174). NNS do not appear to have a significant effect on glycemic management (175,176), and they can reduce overall calorie and carbohydrate intake (174) as long as individuals are not compensating with additional calories from other food sources (50,177). A recent meta-analysis and systematic review of RCTs found no evidence that NNS raise liver enzymes (178).

There is mixed evidence from systematic reviews and meta-analyses for NNS use with regard to weight management, with some finding benefit for weight loss (179–181) while other research suggests an association with weight gain (182,183). This may be explained by reverse causality and residual confounding variables (183). The addition of NNS to eating plans poses no benefit for weight loss or reduced weight gain without energy restriction (184). In a recent systematic review and meta-analysis using low-calorie and no-calorie sweetened beverages as an intended substitute for sugar-sweetened beverages, a small improvement in body weight and cardiometabolic risk factors was seen without evidence of harm and had a direction of benefit similar to that seen with water (185). While health care professionals should promote water as the healthiest beverage option, people with overweight or obesity and diabetes may also use a variety of no-calorie or low-calorie sweetened products so that they do not feel deprived (185).

Health care professionals should encourage reductions in foods and beverages with added sugars and promote reducing overall sugar intake and calories with or without the use of NNS. Assuring people with diabetes that NNS have undergone extensive safety evaluation by regulatory agencies and are continually monitored can allay unnecessary concern for harm. Health care professionals can regularly assess individual use of NNS based on the acceptable daily intake (amount of a substance considered safe to consume each day over a person's life) and recommend moderation. See the chart from the FDA on safe levels of sweeteners found at

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fda.gov/food/food-additives-petitions/aspartame-and-other-sweeteners-food.

Weight Management

Management and reduction of weight is important for people with type 1 diabetes, type 2 diabetes, or prediabetes with overweight or obesity. To support weight loss and improve A1C, CVD risk factors, and well-being in adults with overweight or obesity and prediabetes or diabetes, MNT and DSMES services should include an individualized eating plan resulting in an energy deficit in combination with enhanced physical activity (50). Lifestyle intervention programs should be intensive and have frequent follow-up to achieve significant reductions in excess body weight and improve clinical indicators. Behavior modification goals should address physical activity, calorie restriction, healthy weight management strategies, and motivation. There is strong and consistent evidence that modest, sustained weight loss can delay the progression from prediabetes to type 2 diabetes (82,186,187) (see Section 3, "Prevention or Delay of Diabetes and Associated Comorbidities") and is beneficial for type 2 diabetes management (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes").

In prediabetes, the weight loss goal is at least 3–7% from baseline body weight, and higher for reducing risk of progression to type 2 diabetes. In conjunction with support for healthy lifestyle behaviors, medication-assisted weight loss can be considered for people at risk for type 2 diabetes when needed to achieve and sustain 7–10% weight loss (188,189) (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes"). People with prediabetes at a healthy weight should also be considered for behavioral interventions to help establish routine aerobic and resistance exercise (186, 190,191) as well as healthy eating patterns. Services delivered by health care professionals familiar with diabetes and its management, such as an RDN, have been found to be effective (81).

For many individuals with overweight or obesity alongside type 2 diabetes, at least 5% weight loss is needed to achieve beneficial outcomes in glycemic management, lipids, and blood pressure (192). However, any magnitude of weight loss is recommended. It also should be noted that the clinical benefits of weight loss are progressive, and more intensive weight loss goals (i.e., 15%) may be appropriate to maximize benefit depending on need, feasibility, and safety (193,194). Long-term sustainability of weight loss remains a challenge (195). Medications can augment MNT to support weight loss, weight loss maintenance, and improve cardiovascular outcomes. Newer medications (e.g., glucagon-like peptide 1 receptor agonists [GLP-1 RAs]) may be more viable, positively affect cardiovascular outcomes, and produce weight reduction beyond 10–15% (196–200). For more information on the nutritional considerations important for people undergoing metabolic surgery, including prevention of malnutrition, please see MALNUTRITION, below.

In select individuals with type 2 diabetes, an overall healthy eating plan resulting in energy deficit and pharmacotherapy and/or metabolic surgery should be considered to help achieve weight loss and maintenance goals, lower A1C, and reduce CVD risk (188,201,202). A recent systematic review and meta-analysis concluded that when obesity pharmacotherapy is included in intervention efforts (alone or as part of a multipronged intervention), people with obesity can achieve a more significant weight loss of -2.94 kg ($P < 0.0001$) (203). However, in some populations such as South Asian adults, traditional interventions have not been as effective in preventing or remission of type 2 diabetes, so those groups will benefit from more culturally tailored interventional approaches (204).

Overweight and obesity are increasingly prevalent in people with type 1 diabetes and present clinical challenges regarding diabetes treatment and CVD risk factors (205,206). Like in adults with type 2 diabetes, there is some evidence that GLP-1 RAs are useful in achieving weight loss among those with type 1 diabetes, although with a higher risk of nausea and ketosis (207).

Regardless of diabetes type, maintaining weight loss is challenging (208,209) but has well-recognized long-term benefits. The physiology of weight loss maintenance is complex and involves many hormonal, psychosocial, behavioral, and environmental factors. Following a weight loss of at least 8%, a subsequent "weight loss maintenance" intervention was reported to be only moderately beneficial, as it helped sustain physical health improvements but not glucose metabolism improvements (210). However, in another RCT with long-term, real-world, clinic-based follow-up of 10 years, Tomah et al. reported lasting glycemic benefits in their cohort with an average weight loss of 7.7 ± 0.9 kg ($-6.9 \pm 0.8\%$) maintained for 10 years (211).

Starting a conversation about weight management should be based on motivational interviewing techniques (212) beginning with first asking the individual if they want to discuss their weight. Health care professionals should never assume that a person with overweight or obesity wants to discuss their weight at a medical appointment, especially if the appointment is for a seemingly unrelated issue (e.g., back pain, which many people do not realize is often secondary to excess body weight). Using person-centered approaches to weight management conversations involves meeting the individual where they are at in their life and working with what they and their health care professional agree is the most beneficial approach. Guidance from an RDN with expertise in motivational interviewing and diabetes and weight management MNT during any comprehensive structured weight loss program is strongly recommended.

Along with routine medical management visits, people with diabetes and prediabetes should be screened during DSMES and MNT encounters for a history of dieting and past or current disordered eating behaviors. Characterizing an individual's past efforts with weight loss and their body weight history can also be very useful. Nutrition therapy should be individualized to help address maladaptive eating behavior (e.g., purging) or compensatory changes in medical treatment plan (e.g., overtreatment of hypoglycemic episodes and reduction in medication dosing to reduce hunger) (50) (see DISORDERED EATING BEHAVIOR, below). Disordered eating, eating disorders, and/or disrupted eating can increase challenges for weight and diabetes management. For example, caloric restriction may be essential for glycemic management and weight maintenance, but rigid meal plans and strict tracking of food intake and/or body weight may be contraindicated for individuals who are at increased risk of clinically significant maladaptive eating behaviors (213). If

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eating disorders are identified during screening with diabetes-specific questionnaires, individuals should be referred to a qualified behavioral health professional (1).

Nonreligious Fasting

The primary forms of nonreligious fasting are intermittent fasting or time-restricted eating. These are popular strategies for weight and glucose management. One of the key distinctions between nonreligious and religious fasting is water intake. See **Fig. 5.1** for further details on how religious and nonreligious fasting practices compare.

Intermittent fasting is an umbrella term that includes three main forms of restricted eating: alternate-day fasting (energy restriction of 500–600 calories on alternate days), the 5:2 diet (energy restriction of 500–600 calories on consecutive or nonconsecutive days with usual intake the other five), and time-restricted eating (daily calorie restriction based on window of time of 8–15 h). Each produces mild to moderate weight loss (3–8% loss from baseline) over short durations (8–12 weeks) with no significant differences in weight loss when compared with continuous calorie restriction (214,215). A 2024 systematic review and meta-analysis of RCTs examined the most common types of fasting in studies lasting 2–52 weeks. The authors concluded that intermittent energy restriction produces small but significant reductions in waist circumference and fat-free mass but were otherwise not superior to continuous energy restriction diets (216). Generally, time-restricted eating or shortening the eating window can be adapted to any eating pattern and has been shown to be safe for adults with type 1 or type 2 diabetes (217). People with diabetes who are taking insulin and/or secretagogues should be medically monitored during the fasting period (218). Because of the simplicity of intermittent fasting and time-restricted eating, these may be useful strategies for people with diabetes who are looking for practical eating management tools.

Use of partial or total meal replacements is an additional strategy for energy restriction. Meal replacements are prepackaged foods (bars, shakes, and soups) that contain fixed amounts of macro nutrients and micronutrients. They can improve nutrient quality and glycemic management and, consequently, reduce portion size and energy intake. In a meta-analysis involving 17 studies incorporating both partial and total meal replacements, greater weight loss and improvements in A1C and fasting blood glucose were demonstrated compared with conventional meal plans (219). Furthermore, meal replacements have been used in several landmark clinical trials, including Look AHEAD (Action for Health in Diabetes) (220), DiRECT (Diabetes Remission Clinical Trial) (221), and PREVIEW (Prevention of Diabetes Through Lifestyle Intervention and Population Studies in Europe and Around the World) (222). Results of these trials showed that partial or total meal replacements can be a potential short-term strategy for weight loss. Regardless of the specific eating pattern or meal plan selected, long-term follow-up and support from members of the diabetes care team are needed to optimize self-efficacy and maintain behavioral changes (85).

Chrononutrition is an emerging nutrition and biology subspecialty aimed toward increasing the understanding of how the timing of food ingestion affects metabolic health (223). Glucose metabolism follows a circadian rhythm through diurnal variation of glucose tolerance and peaks during daylight hours when food is consumed. Some preliminary studies show cardiometabolic benefits when food is

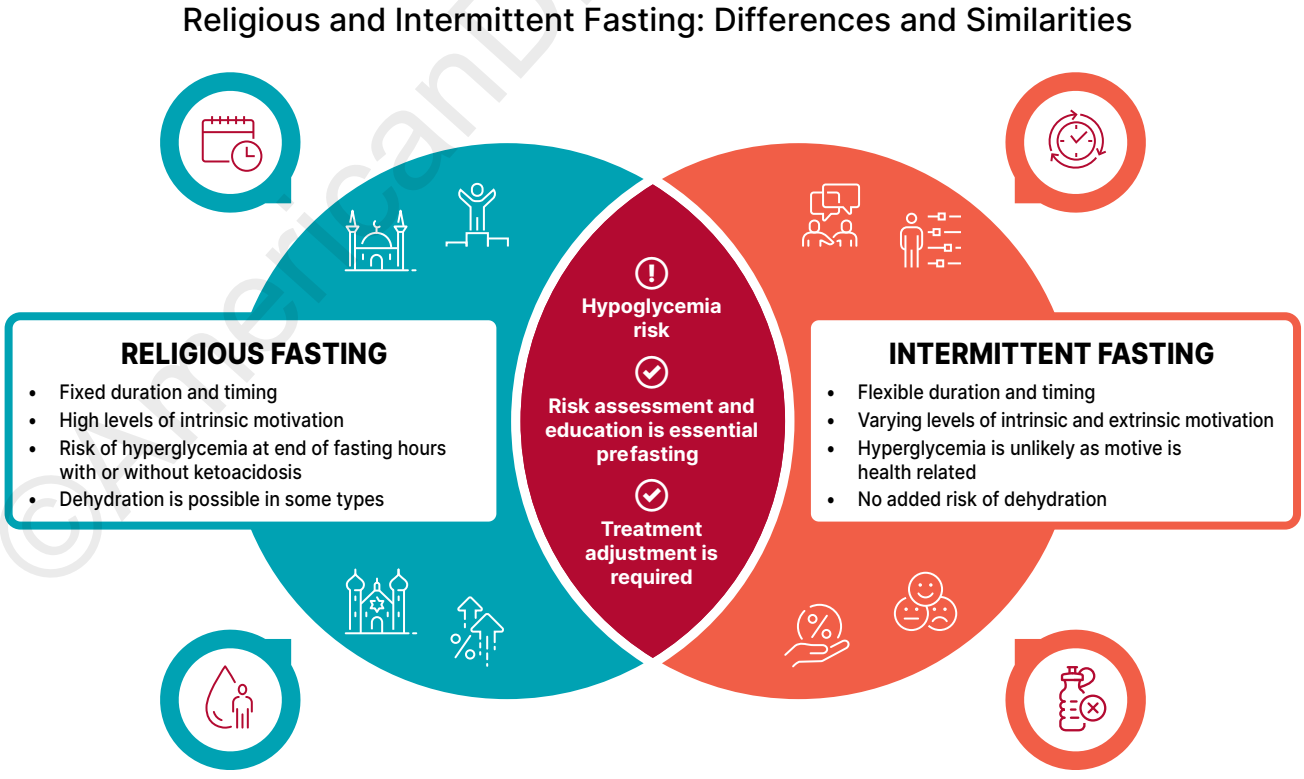

Figure 5.1—Differences and similarities of religious and intermittent fasting for people with diabetes.

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consumed earlier (224). Similarly, circadian disruptions found in shift workers increase risk of type 2 diabetes (225). This evolving area of research currently lacks conclusive evidence, but future studies are anticipated.

Religious Fasting

Recommendations

5.32 Use the International Diabetes Federation along with Diabetes and Ramadan International Alliance comprehensive prefasting risk assessment to generate a risk score for the safety of religious fasting. Provide fasting-focused education to minimize risks. **B**

5.33 Assess and optimize treatment plan, dose, and timing for people with diabetes well in advance of religious fasting to reduce risk of hypoglycemia, dehydration, hyperglycemia, and/or ketoacidosis. **B**

Although intermittent fasting and time-restricted eating are specific dietary strategies for energy restriction, religious fasting has been practiced for thousands of years and is part of many faith-based traditions. Duration, frequency, and type of fast vary among different religions (226). For example, Jewish people abstain from any intake for ~25 h during Yom Kippur (227,228). For Muslims, Ramadan fasting lasts for a full month, when abstinence from any food or drink is required from dawn to dusk (229). Individuals with diabetes who fast have an increased risk for hypoglycemia, dehydration, hyperglycemia, and ketoacidosis (230,231).

Prefasting risk assessment is essential to increase level of safety (230,231). Various risk factors need to be considered for every individual wishing to fast. Some of these factors are related to the type of fast, type of diabetes, and/or the individual. Indeed, health care professionals should inquire about any religious fasting for people with diabetes and provide education and support to accommodate their choice. The number of days of fasting is an important factor to consider. In Ramadan fasting, a person fasts from dawn to dusk for a lunar month (29–30 days). It is important for the health care professional to comprehensively assess these risk factors well in advance of fasting date, as some of them are modifiable. Some of these factors are related to the nature of the fasting practice, others are related to diabetes, and others might be due to individual factors. The International Diabetes Federation along with Diabetes and Ramadan International Alliance adopted a risk calculator for the various risk factors (230,232). Several clinical studies from different countries have been published that assess the validity of the fasting risk score and the ease of use of it (232–235). The accumulation of these risk factors provides a risk score as low, moderate, or high (**Table 5.4**) (230). While the risks of different religious fasting practices may vary, this risk calculator provides some useful guidance for other religious fasting.

Prefasting education regarding the importance of increasing the frequency of glucose monitoring for people wishing to fast is very important. The timing of glucose monitoring is also especially important, as the last few hours of fasting are frequently associated with approximately 50% of hypoglycemic events (236). Consequently, avoiding intense physical activity during the last few hours of fasting seems to be a sensible approach.

During religious fasting, some people change their nutrition habits and overindulge after fasting concludes. In many communities, the meal consumed to break the fast is rich in carbohydrates and includes foods and beverages high in added sugars and fat (230). Indeed, in a recent study in type 2 diabetes, 16.5% of people with diabetes who fasted for Ramadan reported high blood glucose of >300 mg/dL (>16.6 mmol/L) during fasting days (236). Individualized fluid adjustment and meal advice should be provided with emphasis on higher intake of fiber and replacing added sugars with complex carbohydrates to minimize hypoglycemia and hyperglycemia and emphasis on sustaining adequate daily fluid intake (237).

Treatment before and after fasting should be culturally sensitive and individualized. Specific recommendations for diabetes management during religious fasting in different faiths are available (230,231). In general, for people planning to fast for long hours and for multiple consecutive days, choice of treatment should prioritize drugs with low hypoglycemia risk. Hypoglycemia risk while fasting in people using insulin, sulfonylureas, and other insulin secretagogues is higher than those treated with other types of diabetes medications (230). The safety of SGLT2 inhibitors was assessed in several studies during Ramadan fasting. These studies did not show significant change in kidney function, dehydration rates, or ketosis (238). Guidelines do not advise any change in SGLT2 inhibitor dose during fasting; however, they advise against initiating SGLT2 inhibitors close to the start of fasting days to avoid excessive thirst (230). **Table 5.5** summarizes the effect of fasting on different treatment options and the possible change in doses or timing for people with diabetes.

Technology could be an important tool to enhance safety during fasting. Several studies have investigated the use of monitoring technology during Ramadan fasting (e.g., flash glucose monitoring and real-time CGM [rtCGM]) and confirmed that these tools are able to support high-risk groups wishing to fast, especially if combined with Ramadan-focused education (238–240). Meanwhile, the use of insulin pumps has been associated with low rates of hypoglycemia during fasting in people with type 1 diabetes. Diabetes technologies should be considered as a useful adjunct to risk calculation and/or nutrition planning and education during religious fasting for people with diabetes (230).

Malnutrition

Malnutrition is defined by the World Health Organization as "deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients." Malnutrition can occur in people of varying weight status, with the "double burden" of obesity and malnutrition being increasingly recognized among those with chronic conditions. Malnutrition is also more likely to develop in populations experiencing poverty and in older age-groups (241). Often, malnutrition and sarcopenia, which is a condition of loss in lean body mass combined with declined strength and functionality among older adults, codevelop (242). A 2022 meta-analysis examined 45 studies including 12,237 adults and reported that 18% of people with type 2 diabetes had sarcopenia with A1C increasing the risk (odds ratio 1.16; 95% CI, 1.09–1.24) (243).

There is concern that GLP-1 RAs and dual GIP and GLP-1 RAs and metabolic surgery for weight loss, which are more common in some populations with

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Table 5.4—Elements for risk calculation and suggested risk score for people with diabetes who seek to fast during Ramadan

Risk element	Risk score
1. Diabetes classification and duration	
• Type 1 diabetes	1
• Type 2 diabetes	2
2. Duration of diabetes (years)	
• A duration of ≥10 years	1
• A duration of <10 years	0
3. Presence of hypoglycemia	
• Hypoglycemia unawareness	6.5
• Recent severe hypoglycemia	5.5
• Multiple weekly hypoglycemia	3.5
• Hypoglycemia less than one time per week	1
• No hypoglycemia	0
4. Level of glycemic management	
• A1C levels >9% (>75 mmol/mol)	2
• A1C levels 7.5–9% (59–75 mmol/mol)	1
• A1C levels <7.5% (<59 mmol/mol)	0
5. Type of treatment	
• Multiple daily mixed insulin injections	3
• Basal bolus/insulin pump	2.5
• Once-daily mixed insulin	2
• Basal insulin	1.5
• Glibenclamide/glyburide	1
• Gliclazide modified release or glimepiride or repaglinide	0.5
• Other therapy not including sulfonylureas or insulin	0
6. Self-monitoring of glucose	
• Indicated but not conducted	2
• Indicated but conducted suboptimally	1
• Conducted as indicated	0
7. Acute complications	
• DKA or HHS in the last 3 months	3
• DKA or HHS in the last 6 months	2
• DKA or HHS in the last 12 months	1
• No DKA or HHS	0
8. MVD complications and comorbidities	
• Unstable MVD	6.5
• Stable MVD	2
• No MVD	0
9. Renal complications and comorbidities	
• eGFR <30 mL/min/1.73 m^2	6.5
• eGFR 30–45 mL/min/1.73 m^2	4
• eGFR 45–60 mL/min/1.73 m^2	3
• eGFR >60 mL/min/1.73 m^2	0
10. Pregnancy*	
• Pregnant not within glycemic goals	6.5
• Pregnant within glycemic goals	3.5
• Not pregnant	0
11. Frailty and cognitive function	
• Impaired cognitive function or frail	6.5
• >70 years old with no home support	3.5
• No frailty or loss in cognitive function	0
12. Physical labor	
• Highly intense physical labor	4
• Moderately intense physical labor	2
• No physical labor	0
13. Previous Ramadan experience	
• Overall negative experience	1
• No negative or positive experience	0

Continued on p. S100

diabetes, can increase the risk for malnutrition and sarcopenia (244,245). This is especially concerning among those with heart, kidney, or liver disease and obesity and among racial and ethnic minoritized communities (246,247). Health care professionals should encourage resistance training (248), sufficient protein intake, and screening for sarcopenia and malnutrition in people with diabetes who are experiencing significant or rapid weight loss because they could be at risk for malnutrition. While there is no single best method to screen for both malnutrition and sarcopenia, there are individual instruments available to screen for each respective condition including the Simplified Nutritional Appetite Questionnaire (SNAQ), the Malnutrition Universal Screening Tool (MUST), and others (249–251).

Advising a healthy, whole-foods–based eating pattern alongside regular strength training exercise to maintain lean body mass will be of paramount importance for these segments of the diabetes population (244) (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes").

Food Insecurity and Access

Food insecurity is a household-level economic and social condition of limited or uncertain access to adequate food (252). In 2022, almost 13% of Americans were food insecure (252), and food insecurity affects 16% of adults with diabetes compared with 9% of adults without diabetes (253). There is a complex bidirectional association between food insecurity and co-occurring diabetes. Food security screening should happen at all levels of the health care system. Any member of the health care team can screen for food insecurity using the Hunger Vital Sign. Households are considered at risk if they answer either or both of the following statements as "often true" or "sometimes true" (compared with "never true") (254):

- "Within the past 12 months, we worried whether our food would run out before we got money to buy more."
- "Within the past 12 months, the food we bought just didn't last, and we didn't have money to get more."

If screening is positive for food insecurity, efforts should be made to refer to appropriate programs and resources. See

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Table 5.4—Continued

Risk element	Risk score
14. Fasting hours (varies by geographical location for time of sunrise and sunset)	
• ≥16 h	1
• <16 h	0

Risk categories are defined as follows: score 0–3, low risk, fasting is probably safe; score 3.5–6, moderate risk, fasting is uncertain; score >6, high risk, fasting is probably unsafe. DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; HHS, hyperglycemic hyperosmolar state; MVD, macrovascular disease (cardiac, cerebral, or peripheral). *Individuals who are pregnant or breastfeeding have the right to not fast regardless of whether they have diabetes or not. Adapted from Hassanein et al. (230).

Section 1, "Improving Care and Promoting Health in Populations," for more information concerning the social determinants of health and related issues like food insecurity and access.

PHYSICAL ACTIVITY

Recommendations

5.34 Counsel youth with type 1 diabetes **C** or type 2 diabetes **B** to engage in 60 min/day or more of moderate- or vigorous-intensity aerobic activity, with muscle-strengthening and bone-strengthening activities at least 3 days/week, and to limit the amount of time being spent sedentary, including recreational screen time. **C**

5.35 Counsel most adults with type 1 diabetes **C** and type 2 diabetes **B** to engage in 150 min or more of moderate- to vigorous-intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity. Shorter durations (minimum 75 min/week) of vigorous-intensity or interval training may be sufficient for more physically fit individuals.

5.36 Counsel adults with type 1 diabetes **C** and type 2 diabetes **B** to engage in 2–3 sessions/week of resistance exercise on nonconsecutive days.

5.37 Recommend flexibility training and balance training 2–3 times/week for older adults with diabetes. Yoga and tai chi may be included based on individual preferences to increase flexibility, muscular strength, and balance. **C**

5.38 For all people with diabetes, evaluate baseline physical activity and time spent in sedentary behavior (i.e., quiet sitting, lying, and leaning). For people who do not meet activity guidelines, encourage an increase in physical activities (e.g., walking, yoga, housework, gardening, swimming, and dancing) above baseline. **B** Counsel that prolonged sitting should be interrupted at least every 30 min for blood glucose benefits. **C**

5.39 Counsel adults and youth treated with weight management pharmacotherapy or metabolic surgery that meeting physical activity recommendations, and in particular muscle-strengthening exercises, may be beneficial for maintaining lean body mass. **E**

Table 5.5—Changes in medications during fasting

Medication name	Risk of hypoglycemia	Timing	Total daily dose
Metformin, SGLT2 inhibitor, DPP-4 inhibitor, GLP-1 receptor agonist, acarbose, or pioglitazone	Low	• If once daily, then take at main mealtime. • If twice daily, then split dose between the two meals. • If once weekly, no change of time.	• No change
New generation sulfonylurea (glimepiride and gliclazide)	Low to moderate	• If once daily, then take at main mealtime. • If twice daily, then split dose between the two meals.	• Reduce dose if glucose levels are within individualized goal range and if no hypoglycemia or hyperglycemia is present at baseline.
Older generation of sulfonylurea (glyburide)	Moderate to high	• Take at time of main meal	• Replace with newer-generation sulfonylurea or reduce dose by 50%.
Basal insulin	Moderate to high	• For longer-acting basal analogs (glargine 300 or degludec), no need to change timing. • For other basal insulins, take at beginning of breaking fast meal.	• Choose the insulin with lower risk of hypoglycemia among the class. • Reduce dose by 25–35% if not well managed.
Prandial insulin	High	• At mealtime	• Reduce dose of insulin for the meal followed by fasting (35–50%). • For other meals, insulin dose should match carbohydrate intake.
Mixed insulin and insulin coformulations	High	• If once daily, then take at main mealtime. • If twice daily, then split dose between the two meals	• Reduce dose of insulin for the meal followed by fasting (35–50%). • For other meals, no change of dose.

DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SGLT2, sodium–glucose cotransporter 2.

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Physical activity includes all movement that increases energy use, and it is an important part of the diabetes management plan. Exercise is a more specific form of physical activity that is structured and designed to improve physical fitness. Both physical activity and exercise are important. Exercise has been shown to improve blood glucose levels, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being (255). Physical activity is important for the general population as well as people at risk for and with established diabetes. Exercise plays a specific role in glucose management and in the prevention of diabetes complications in those with type 2 diabetes. Many individuals with type 2 diabetes do not meet the recommended physical activity levels (150 min/week). Objective measurement by accelerometer in 871 individuals with type 2 diabetes showed that 44.2%, 42.6%, and 65.1% of White, African American, and Hispanic individuals, respectively, met the recommended physical activity threshold (256). An RCT in 1,366 individuals with prediabetes combined a physical activity intervention with text messaging and telephone support, which showed improvement in daily step count at 12 months compared with the control group, but this was not sustained at 48 months (257). Another RCT, including 324 individuals with prediabetes, showed increased physical activity at 8 weeks with supportive text messages, but by 12 weeks there was no difference between groups (258). It is important for diabetes care management teams to understand the difficulty that many people have reaching recommended physical activity goals and to identify individualized approaches to improve physical activity and exercise goal achievement, which may need to change over time.

Moderate to high volumes of aerobic activity are associated with substantially lower cardiovascular and overall mortality risks in both type 1 and type 2 diabetes (259). A prospective observational study of adults with type 1 diabetes suggested that higher amounts of physical activity led to reduced cardiovascular mortality after a mean follow-up time of 11.4 years for people with and without chronic kidney disease (260). There are also considerable data for the health benefits (e.g., increased cardiovascular fitness, greater muscle strength, and improved insulin sensitivity) of regular exercise for those with type 1 diabetes (261). Exercise training in type 1 diabetes may also improve several important markers such as triglyceride level, LDL cholesterol, waist circumference, and body mass (262).

Structured exercise interventions of at least 8 weeks have been shown to lower A1C by 0.66% in people with type 2 diabetes, even without a significant change in BMI (263). In adults with type 2 diabetes, higher levels of exercise intensity are associated with greater improvements in A1C and in cardiorespiratory fitness (264); sustained improvements in cardiorespiratory fitness and weight loss have also been associated with a lower risk of heart failure (265). Other benefits include slowing the decline in mobility among people with diabetes and overweight (266).

Physical activity and exercise should be recommended and prescribed to all individuals who are at risk for or have diabetes as part of management of glycemia and overall health, unless otherwise contraindicated. Specific recommendations and precautions will vary by the type of diabetes, age, physical activity, and presence of diabetes-related health complications. Recommendations should be tailored to meet the specific needs of each individual (267), and different strategies may be used in specific populations to increase engagement in physical activity (268). Furthermore, physical activity and exercise plans can be modified or adapted to best suit the fitness level of the individual, which may vary due to disability or other complications. Individuals with diabetes may benefit from a team-based approach, including working with an exercise physiologist, physical therapist, or personal trainer, among others, where available and affordable (269). The ADA position statement "Physical Activity/Exercise and Diabetes" reviews the evidence for the benefits of exercise in people with type 1 and type 2 diabetes and offers specific recommendations (267).

Exercise and Youth

Youth with diabetes or prediabetes should be encouraged to engage in regular physical activity, including at least 60 min of moderate-to-vigorous aerobic activity every day and muscle- and bone-strengthening activities at least 3 days per week (270). Structured exercise programs promoting nutrition modification and increasing exercise in adolescents at risk for type 2 diabetes have been shown to reduce risk of type 2 diabetes development (271). In general, youth with type 1 diabetes benefit from being physically active, and meta-analyses have demonstrated a significant association between physical activity and lower A1C (272). Thus, an active lifestyle should be recommended to all children and adolescents with type 1 and type 2 diabetes (273). Youth with type 1 diabetes who engage in more physical activity may have better health outcomes and health-related quality of life (274,275). Youth are recommended to limit the amount spent as sedentary time, including recreational screen time, to less than 2 h per day (276,277). See Section 14, "Children and Adolescents," for details.

Frequency and Type of Physical Activity

For all people with diabetes, baseline physical activity and time spent in sedentary behavior should be evaluated. People who do not meet activity guidelines should be encouraged to increase physical activity (e.g., walking, yoga, housework, gardening, swimming, and dancing) above baseline (278). Health care professionals should counsel people with diabetes to engage in aerobic and resistance exercise regularly (267). Aerobic activity bouts should last at least 10 min, with the goal of ~30 min/day or more most days of the week for adults with type 2 diabetes. Daily exercise, or at least not allowing more than 2 days to elapse between exercise sessions, is recommended to decrease insulin resistance, regardless of diabetes type (279,280). A study in adults with type 1 diabetes found a dose-response inverse relationship between self-reported bouts of physical activity per week and A1C, BMI, hypertension, dyslipidemia, and diabetes-related complications such as hypoglycemia, DKA, retinopathy, and microalbuminuria (281), and higher physical activity reduces mortality risk in people with type 1 diabetes (260). Over time, activities should progress in intensity, frequency, and/or duration to at least 150 min/week of moderate-intensity exercise. Adults able to run at 6 mph (9.7 km/h) for at least 25 min can benefit sufficiently from shorter durations of vigorous-intensity activity or interval training (75 min/week) (267). Many adults, including most with type 2 diabetes,

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may be unable or unwilling to participate in such intense exercise and should engage in moderate exercise for the recommended duration.

Adults with diabetes are encouraged to engage in 2–3 sessions/week of resistance exercise on nonconsecutive days (282). Although heavier resistance training with free weights or weight machines may improve glycemia and strength (283,284), resistance training of any intensity is recommended to improve strength, balance, and the ability to engage in activities of daily living throughout the life span. Health care professionals should support people with diabetes to set stepwise goals toward meeting the recommended exercise goals. As individuals intensify their exercise program, medical monitoring may be indicated to ensure safety and evaluate the effects on glucose management. (See PHYSICAL ACTIVITY AND GLYCEMIC MANAGEMENT, below.)

The use of weight management pharmacotherapy has recently increased. Both weight management pharmacotherapy and metabolic surgery can lead to a decrease in body weight, which often induces fat mass loss as well as loss of lean body mass. This has raised concern about the loss of muscle mass leading over time to the development or worsening of frailty and sarcopenic obesity (285). One study demonstrated that after discontinuation of weight management pharmacotherapy with GLP-1 RAs in people with obesity but without diabetes, the combination of supervised exercise and GLP-1 RA therapy was more favorable in maintaining body weight and body composition compared with GLP-1 RA therapy alone. Data in people with diabetes and overweight or obesity are emerging. It is recommended that people with diabetes be encouraged to follow the physical activity recommendations, in particular muscle-strengthening activities, to reduce the loss of lean mass (285).

Evidence supports that all individuals, including those with diabetes, should be encouraged to reduce the amount of time spent being sedentary—waking behaviors with low energy expenditure (e.g., seated work at a computer and watching television)—by breaking up bouts of sedentary activity (at least every 30 min) by briefly standing, walking, or performing other light physical activities (286–288). Participating in leisure-time activity and avoiding extended sedentary periods may help prevent type 2 diabetes for those at risk and may also aid in glycemic management for those with diabetes (289,290).

A systematic review and meta-analysis found that higher frequency of regular leisure-time physical activity was more effective in reducing A1C (291). A wide range of activities, including yoga, tai chi, and other types, can significantly affect A1C, flexibility, muscle strength, and balance (255,292–294). Flexibility and balance exercises may be particularly important in older adults with diabetes for maintenance of range of motion, strength, and balance (267) (**Fig. 5.2**). There is strong evidence that exercise interventions in individuals with type 2 diabetes improve depression, A1C, and overall psychosocial well-being (295).

Physical Activity and Glycemic Management

Clinical trials have provided strong evidence for the A1C-lowering value of resistance training in older adults with type 2 diabetes (267) and for an additive benefit of combined aerobic and resistance exercise on A1C reduction in adults with type 2 diabetes (296). If not contraindicated, people with type 2 diabetes should be encouraged to do at least two weekly sessions of resistance exercise (free weights, machines, elastic bands, or body weight as resistance), with each session consisting of at least one set (group of consecutive repetitive exercise motions) of five or more different resistance exercises involving the large muscle groups (297).

For people with type 1 diabetes, there can be a variable glucose response to exercise, possibly leading to hypoglycemia or hyperglycemia. This variability should be taken into consideration when recommending the type, intensity, and duration of exercise for a given individual (261).

Individuals of childbearing potential with preexisting diabetes, particularly type 2 diabetes, and those at risk for or presenting with gestational diabetes mellitus should be advised to engage in regular moderate-intensity physical activity prior to and during their pregnancies, as tolerated (267).

High-Intensity Interval Training

High-intensity interval training (HIIT) involves short bursts of aerobic training performed between 65% and 90% VO_{2peak} (a measure of maximal aerobic capacity) or 75% and 95% heart rate peak for 10 s to 4 min with 12 s to 5 min of active or passive recovery. HIIT is a potentially time-efficient modality that can elicit significant physiologic and metabolic adaptations for individuals with type 1 and type 2 diabetes (298,299). Higher intensities of aerobic training are generally considered superior to low-intensity training (300). HIIT reduces A1C and BMI and improves fitness levels in individuals with type 2 diabetes. Because HIIT can lead to transient increases in post-exercise hyperglycemia, individuals with type 1 diabetes may need to use bolus correction (301) and individuals with type 2 diabetes are encouraged to monitor blood glucose when starting HIIT (297). In type 1 diabetes, HIIT reduces A1C and insulin requirements and improves cardiometabolic risk profiles (299). Variability in glucose may occur with an increased risk in delayed hypoglycemia, so careful monitoring of glucose during and after HIIT is advised (299).

Pre-exercise Evaluation

As discussed more fully in Section 10, "Cardiovascular Disease and Risk Management," the best protocol for assessing asymptomatic people with diabetes for coronary artery disease remains unclear. The ADA consensus report "Screening for Coronary Artery Disease in Patients With Diabetes" (302) concluded that routine testing is not recommended. However, health care professionals should perform a careful history, assess cardiovascular risk factors, and be aware of the atypical presentation of coronary artery disease, such as a recently reported or measured decrease in exercise tolerance. Certainly, those with high risk should be encouraged to start with short periods of low--intensity exercise and slowly increase the duration and intensity as tolerated. Health care professionals should assess for conditions that might contraindicate certain types of exercise or predispose to injury, such as uncontrolled hypertension, untreated proliferative retinopathy, autonomic neuropathy, orthostatic hypotension, peripheral neuropathy, balance impairment, and a history of foot ulcers or Charcot foot. Age and previous physical activity level should be considered when customizing the exercise plan

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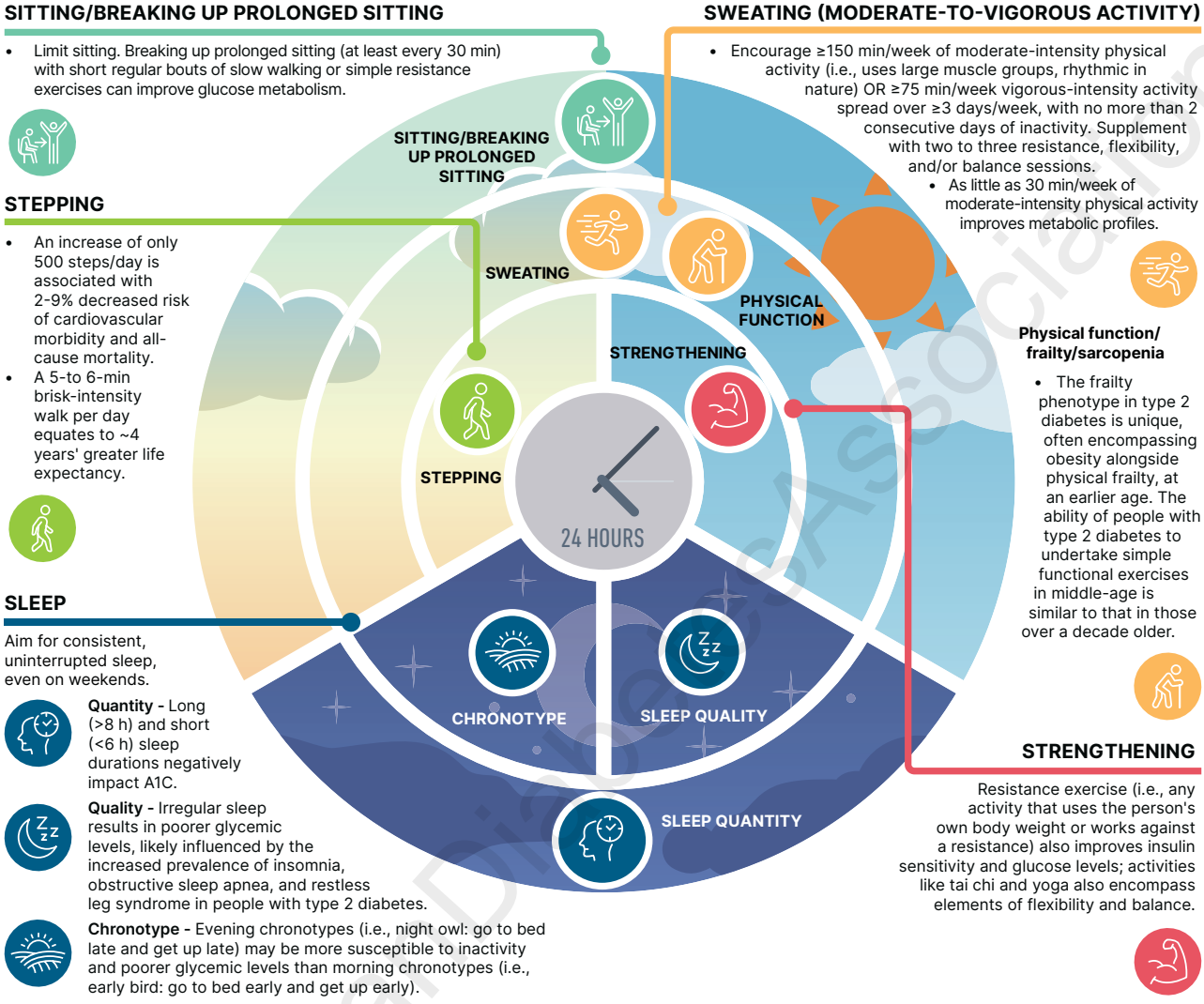
Importance of 24-Hour Physical Behaviors for Type 2 Diabetes



	Glucose/ insulin	Blood pressure A1C	A1C	Lipids	Physical function	Depression	Quality of life
SITTING/BREAKING UP PROLONGED SITTING	↓	↓	↓	↓	↑	↓	↑
STEPPING	↓	↓	↓	↓	↑	↓	↑
SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)	↓	↓	↓	↓	↑	↓	↑
STRENGTHENING	↓	↓	↓	↓	↑	↓	↑
ADEQUATE SLEEP DURATION	↓	↓	↓	↓	?	↓	↑
GOOD SLEEP QUALITY	↓	↓	↓	↓	?	↓	↑
CHRONOTYPE/CONSISTENT TIMING	↓	?	↓	?	?	↓	?

IMPACT OF PHYSICAL BEHAVIORS ON CARDIOMETABOLIC HEALTH IN PEOPLE WITH TYPE 2 DIABETES

↑ Higher levels of improvement (physical function, quality of life) ↓ Lower levels of improvement (glucose/insulin, blood pressure, A1C, lipids, depression)
? No data available
↑ Green arrows = strong evidence ↑ Yellow arrows = medium-strength evidence ↑ Red arrows = limited evidence

Figure 5.2—Importance of 24-h physical behaviors for type 2 diabetes. Adapted from Davies et al. (75).

to the individual's needs. Those with complications may need a more thorough evaluation prior to starting an exercise program (261).

Hypoglycemia

For individuals taking insulin and/or insulin secretagogues, physical activity may cause hypoglycemia if the medication dose or carbohydrate consumption is not adjusted for the exercise session and post-bout effect on glucose. Individuals on these therapies may need to ingest

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carbohydrates if pre-exercise glucose levels are <90 mg/dL (<5.0 mmol/L), depending on whether they are able to lower insulin doses during the workout (such as with an insulin pump or reduced pre-exercise insulin dosage), the time of day exercise is done, and the intensity and duration of the activity (261). In some people with diabetes, hypoglycemia after exercise may occur and last for several hours due to increased insulin sensitivity. Hypoglycemia is not common in those who are not treated with insulin or insulin secretagogues, and no routine preventive measures for hypoglycemia are usually advised in these cases. Intense activities, such as HIIT, may actually raise glucose levels instead of lowering them, especially if pre-exercise glucose is elevated (261). Because of variation in glycemic response to exercise, people with diabetes should be taught to check blood glucose levels and/or monitor CGM values during and after exercise, how to understand the effect of exercise on glucose, and about the potential prolonged effects (depending on intensity and duration) (303). See Section 6, "Glycemic Goals and Hypoglycemia," for more information on hypoglycemia prevention and management.

Exercise in the Presence of Microvascular Complications

See Section 11, "Chronic Kidney Disease and Risk Management," and Section 12, "Retinopathy, Neuropathy, and Foot Care," for more information on these long-term complications. A meta-analysis demonstrated that high versus low levels of physical activity were associated with lower CVD incidence and mortality (summary risk ratio 0.84 [95% CI 0.77–0.92], *n* = 7, and 0.62 [0.55–0.69], *n* = 11) and fewer microvascular complications (0.76 [0.67–0.86], *n* = 8). Dose-response meta-analyses showed that physical activity was associated with lower risk of diabetes-related complications even at lower activity levels (304).

Retinopathy

If proliferative diabetic retinopathy or severe nonproliferative diabetic retinopathy is present, then vigorous-intensity aerobic or resistance exercise may be contraindicated because of the risk of triggering vitreous hemorrhage or retinal detachment (305). Consultation with an ophthalmologist prior to engaging in an intense exercise plan may be appropriate.

Peripheral Neuropathy

Decreased pain sensation and a higher pain threshold in the extremities can result in an increased risk of skin breakdown, infection, and Charcot joint destruction with some forms of exercise. Therefore, a thorough assessment should be done to ensure that neuropathy does not alter kinesthetic or proprioceptive sensation during physical activity, particularly in those with more severe neuropathy. Moderate-intensity walking may not lead to an increased risk of foot ulcers or reulceration in those with peripheral neuropathy who use proper footwear (306,307). In addition, 150 min/week of moderate exercise improved outcomes in people with prediabetic neuropathy (308). All individuals with peripheral neuropathy should wear proper footwear and examine their feet daily to detect lesions early. Anyone with a foot injury or open sore should be restricted to non–weight-bearing activities.

Autonomic Neuropathy

Autonomic neuropathy can increase the risk of exercise-induced injury or adverse events through decreased cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation, impaired night vision due to impaired papillary reaction, and greater susceptibility to hypoglycemia (309). Cardiovascular autonomic neuropathy is also an independent risk factor for cardiovascular death and silent myocardial ischemia (310). Therefore, individuals with diabetic autonomic neuropathy should undergo cardiac investigation before beginning physical activity more intense than that to which they are accustomed.

Chronic Kidney Disease

Physical activity can acutely increase urinary albumin excretion. However, there is no evidence that vigorous-intensity exercise accelerates the rate of progression of CKD, and there appears to be no need for specific exercise restrictions for people with CKD in general (305).

SMOKING CESSATION: TOBACCO, E-CIGARETTES, AND CANNABIS

Recommendations

5.40 Advise all people with diabetes not to use cigarettes and other tobacco products or e-cigarettes. **A**

5.41 Ask people with diabetes routinely about the use of cigarettes or other tobacco products. After identification of use, recommend and refer for combination treatment consisting of both tobacco/smoking cessation counseling and pharmacologic therapy. **A**

5.42 Advise people with type 1 diabetes **C** and those with other forms of diabetes at risk for diabetic ketoacidosis **E** not to use recreational cannabis in any form.

A causal link between cigarette smoking and diabetes has been established and reported on by the Surgeon General for over a decade (311). Results from epidemiologic, case-control, and cohort studies provide convincing evidence to support the causal link between cigarette smoking and multiple health risks that can have a profound effect on morbidity and mortality for people with diabetes (311). People with diabetes who smoke and are exposed to second-hand smoke have a heightened risk of macrovascular complications (e.g., cardiovascular and peripheral vascular disease), microvascular complications (e.g., kidney disease and visual impairment), worsened glycemic outcomes, and premature death compared with those who do not smoke (312–315). Emerging data suggest that smoking has a role in the development of type 2 diabetes, and quitting has been shown to significantly decrease this risk over time (316).

Routine (every visit with every person), thorough assessment of all types of tobacco use is essential to prevent tobacco product initiation and promote cessation. Evidence demonstrates significant benefits to quitting smoking for all people, resulting in a reduction and even reversal of adverse health effects in addition to an increase in life expectancy by as much as a decade (317). However, data show that tobacco use prevalence among adults with chronic conditions has remained persistently higher than that in the general population, though with recent declines in smoking in middle-aged and older adults with diabetes (318). Numerous large RCTs have demonstrated the efficacy and cost-effectiveness of both intensive and brief counseling on smoking cessation, including the use of telephone quit lines and web-based interventions, in reducing tobacco use and maintaining abstinence from smoking (317,319). Current

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recommendations include both counseling and pharmacologic therapy to assist with smoking cessation in nonpregnant adults (320). A secondary data analysis of the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES), a randomized, double-blind, triple-dummy, placebo-controlled and active-controlled trial, found varenicline to be the most efficacious pharmacotherapy for people with diabetes when compared with placebo (321). These findings support the American Thoracic Society 2020 guideline recommending varenicline as a first-line pharmacotherapy for tobacco dependence (322). However, despite the effectiveness of pharmacologic therapy and counseling, more than two-thirds of people trying to quit do not receive treatment following evidence-based guidelines (317).

Weight gain after smoking cessation has been a concern related to diabetes management and risk for new onset of disease (323). While post-cessation weight gain is an identified issue, studies have found that an average weight gain of 3–5 kg does not necessarily persist long term nor diminish the substantial cardiovascular benefit realized from smoking cessation (316). These findings highlight the need for tobacco cessation treatment that addresses eating and physical activity needs. One study in people with newly diagnosed type 2 diabetes who smoke found that smoking cessation was associated with amelioration of microalbuminuria and reduction in blood pressure after 1 year (324).

In recent years, there has been an increase in the use and availability of multiple noncigarette nicotine products. The evidence regarding the effect of these products on diabetes is not as clear as that for combustible cigarettes. It is known that smokeless tobacco products, such as dip and chew, pose an increased risk for CVD and oral cancer (325,326). Vaping with e-cigarettes and related devices has gained public awareness and popularity because of perceptions that e-cigarette use is less harmful than regular cigarette smoking (327). While combustible tobacco products are clearly the most harmful, electronic products should not be characterized as harmless, as health risks with use that affect the cardiovascular and respiratory systems have been identified (328,329). Findings from the Population Assessment of Tobacco and Health (PATH) Study suggest e-cigarettes may contribute to nicotine dependence, confirming there is no safe tobacco product (330,331). Individuals with diabetes should be advised to avoid vaping and using e-cigarettes, either as an approach to stop smoking combustible cigarettes or as a recreational drug. If people are using e-cigarettes to quit, they should be advised to avoid using both combustible and electronic cigarettes, and if using only e-cigarettes, they should be advised to have a plan to quit these also (319).

Increased legalization and multiple formulations of cannabis products have resulted in increased prevalence in the use of these products in all age-groups (332,333). Cannabidiol (CBD), which in its pure form has no psychoactive effect, has received attention for its potential therapeutic benefits in diabetes management. However, research shows no noticeable effect on glucose or insulin levels in adults with type 2 diabetes who use CBD (334). Significant increases in tetrahydrocannabinol (THC) concentrations in CBD products and use of additional psychoactive cannabinoid products, such as delta-8 THC, are of specific concern (335). Most of these products are currently unregulated by the FDA, and public health warnings regarding use have been issued (336). The FDA reports adverse effects related to delta-8 THC, some of which may have health implications for people with diabetes (e.g., vomiting) (336). Evidence of specific increased risk of diabetic ketoacidosis associated with cannabis use has been reported in adults with type 1 diabetes (337–339). Diabetic ketoacidosis in individuals with type 1 diabetes using cannabis is associated with cannabis hyperemesis syndrome, which is marked by severe nausea, abdominal pain, and vomiting (337–339). Recommended diagnostic criteria for cannabis hyperemesis syndrome include a blood glucose of $\geq$250 mg/dL, an anion gap of $>$10, a serum β-hydroxybutyrate level of $>$0.6 mmol/L, a pH level of $\geq$7.4, and a bicarbonate level of $\geq$15 mmol/L (339). Health care professionals should consider cannabis hyperemesis syndrome in people with type 1 diabetes with pH $\geq$7.4 and bicarbonate $>$15 mmol/L in the presence of ketosis (339).

Diabetes education programs offer potential to systematically reach and engage individuals with diabetes in smoking cessation efforts. A cluster randomized trial found statistically significant increases in quit rates and long-term abstinence rates ($>$6 months) when smoking cessation interventions were offered through diabetes education clinics, regardless of motivation to quit at baseline (340). The increased prevalence in availability and use of tobacco and cannabis products and the effect on the health of people with diabetes highlights the need to ask about use of these products, educate individuals regarding the associated risks, and provide support for cessation.

SUPPORTING POSITIVE HEALTH BEHAVIORS

Recommendation

5.43 Behavioral strategies should be used to support diabetes self-management and engagement in health behaviors (e.g., taking medications, using diabetes technologies, and engaging in physical activity and healthy eating) to promote optimal health-related quality of life and health outcomes. **A**

Given associations with glycemic outcomes and risk for future complications (341,342), diabetes care professionals should support people with diabetes engaging in health-promoting behaviors (preventive, treatment, and maintenance), including blood glucose monitoring, taking insulin and medications, using diabetes technologies, engaging in physical activity, and making nutritional changes. Evidence-based behavioral strategies and multicomponent interventions, including motivational interviewing (343,344), activation (40), goal setting and action planning (344–346), problem-solving (7,345), tracking or self-monitoring health behaviors with or without feedback from a health care professional (344–346), and facilitating opportunities for social support (344–346), help people with diabetes and their caregivers or family members develop health behavior routines and overcome barriers to self-management. Behavioral economics strategies (e.g., financial incentives and exposure to information about social norms) show mixed results in the promotion of health behaviors; however, they tend to enhance motivation and demonstrate short-term benefits for behavior change (347). Multicomponent behavior change interventions have the highest efficacy for behavioral and glycemic outcomes (346,348). For youth with diabetes, family-based behavioral intervention packages

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and interventions that address multiple areas of the person's life (i.e., multisystem interventions) demonstrate benefits for increasing management behaviors and improving glycemic outcomes (349). Importantly, adapting and tailoring behavior change strategies to the characteristics and needs of the individual and population are crucial (350,351). Health behavior change strategies can be delivered by behavioral health professionals, CDCES, other trained health care professionals (352,353), or qualified community health workers (345). Additionally, these approaches can be delivered via digital health tools (346,353,354). Finally, diabetes care professionals should be trained to use these methods effectively (e.g., motivational interviewing) (355).

PSYCHOSOCIAL CARE

Recommendations

5.44 Psychosocial care should be provided to all people with diabetes, with the goal of optimizing health-related quality of life and health outcomes. Such care should be integrated with routine medical care and delivered by trained health care professionals using a collaborative, person-centered, culturally informed approach. **A**

5.45 Implement screening protocols for psychosocial concerns, including diabetes distress, depression, anxiety, fear of hypoglycemia, and disordered eating behaviors. Screen at least annually or when there is a change in disease, treatment, or life circumstances. **C**

5.46 When indicated, refer to behavioral health professionals or other trained health care professionals, ideally those with experience in diabetes, for further assessment and treatment for symptoms of diabetes distress, depression, suicidality, anxiety, treatment-related fear of hypoglycemia, disordered eating, and/or cognitive capacities. Such specialized psychosocial care should use age-appropriate standardized and validated tools and treatment approaches. **B**

5.47 Consider developmental factors and use age-appropriate validated tools for psychosocial screening in people with diabetes. **E**

Please refer to the ADA position statement "Psychosocial Care for People With Diabetes" for a list of assessment tools and additional details (1) and the ADA Behavioral Health Toolkit for assessment questionnaires and surveys (professional.diabetes.org/meetings/behavioral-health-toolkit). Throughout the Standards of Care, the broad term "behavioral health" is used to encompass both *1*) health behavior engagement and relevant factors and *2*) behavioral health concerns and care related to living with diabetes.

Psychosocial factors, including environmental, social, family, behavioral, and emotional factors, influence living with diabetes and achieving optimal health outcomes. People with diabetes and their families or caregivers face complex, multifaceted challenges integrating diabetes care into daily life (356). Clinically significant behavioral health diagnoses are considerably more prevalent in people with diabetes than in those without (357,358). Psychosocial well-being is a critical component of diabetes care and self-management. Psychological and social problems can interfere with a person's (359–361) or family's (361) ability to perform diabetes care tasks and negatively affect health status. In addition to affecting a person's ability to conduct self-management, behavioral health diagnoses are associated with reduced short-term glycemic stability and increased mortality risk (358,362). Therefore, psychological symptoms, both clinical and subclinical, must be addressed.

Diabetes health care professionals should routinely monitor and screen for psychosocial concerns in a timely and efficient manner and refer to appropriate services (363,364). Various health care professionals can contribute to psychosocial care based on training, experience, need, and availability (353,365,366). Ideally, qualified behavioral health professionals with specialized training and experience in diabetes should be integrated with or provide collaborative care as part of diabetes care teams (367,368). Referrals for in-depth assessment and treatment for psychosocial concerns should be made to such behavioral health professionals when indicated (369, 370). A systematic review and meta-analysis showed that psychosocial interventions modestly but significantly improved A1C and behavioral health outcomes (371). It should be noted that the association between the effects on A1C and behavioral health was limited, and no intervention characteristics predicted benefit on both outcomes. Cost analyses also have shown that behavioral health interventions are both effective and cost-effective approaches for the prevention of diabetes (372).

Screening

Health care teams and clinical practices should develop and implement psychosocial screening protocols to ensure routine monitoring of psychosocial well-being and to identify potential concerns among people with diabetes, following published guidance and recommendations (373–376). Topics to screen for may include, but are not limited to, attitudes about diabetes, expectations for treatment and outcomes (especially related to starting a new treatment or technology), general and diabetes-related mood, stress, and/or quality of life (e.g., diabetes distress, depressive symptoms, anxiety symptoms, and fear of hypoglycemia), available resources (financial, social, family, and emotional), and/or psychiatric history. Given elevated rates of suicidality among people with diabetes (377,378), screening for suicidality may also be appropriate (379–381), similar to U.S. Preventive Services Task Force statements regarding screening for some adolescents and adults in the general population (382,383). A list of age-appropriate screening and evaluation measures is provided in the ADA position statement "Psychosocial Care for People with Diabetes" (1), and guidance has been published about selection of screening tools, clinical thresholds, and frequency of screening (374,384).

Key opportunities for psychosocial screening occur at diabetes diagnosis, during regularly scheduled management visits, during hospitalizations, with new onset of complications, during significant transitions in care such as from pediatric to adult care teams (385), at the time of medical treatment changes, or when problems with achieving A1C goals, quality of life, or self-management are identified. Additionally, significant changes in life circumstances and SDOH are known to affect a person's ability to self-manage their diabetes. Thus, screening for SDOH should also be incorporated into routine care (386). In circumstances where individuals other than the person with diabetes are significantly involved in diabetes management (e.g., caregivers or family members), these issues should be monitored and treated by appropriate professionals (385,387).

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Standardized, validated, age-appropriate tools for psychosocial monitoring and screening can also be used (1). The ADA provides access to tools for screening specific psychosocial topics, such as diabetes distress, fear of hypoglycemia, and other relevant psychological symptoms at professional.diabetes.org/sites/default/files/media/ada_mental_health_toolkit_questionnaires.pdf. Additional information about developmentally specific psychosocial screening topics is available in Section 14, "Children and Adolescents," and Section 13, "Older Adults." Health care professionals may also use informal verbal inquires, for example, by asking whether there have been persistent changes in mood during the past 2 weeks or since the individual's last appointment and whether the person can identify a triggering event or change in circumstances. Diabetes care professionals should also ask whether there are new or different barriers to treatment and self-management, such as feeling overwhelmed or stressed by having diabetes (see DIABETES DISTRESS, below), changes in finances, or competing medical demands (e.g., the diagnosis of a comorbid condition).

Psychological Assessment and Treatment

When psychosocial concerns are identified, referral to a qualified behavioral health professional, ideally one specializing in diabetes, should be made for comprehensive evaluation, diagnosis, and treatment (353,369,370). Indications for referral may include positive screening for diabetes distress, depression, anxiety, disordered eating, or cognitive dysfunction (see **Table 5.6** for a complete list). Incorporating psychosocial assessment and treatment into routine care is preferable to waiting for a specific problem or deterioration in glycemic or psychological status to occur (37,361). Health care professionals should identify and refer to behavioral health professionals knowledgeable about diabetes and psychosocial care. The ADA provides a list of behavioral health professionals who have specialized expertise or who have received education about psychosocial and behavioral issues related to diabetes in the ADA Mental Health Professional Directory (professional.diabetes.org/ada-mental-health-provider-directory). Ideally, behavioral health professionals should be embedded in diabetes care settings. In recognition of limited behavioral health resources and to optimize availability, other health care professionals who have been trained in behavioral health interventions may also provide this specialized psychosocial care (365,367,388). Although some health care professionals may not feel qualified to treat psychological problems (389), strengthening the relationship between a person with diabetes and the health care professional may increase the likelihood of a person accepting a referral for other services. Collaborative care interventions and a team approach have demonstrated efficacy in diabetes self-management, outcomes of depression, and psychosocial functioning (5,6). The ADA provides resources for a range of health professionals to support behavioral health in people with diabetes at professional.diabetes.org/meetings/behavioral-health-toolkit.

Evidence supports interventions for people with diabetes and psychosocial concerns, including issues that affect behavioral health. Successful therapeutic approaches include cognitive behavioral (369,390,391) and mindfulness-based therapies (392). See the sections below for details about interventions for specific psychological concerns. Behavioral interventions may also be indicated in a preventive manner even in the absence of positive psychosocial screeners, such as resilience-promoting interventions to prevent diabetes distress in adolescence (393,394) and behavioral family interventions to promote collaborative family diabetes management in early adolescence (395,396) or to support adjustment to a new treatment plan or technology (64). Psychosocial interventions can be delivered via digital health platforms (397). Group-based or shared diabetes appointments that address both medical and psychosocial issues relevant to living with diabetes are a promising model to consider (366,398).

Although psychosocial interventions have demonstrated short-term efficacy, their success in sustained engagement in health behaviors and improved glycemic outcomes associated with behavioral health issues has varied. Thus, health care professionals should systematically monitor these outcomes following implementation of current evidence-based psychosocial treatments to determine ongoing needs.

Diabetes Distress

Recommendation

5.48 Screen for diabetes distress at least annually in people with diabetes, caregivers, and family members, and repeat screening when treatment goals are not met, at transitional times, and/or in the presence of diabetes complications. Health care professionals can

Table 5.6—Situations that warrant referral of a person with diabetes to a qualified behavioral health professional for evaluation and treatment

• A positive screen on a validated screening tool for depressive symptoms, diabetes distress, anxiety, fear of hypoglycemia, suicidality, or cognitive impairment
• The presence of symptoms or suspicions of disordered eating behavior, an eating disorder, or disrupted patterns of eating
• Intentional omission or underdosing of insulin or noninsulin medication to cause weight loss
• A serious mental illness is suspected
• In youth and families with behavioral self-care difficulties, repeated hospitalizations for diabetic ketoacidosis, failure to achieve expected developmental milestones, or significant distress
• Low engagement in diabetes self-management behaviors, including declining or impaired ability to perform diabetes self-management behaviors
• Before undergoing metabolic surgery and after surgery, if assessment reveals an ongoing need for adjustment support

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address diabetes distress and may consider referral to a qualified behavioral health professional, ideally one with experience in diabetes, for further assessment and treatment if indicated. **B**

Diabetes distress is very common (361, 399,400). Distress is distinct from depression and anxiety and has unique relationships with glycemic and other outcomes (401,402) (**Tables 5.7** and **5.8**). Diabetes distress refers to significant negative psychological reactions related to emotional burdens and worries specific to an individual's experience in having to manage a demanding chronic condition such as diabetes (403). The constant behavioral demands of diabetes self-management (medication dosing, frequency, and titration as well as monitoring of glucose, food intake, eating patterns, and physical activity) and the potential or actual disease progression are directly associated with reports of diabetes distress (404). Diabetes distress in people with type 2 diabetes is common and persistent, with prevalence rates over 60% (404,405). Among people with type 1 diabetes, the prevalence of diabetes distress is 22–42%, with a 9-month incidence of 54% (400,406). In the second Diabetes Attitudes, Wishes, and Needs (DAWN2) study, 45% of the participants reported significant diabetes distress, but only 24% reported that their health care teams asked them how diabetes affected their lives (361). Similar rates of diabetes distress have been identified among adolescents with type 1 diabetes (399) and in parents of youth with type 1 diabetes. Diabetes distress negatively affects medication-taking behaviors and is linked to higher A1C, lower self-efficacy, and less optimal eating and exercise behaviors (5,403,407). Diabetes distress is also associated with symptoms of anxiety, depression, and reduced health-related quality of life (408). The experience of stigma related to living with diabetes may contribute to increased diabetes distress (409,410).

Diabetes distress should be routinely monitored (411) using diabetes-specific validated measures (1), such as those available through the ADA's website (professional.diabetes.org/sites/default/files/media/ada_mental_health_toolkit_questionnaires.pdf). As there are validated diabetes distress measures for people with type 1 and type 2 diabetes

Table 5.7—Psychosocial concerns and their association with diabetes-related outcomes in adults with type 1 diabetes

	Increased A1C	Increased blood pressure	Increased cholesterol	Increased macrovascular complications	Increased microvascular complications	Decreased self-care behaviors	Comorbid psychosocial concerns	Decreased quality of life	Increased mortality
Diabetes distress (406,528–530)	+++	?	+	+++	+++	+++	+++	+++	?
Depression and depressive symptoms (528,529,531,532)	+++	?	+++	+++	+++	+++	+++	+++	+++
Anxiety (359,533,534)	+++	?	?	?	?	+++	+++	+++	?
Disordered eating behaviors (insulin omission) (535,536)	+++	?	?	?	+++	+++	+++	+++	+++
Serious mental illness (schizophrenia, personality disorders) (537–539)	+++	?	+	+++	+++	?	+++	?	+++
Cognitive impairment (540–544)	+++	+++	+++	+++	+++	++	+++	?	+++

+++, strong evidence (consistent findings in multiple studies of good methodological quality or one study of excellent methodological quality); **++**, moderate evidence (consistent findings in multiple studies of fair methodological quality or one study of good methodological quality); **+**, limited evidence (evidence from one study of fair methodological quality); ?, no data available.

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Table 5.8—Psychosocial concerns and their association with diabetes-related outcomes in adults with type 2 diabetes

	Increased A1C	Increased blood pressure	Increased dyslipidemia	Increased macrovascular complications	Increased microvascular complications	Decreased self-care behaviors	Comorbid psychosocial concerns	Decreased quality of life	Increased mortality
Diabetes distress (545–551)	+++	+	+	+++	+++	+++	+++	+++	+++
Depression and depressive symptoms (552–559)	+++	++	+++	+++	+++	+++	+++	+++	+++
Anxiety (358,408,553,560–563)	+++	++	+	+++	+	+++	+++	+++	+++
Disordered eating behaviors (binge eating disorder, night eating syndrome) (564–567)	+/–	?	?	?	?	+	+++	+++	?
Serious mental illness (schizophrenia, bipolar disorder) (568–575)	+/–	?	?	+++	+++	+++	+++	+++	+++
Cognitive impairment (576–583)	+++	+++	+++	+++	+++	+++	+++	+++	+++

+++, strong evidence (consistent findings in multiple studies of good methodological quality or one study of excellent methodological quality); ++, moderate evidence (consistent findings in multiple studies of fair methodological quality or one study of good methodological quality); +, limited evidence (evidence from one study of fair methodological quality); +/–, inconclusive evidence; ?, no data available.

at different life stages, it is important to select a tool that is appropriate for each person or population. If diabetes distress is identified, it should be acknowledged and addressed (412). If indicated, the person should be referred for follow-up care (370). This may include specific DSMES to address areas of diabetes self-care causing distress and affecting clinical management and/or behavioral intervention from a qualified behavioral health professional, ideally one with expertise in diabetes, or from another trained health care professional (413).

Several educational and behavioral intervention strategies have demonstrated benefits for diabetes distress and, to a lesser degree, glycemic outcomes. These interventions include educational, psychological, and health behavior change approaches such as DSMES, cognitive behavioral therapy (CBT), mindfulness-based therapies, motivational interviewing, and others (390,391,414,415). Interventions delivered via telephone, smartphone applications, video visits, and/or self-help modalities can be effective in reducing diabetes distress (397,416–418). DSMES has been shown to reduce diabetes distress (5,419) and may also benefit A1C when combined with peer support (420). It may be helpful to provide counseling regarding expected diabetes-related emotional distress at diagnosis and when the disease state, treatment, or life context changes (413). Two multisite RCTs with adults with type 1 diabetes, elevated diabetes distress, and elevated A1C demonstrated clinically meaningful improvements in diabetes distress and A1C through a combination of group-based intervention approaches including an educational diabetes self-management program and a psychological intervention that included emotion-focused skills (417). In adults with type 2 diabetes in the Veterans Affairs system, an RCT demonstrated that integrating a single session of mindfulness into DSMES, followed by a booster session and 24 weeks of mobile app–based home practice, significantly reduced diabetes distress compared with a DSMES-only control group (421). An RCT of CBT demonstrated positive benefits for diabetes distress, A1C, and depressive symptoms for up to 1 year among adults with type 2 diabetes and elevated symptoms of distress or depression (422). An RCT among people with type 1 and type 2 diabetes found mindful self-compassion

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training increased self-compassion, reduced depression and diabetes distress, and improved A1C (423). An RCT of a resilience-focused cognitive behavioral and social problem-solving intervention compared with diabetes education in teens with type 1 diabetes showed that diabetes distress and depressive symptoms were significantly reduced for up to 3 years post-intervention, although neither A1C nor self-management behaviors improved over time (394). A meta-analysis of RCTs found that in type 1 diabetes, use of automated insulin delivery systems contributed to decreases in diabetes distress compared with usual care (i.e., sensor augmented pumps, multiple daily insulin injections, continuous glucose monitoring, and predictive low-glucose suspend) (424). These recent studies support that a combination of educational, behavioral, and psychological intervention approaches is needed to address distress, depression, and A1C.

There are few outcome data on long-term systematic treatment of diabetes distress integrated into routine care. As the burden of diabetes management can vary over time, diabetes distress may fluctuate and may need varying treatment approaches at different life stages and at different levels of diabetes progression.

Anxiety

Recommendations

5.49 Screen people with diabetes for anxiety symptoms. Health care professionals can discuss diabetes-related worries and should consider referral to a qualified behavioral health professional for further assessment and treatment if anxiety symptoms indicate interference with diabetes self-management behaviors or quality of life. **B**

5.50 Screen people with diabetes at risk for hypoglycemia or fear of hypoglycemia, especially if they have experienced severe and/or frequent hypoglycemic events. **B**

Anxiety symptoms are common in people with diabetes (425) (see **Tables 5.7** and **5.8**), and there appear to be higher rates of generalized anxiety disorder, body dysmorphic disorder, obsessive compulsive disorder, specific phobias, and posttraumatic stress disorder in people with diabetes than in those without diabetes. The Behavioral Risk Factor Surveillance System estimated the lifetime prevalence of generalized anxiety disorder to be 19.5% in people with either type 1 or type 2 diabetes (426). A common diabetes-specific concern is fear related to hypoglycemia (427–429), which may explain avoidance of behaviors associated with lowering glucose, such as increasing insulin doses or frequency of monitoring. Factors related to greater fear of hypoglycemia in people with diabetes and family members include history of nocturnal hypoglycemia, presence of other psychological concerns, and sleep concerns (430). See Section 6, "Glycemic Goals and Hypoglycemia," for more information about impaired awareness of hypoglycemia and related fear of hypoglycemia. Other common sources of diabetes-related anxiety include not meeting glycemic goals (425), insulin injections or infusion (431), and onset of complications (1). People with diabetes who exhibit excessive diabetes self-management behaviors well beyond what is prescribed or needed to achieve glycemic goals may be experiencing symptoms of obsessive-compulsive disorder (432). General anxiety is a predictor of injection-related anxiety and is associated with fear of hypoglycemia (433).

Psychological and behavioral care can be helpful to address symptoms of anxiety in people with diabetes. Among adults with type 2 diabetes and elevated depressive symptoms, an RCT of collaborative care demonstrated benefits on anxiety symptoms for up to 1 year (434). An RCT of CBT for adults with type 2 diabetes showed a reduction in health anxiety, with CBT accounting for 77% of the reduction in health anxiety at 16 weeks of follow-up; this trial also found decreased depressive symptoms and diabetes distress (435). Additionally, an RCT showed switching from isCGM without alerts to rtCGM with alert functionality in adults with type 1 diabetes decreased hypoglycemia-related anxiety at 24 months of follow-up while reducing A1C (436). Similarly, a systematic review and meta-analysis found that people with type 1 diabetes using diabetes technologies, specifically rtCGM, sensor-augmented pumps, and automated insulin delivery, reported decreased fear of hypoglycemia independent of the reduction of hypoglycemia frequency (437). Another RCT of a CBT-based intervention reported reduced fear of hypoglycemia by 8.5% compared with control participants, increased time in range, and improved self-management behaviors in young adults with type 1 diabetes over an 8-week period (438). Thus, specialized behavioral intervention with positive adjunct of diabetes technology from a qualified professional is needed to treat hypoglycemia-related anxiety.

Depression

Recommendations

5.51 Conduct at least annual screening of depressive symptoms in all people with diabetes and more frequently among those with a history of depression. Use age-appropriate, validated depression screening measures, recognizing that further evaluation will be necessary for individuals who have a positive screen. **B**

5.52 Rescreen for depression at diagnosis of complications or when there are significant changes in medical status. **B**

5.53 Refer to qualified behavioral health professionals or other trained health care professionals with experience using evidence-based treatment approaches for depression in conjunction with collaborative care with the diabetes treatment team. **A**

History of depression, current depression, and antidepressant medication use are risk factors for the development of type 2 diabetes, especially if the individual has other risk factors, such as obesity and family history of type 2 diabetes (439,440). Elevated depressive symptoms and depressive disorders are common among people with diabetes (357,429) (**Tables 5.7** and **5.8**), affecting approximately one in four people with type 1 or type 2 diabetes (360), and among parents of youth with diabetes (441). Routine screening for depressive symptoms is indicated for people with type 1 or type 2 diabetes and gestational diabetes mellitus. Regardless of diabetes type, women have significantly higher rates of depression than men (442). For individuals with type 2 diabetes, the experience of diabetes-related stigma is associated with increased depressive symptoms (410).

Routine monitoring with age-appropriate validated measures (1) can help to identify if referral is warranted (370). Multisite studies have demonstrated feasibility of implementing depressive symptom screening protocols in diabetes clinics and published practical guides for

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implementation (374,375). Person-centered integrated care approaches have been shown to improve both depression and glycemic outcomes (443). The behavioral health professional providing treatment for depression should be incorporated into or collaborate with the diabetes treatment team (443). Depressive symptoms may also be a manifestation of reduced quality of life secondary to diabetes burden (also see DIABETES DISTRESS, above) (411). When depressive symptoms are identified, it is important to query origins and exacerbating factors, both diabetes-specific ones and those due to other life circumstances (408,444).

Trials have shown consistent evidence of improvements in depressive symptoms and variable benefits for A1C when depression is treated simultaneously with diabetes (445), whether through pharmacologic treatment, group therapy, psychotherapy, parenting intervention, mindfulness-based approaches, or collaborative care (6,390,446–449). Psychological interventions addressing depressive symptoms have shown efficacy when delivered via digital technologies (447,450). A meta-analysis found that internet- and phone-delivered CBT and self-guided interventions improved depressive symptoms (451). For people with diabetes, an RCT comparing internet plus telephonic CBT to usual care found moderate to large improvements in depressive symptoms at 12 months (452). Lifestyle interventions (i.e., changing nutrition and/or physical activity) also demonstrate benefits for depressive symptoms and A1C (295) on their own and when combined with CBT (453–455). Finally, a systematic review and meta-analysis found that use of GLP-1 RAs led to significant improvement in depressive symptoms among adults with type 2 diabetes (456). It is important to note that the medical treatment plan should also be monitored in response to reduction in depressive symptoms.

Disordered Eating Behavior

Recommendations

5.54 Screen for disordered or disrupted eating using validated screening measures. In addition, a review of the medical treatment plan is recommended to identify potential treatment-related effects on hunger/caloric intake. **B**

5.55 Consider reevaluating the treatment plan of people with diabetes who present with symptoms of disordered eating behavior, an eating disorder, or disrupted patterns of eating, in consultation with a qualified professional. Key qualifications include familiarity with diabetes disease physiology, treatments for diabetes and disordered eating behaviors, and weight-related and psychological risk factors for disordered eating behaviors. **B**

Estimated prevalence of disordered eating behavior and diagnosable eating disorders in people with diabetes varies (457–459) (see **Tables 5.7** and **5.8**). People with type 1 diabetes have been found to be at greater risk for eating disorders than people without diabetes (460). Prevalence of intentional insulin omission to lose weight is 10% and more common among women than men with type 1 diabetes (460). In people with type 2 diabetes, bingeing (excessive food intake with an accompanying sense of loss of control) is most commonly reported. For people with type 2 diabetes treated with insulin, intentional omission is also frequently reported (461). People with diabetes and diagnosable eating disorders have high rates of comorbid psychiatric disorders (462). People with type 1 diabetes and eating disorders often have high rates of diabetes distress and fear of hypoglycemia (463).

Diabetes care professionals should monitor for disordered eating behaviors using validated measures; diabetes-specific measures are recommended to assess presence of intentional insulin omission and were found in a meta-analysis to be more strongly associated with A1C (464). When evaluating symptoms of disordered or disrupted eating (when the individual exhibits eating behaviors that appear maladaptive but are not volitional, such as bingeing caused by loss of satiety cues), etiology and motivation for the behavior should be evaluated by a qualified disordered eating professional (465). Inconsistent intervention findings point to the need for treatment of eating disorders and disordered eating behavior in the context of the condition and its treatment. Recent intervention efforts have focused on preventing disordered eating behaviors among individuals with type 1 diabetes and on supporting parents of youth with type 1 diabetes who are at risk for disordered eating; however, more RCTs with longer-term follow-up are needed (466–468).

Given the complexities of treating disordered eating behaviors and disrupted eating patterns in people with diabetes, it is recommended that interprofessional care teams include or collaborate with a health professional trained to identify and treat eating behaviors and with expertise in disordered eating and diabetes (469). Key qualifications for such professionals include familiarity with diabetes physiology, weight-related and psychological risk factors for disordered eating behaviors, and treatments for diabetes and disordered eating behaviors. More rigorous methods to identify underlying mechanisms of action that drive change in eating and treatment behaviors, as well as associated mental distress, are needed (470). Health care teams may consider the appropriateness of technology use among people with diabetes and disordered eating behaviors, although more research on the risks and benefits is needed (471). Caution should be taken in labeling individuals with diabetes as having a diagnosable psychiatric disorder, i.e., an eating disorder, when disordered or disrupted eating patterns are found to be associated with the disease and its treatment. In other words, patterns of maladaptive food intake that appear to have a psychological origin may be driven by physiologic disruption in hunger and satiety cues, metabolic perturbations, and/or secondary distress because of the individual's inability to control their hunger and satiety (465).

The use of incretin therapies, specifically GLP-1 RAs and potentially dual GIP and GLP-1 RAs, may have relevance to the treatment of disrupted or disordered eating (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes"). These therapies work in the appetite and reward circuitries to modulate food intake, reducing uncontrollable hunger and overeating (472). A systematic review found early evidence for GLP-1 RAs being effective in reducing binge-eating behaviors, but clinical trials are needed (473).

Serious Mental Illness

Recommendations

5.56 Provide an increased level of support for people with diabetes and serious mental illness through enhanced

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monitoring of and assistance with diabetes self-management behaviors. **B**

5.57 Monitor changes in body weight, glycemia, and lipids in adolescents and adults with diabetes who are prescribed second-generation antipsychotic medications; adjust the treatment plan accordingly, if needed. **C**

Studies of individuals with serious mental illness, particularly schizophrenia and other thought disorders, show significantly increased rates of type 2 diabetes (474) (see **Tables 5.7** and **5.8**). People with schizophrenia and other thought disorders who are prescribed antipsychotic medications should be monitored for prediabetes and type 2 diabetes because of the known comorbidity. Changes in body weight, glycemia, and lipids should be monitored every 12–16 weeks, unless clinically indicated to be monitored sooner (475). Disordered thinking and judgment can make it difficult to engage in behaviors that reduce risk factors for type 2 diabetes, such as restrained eating for weight management. Further, people with serious mental illness and diabetes frequently experience moderate psychological distress, suggesting pervasive intrusion of behavioral health issues into daily functioning (476). Serious mental illness is often associated with the inability to evaluate and apply information to make judgments about treatment options. For a person with an established diagnosis of a mental illness affecting judgment, activities of daily living, and the ability to collaborate with care professionals, including a nonmedical caretaker, in treatment decision-making is beneficial. This caretaker can help improve the person's ability to follow the agreed-upon treatment plan through both monitoring and caretaking functions (477).

Coordinated management of prediabetes or diabetes and serious mental illness is recommended to achieve diabetes treatment goals. The diabetes care team, in collaboration with other care professionals, should work to provide an enhanced level of care and self-management support for people with diabetes and serious mental illness based on individual capacity and needs. Such care may include remote monitoring, facilitating health care aides, and providing diabetes training for family members, community support personnel, and other caregivers. A systematic review and meta-analysis of nonpharmacologic interventions for people with type 2 diabetes and serious mental illness showed significant reductions in psychiatric symptoms, total cholesterol, and LDL cholesterol. These nonpharmacologic interventions did not reduce A1C, triglycerides, or BMI (478). Qualitative research suggests that educational and behavioral interventions provide benefit via group support, accountability, and assistance with applying diabetes knowledge (479).

Cognitive Capacity and Impairment

Recommendations

5.58 Cognitive capacity should be monitored throughout the life span for all individuals with diabetes, particularly in those who have documented cognitive disabilities, those who experience severe hypoglycemia, very young children, and older adults. **B**

5.59 If cognitive capacity changes or appears to be suboptimal for decision-making and/or behavioral self-management, referral for a formal assessment should be considered. **E**

Cognitive capacity is generally defined as attention, memory, logic and reasoning, and auditory and visual processing, all of which are involved in diabetes self-management behavior (480) (see **Tables 5.7** and **5.8**). Long-term diabetes (type 1 or type 2) has been associated with cognitive decline (481,482). In people with type 1 diabetes, the following factors have been linked with cognitive impairment: diabetes-specific factors (e.g., younger age at diagnosis, longer disease duration, more time in glycemic extremes, recurrent DKA, higher A1C, and presence of microvascular complications), other medical factors (e.g., dyslipidemia, intestinal flora, and poorer sleep quality), and sociodemographic factors (e.g., female sex and lower educational level) (483). Diagnosis of dementia is more prevalent among people with diabetes, both type 1 and type 2 (484). Executive functioning is an aspect of cognitive capacity that has particular relevance to diabetes management. Declines in cognitive capacity have been shown to affect executive function and information processing speed; they are not consistent between people, and evidence is lacking regarding a known course of decline (485).

Attention deficit hyperactivity disorder, which involves deficits in executive functions, has been linked with twice the risk of type 2 diabetes (486). Among youth and young adults with type 1 diabetes, lower executive functioning has been linked with more difficulties with diabetes self-management and higher A1C (487). In contrast, higher self-regulation has been linked with improved emotional and diabetes-specific functioning (488). Thus, monitoring cognitive capacity and skills among individuals with or at risk for diabetes is recommended, particularly regarding their ability to self-monitor and make judgments about their symptoms, physical status, and needed adjustments to their self-management behaviors, all of which are mediated by executive function (484).

As with other disorders affecting mental capacity (e.g., major psychiatric disorders), the key issue is whether the person can collaborate with the care team to achieve optimal metabolic outcomes and prevent complications, both short term and long term (476). When cognitive ability is altered, declining, or absent, a lay care professional should be introduced into the care team to serve in the capacity of a day-to-day monitor as well as a liaison to the care team (1). Cognitive capacity also contributes to the ability to benefit from DSMES and may indicate the need for alternative teaching approaches as well as remote monitoring. Youth will need second-party monitoring (e.g., parents and adult caregivers) until they are developmentally able to evaluate necessary information for self-management decisions and to inform resultant behavior changes.

Episodes of severe hypoglycemia are independently associated with cognitive decline as well as the more immediate symptoms of mental confusion (489). Early-onset type 1 diabetes is associated with potential long-term deficits in intellectual abilities, especially in the context of repeated episodes of severe hypoglycemia (490), and is correlated with higher A1C and sensor glucose values (491) (See Section 14, "Children and Adolescents," for information on early-onset diabetes and cognitive abilities and the effects of severe hypoglycemia on children's cognitive and academic performance). Thus, for myriad reasons, cognitive capacity should be assessed during routine care to ascertain the person's ability to maintain and adjust self-management behaviors,

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such as dosing of medications, remediation approaches to glycemic excursions, etc., and to determine whether to enlist a caregiver in monitoring and decision-making regarding management behaviors. If cognitive capacity to conduct self-management behaviors is questioned, an age-appropriate test of cognitive capacity is recommended (1). Cognitive capacity should be evaluated in the context of the person's age, such as in very young children who are not expected to manage their disease independently and in older adults who may require active monitoring of treatment plan behaviors.

Cognitive decline is more severe in older adults with type 2 diabetes (492). Longitudinal epidemiological studies have documented that chronic hyperglycemia, acute glucose variability, older age, less education, retinopathy, and nephropathy are associated with diabetes-related cognitive dysfunction (493,494). Importantly, the risk of cognitive decline can be reduced through improved A1C (495). Further, glucose-lowering treatments may decrease the risk of cognitive decline. A systematic review and network meta-analysis showed that treatment with SGLT2 inhibitors and GLP-1 RAs had a decreased risk for cognitive impairment, whereas sulfonylureas had the highest increased risk for cognitive impairment (496). Additionally, exercise may be a potential nonpharmacologic treatment pathway for cognitive impairment in older adults with type 2 diabetes (497).

Sleep Health

Recommendations

5.60 Consider screening for sleep health in people with diabetes, including symptoms of sleep disorders, disruptions to sleep due to diabetes symptoms or management needs, and worries about sleep. Refer to sleep medicine specialists and/or qualified behavioral health professionals as indicated. **B**

5.61 Counsel people with diabetes to practice sleep-promoting routines and habits. **A**

The associations between sleep problems and diabetes are complex: sleep disorders are a risk factor for developing type 2 diabetes (498,499) and possibly gestational diabetes mellitus (500). People with diabetes across the life span often experience sleep disruptions and reduced sleep quality (501,502), and sleep problems are also common in parents of youth with diabetes, especially soon after diagnosis (503,504). Disrupted sleep and sleep disorders, including obstructive sleep apnea (OSA) (505), insomnia, and sleep disturbances (506), are common among people with diabetes. In type 1 diabetes, estimates of poor sleep range from 30% to 50% (507), and estimates of moderate to severe OSA are >50% (505). In type 2 diabetes, 24–86% of people are estimated to have OSA (508), 39% to have insomnia, and 8–45% to have restless leg syndrome (i.e., an uncontrollable urge to move legs) (509). Further, people with type 2 diabetes and restless leg syndrome are more likely to experience microvascular and macrovascular complications (510) as well as depression (511). Additionally, people with diabetes who perform shift work increase their risk for circadian rhythm disorders, which are associated with higher A1C (512), neuropathy (513), and decreased psychological well-being (513). Health care professionals should consider a comprehensive evaluation of the daily lifestyles of people with diabetes to decrease risk factors, including low sleep duration, shift work, and days off, given their associations with hyperglycemia, hypertension, dyslipidemia, and weight gain (514).

The high prevalence of OSA in people with diabetes poses significant clinical implications for diabetes management. Sleep fragmentation and hypoxemia activate the sympathetic nervous system, contributing to hyperglycemia, insulin resistance, increased circulating free fatty acids, impaired microcirculation, oxidative stress, and psychological stress (515). A systematic review and meta-analysis of 11 RCTs with 964 total participants found that continuous positive airway pressure (CPAP) significantly reduced A1C by 0.24% (95% CI −0.43 to −0.06%, P = 0.001) (516). Similarly, a randomized proof-of-concept study with 30 adults with OSA and obesity compared CPAP therapy, GLP-1 RA–mediated weight loss, and both in combination for 24 weeks (517). Findings showed that CPAP alone and in combination reduced apnea-hypopnea severity more than GLP-1 RA–mediated weight loss alone. CPAP therapy also improved vascular inflammation and reduced unstable plaque volume, suggesting potential benefits for early CVD. Two phase 3, double-blind RCTs with 469 adults with OSA and obesity showed that a dual GIP and GLP-1 RA significantly reduced sleep apnea severity and body weight compared with placebo after 52 weeks (518). More RCTs with people with diabetes are needed to determine the effectiveness of GLP-1 RAs and dual GIP and GLP-1 RAs as potential treatments for OSA.

Sleep disturbances are associated with less engagement in diabetes self-management and can interfere with achieving and maintaining glucose levels within the goal range among people with type 1 and type 2 diabetes (502,505). Risk of hypoglycemia poses specific challenges for sleep in people with type 1 diabetes and may require detailed assessment and treatment approaches (519). People with type 1 diabetes and their family members also describe diabetes management needs interfering with sleep and experiencing worries about poor sleep (520). Both helpful and challenging aspects of diabetes technology use have been described in relation to sleep (520), with the greatest perceived benefits being related to automated insulin delivery systems (521–523). For these reasons, detection and treatment of sleep disorders should be considered a part of standardized care for people with type 1 and type 2 diabetes.

As for the general population, there are evidence-based strategies to improve sleep for people with diabetes. CBT shows benefits for sleep in people with diabetes (390), including CBT for insomnia, which demonstrates improvements in sleep outcomes and possible small improvements in A1C (524), fasting glucose (524), and depressive symptoms (525). There is also evidence that sleep extension and pharmacologic treatments for sleep can improve sleep outcomes and possibly insulin resistance (519, 524). Lastly, sleep education, or sleep hygiene, improves sleep quality, reduces A1C, and decreases insulin resistance in adults with type 2 diabetes (526). Thus, diabetes care professionals are encouraged to counsel people with diabetes to use sleep-promoting routines and practices, such as establishing a regular bedtime and rise time, creating a dark, quiet area for sleep with temperature and humidity control, establishing a pre-sleep routine, putting electronic devices (except diabetes management devices) in silent/off mode, exercising during the day, avoiding daytime naps, limiting caffeine and nicotine in the evening, avoiding spicy foods at night, and avoiding alcohol before bedtime (527). For people with diabetes who have significant

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sleep difficulties, referral to sleep specialists to address the medical and behavioral aspects of sleep is recommended, ideally in collaboration with the diabetes care team (**Fig. 5.2**).

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6. Glycemic Goals and Hypoglycemia: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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ASSESSMENT OF GLYCEMIC STATUS

Glycemic status is assessed by A1C measurement, blood glucose monitoring (BGM) by capillary (finger-stick) devices, and continuous glucose monitoring (CGM) using time in range (TIR) or mean CGM glucose. Clinical trials of interventions that lower A1C have demonstrated the benefits of improved glycemia. Glucose monitoring via CGM or BGM (discussed in detail in Section 7, "Diabetes Technology") is useful for diabetes self-management, can provide nuanced information on glucose responses to meals, physical activity, and medication changes, and may be particularly useful in individuals taking insulin. CGM serves an increasingly important role in optimizing the effectiveness and safety of treatment in many people with type 1 diabetes, type 2 diabetes, or other forms of diabetes (e.g., cystic fibrosis–related diabetes). Individuals on a variety of insulin treatment plans can benefit from CGM with improved glucose levels, decreased hypoglycemia, and enhanced self-efficacy (Section 7, "Diabetes Technology") (1).

Glycemic Assessment

Recommendations

6.1 Assess glycemic status by A1C **A** and/or continuous glucose monitoring (CGM) metrics such as time in range, time above range, and time below range. **B** Fructosamine or CGM can be used for glycemic monitoring when an alternative to A1C is required. **B**

6.2 Assess glycemic status at least two times a year, and more frequently (e.g., every 3 months) for individuals not meeting glycemic goals or with recent treatment changes, frequent or severe hypoglycemia or hyperglycemia, or changes in health status, or during periods of rapid growth and development in youth. **E**

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.*

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Glycemic Assessment by A1C

The A1C test is the primary tool for assessing glycemic status in both clinical practice and clinical trials, and it is strongly linked to diabetes complications (2–4). A1C reflects average glycemia over approximately 2–3 months. The performance of laboratory tests for A1C is generally excellent for National Glycohemoglobin Standardization Program (NGSP)–certified assays (ngsp.org). Thus, A1C testing should be performed routinely in all people with diabetes at initial assessment and as part of continuing care. Measurement approximately every 3 months determines whether glycemic goals have been reached and maintained. Adults with type 1 or type 2 diabetes who have achieved and are maintaining glucose levels within their target range may only need A1C testing or other glucose assessments twice a year. Individuals with less stable glucose levels, those with intensive care plans, or those not meeting their treatment goals may require more frequent testing, typically every 3 months, with additional assessments as needed. Point-of-care A1C testing can offer timely opportunities for treatment adjustments during appointments with health care professionals.

The A1C test is an indirect measure of average glycemia. Factors that affect hemoglobin or red blood cells may affect A1C. For example, conditions that affect red blood cell turnover (hemolytic anemia and other anemias, glucose-6-phosphate dehydrogenase deficiency, recent blood transfusion, use of drugs that stimulate erythropoiesis, end-stage kidney disease, and pregnancy) can interfere with the accuracy of A1C (5). Some hemoglobin variants can interfere with some A1C assays; however, most assays in use in the U.S. are accurate in individuals who are heterozygous for the most common variants (6). A1C cannot be measured in individuals with sickle cell disease (HbSS) or other homozygous hemoglobin variants (e.g., HbEE), since these individuals lack HbA (7). In individuals with conditions that interfere with the interpretation of A1C, alternative approaches to monitoring glycemic status should be used, including self-monitoring of blood glucose, CGM, and/or the use of glycated serum protein assays (discussed below). A1C does not provide a measure of glycemic variability or hypoglycemia. For individuals prone to glycemic variability, especially people with type 1 diabetes or type 2 diabetes with insulin deficiency and/or treatment with intensive insulin therapy, glycemic status is best evaluated by the combination of results from BGM or CGM and A1C. Discordant results between A1C and BGM or CGM can occur due to high glycemic variability, inaccurate BGM or CGM measurement, or inaccurate A1C due to the factors discussed above.

As discussed in Section 2, "Diagnosis and Classification of Diabetes," there is controversy regarding the clinical significance of differences in A1C by self-reported race and ethnicity (8–11). There is an emerging understanding of genetic determinants that may modify the association between A1C and glucose levels (12). However, race and ethnicity are not good proxies for these genetic differences that are likely present in a small minority of individuals of all racial groups. Therefore, race and ethnicity should not be considerations for how A1C is used clinically for glycemic monitoring. Limitations of laboratory tests and within-person variability in glucose and A1C underscore the importance of using multiple approaches to glycemic monitoring and further evaluation of discordant results in all racial or ethnic groups.

Serum Glycated Protein Assays as Alternatives to A1C

Fructosamine and glycated albumin are alternative measures of glycemia that are approved for clinical use for monitoring glycemic status in people with diabetes. Fructosamine reflects total glycated serum proteins (mostly albumin). Glycated albumin assays reflect the proportion of total albumin that is glycated. Due to the turnover rate of serum protein, fructosamine and glycated albumin reflect glycemia over the past 2–4 weeks, a shorter-term time frame than that of A1C. Fructosamine and glycated albumin are highly correlated in people with diabetes, and the performance of modern assays is typically excellent. Fructosamine and glycated albumin have been linked to long-term complications in epidemiologic cohort studies (13–17). However, there have been few clinical trials, and the evidence base supporting the use of these biomarkers to monitor glycemic status is much weaker than that for A1C. In people with diabetes who have conditions where the interpretation of A1C may be problematic or when A1C cannot be measured (e.g., homozygous hemoglobin variants), fructosamine or glycated albumin may be useful alternatives to monitor glycemic status (7).

Correlation Between A1C and Blood Glucose Monitoring and Continuous Glucose Monitoring

Table 6.1 provides rough equivalents of A1C and mean glucose levels based on data from the international A1C-Derived Average Glucose (ADAG) study. The ADAG study assessed the correlation between A1C and frequent BGM and CGM in 507 adults (83% non-Hispanic White) with type 1, type 2, and no diabetes (18,19). The American Diabetes Association (ADA) and the American Association for Clinical Chemistry have determined that the correlation (r = 0.92) in the ADAG trial is strong enough to justify reporting both the A1C result and the estimated average glucose (eAG) result when a clinician orders the A1C test. Clinicians should note that the mean plasma glucose numbers in **Table 6.1** are based on ~2,700 readings per A1C measurement in the ADAG trial.

Caveats in interpretation of **Table 6.1** include that these data are from a single study published in 2008. Mean glucose in the ADAG study was calculated from a combination of measurements from an early CGM system and capillary glucose, intermittently, during a 3-month period. This older system required calibration several times a day using a self-monitoring

Table 6.1—Equivalent A1C levels and estimated average glucose (eAG)

A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at professional.diabetes.org/eAG. *These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, or no diabetes. The correlation between A1C and average glucose was 0.92 (18,19). Adapted from Nathan et al. (18).

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glucose meter. It is unclear how generalizable these estimates are to mean glucose measurements obtained using modern CGM systems. The comparability of A1C and mean glucose from CGM systems will depend on the number of days of CGM wear, timing of the A1C measurement relative to the CGM wear period, calibration and accuracy of the CGM system, lag time between interstitial glucose and venous glucose, and any factors that affect A1C or red cell turnover (see Section 2, "Diagnosis and Classification of Diabetes").

Glycemic Assessment by Blood Glucose Monitoring

For many people with diabetes, glucose monitoring, either using BGM by capillary (finger-stick) devices or CGM in addition to regular A1C testing, is key for achieving glycemic goals. Major clinical trials of insulin-treated individuals have included BGM as part of multifactorial interventions to demonstrate the benefit of intensive glycemic management on diabetes complications (20). BGM is thus an integral component of effective therapy for individuals taking insulin. In recent years, CGM has become a standard method for glucose monitoring for most people with type 1 diabetes. Both approaches to glucose monitoring allow people with diabetes to evaluate individual responses to therapy and assess whether glycemic goals are being safely achieved. The specific needs and goals of individuals with diabetes should dictate BGM frequency and timing. Please refer to Section 7, "Diabetes Technology," for a more complete discussion of the use of BGM and CGM.

Glycemic Assessment by Continuous Glucose Monitoring

CGM is particularly useful in people with diabetes who are at risk for hypoglycemia and is commonly used in people with type 1 diabetes (20). Use of CGM in type 2 diabetes (as well as in several other forms of diabetes) is growing, especially in people who are taking insulin. TIR is a useful metric of glycemic status. A 10- to 14-day CGM assessment of TIR, with CGM wear of 70% or higher, and other CGM metrics can be used to assess glycemic status and are useful in clinical management (21–25). TIR, and especially mean CGM glucose, correlates with A1C (26–30). Time below range (<70 and <54 mg/dL [<3.9 and <3.0 mmol/L]) and time above range (>180 mg/dL [>10.0 mmol/L]) are useful parameters for insulin dose adjustments and reevaluation of the treatment plan.

The international consensus on CGM provides guidance on CGM metrics (**Table 6.2**) and their clinical interpretation (31). To make these metrics actionable, standardized reports with visual summaries, such as the ambulatory glucose profile (**Fig. 6.1**), are recommended (31) and can help individuals with diabetes and health care professionals interpret the data to guide treatment decisions (26,29). BGM and CGM can be useful to guide medical nutrition therapy and physical activity, detect and prevent hypoglycemia, and aid medication management. CGM metrics, including TIR (with time below range and time above range), can provide helpful insights to inform a personalized diabetes management plan. Remote access to glucose data is growing and may help improve diabetes management (32–34).

CGM systems have evolved rapidly in both accuracy and affordability. As such, many individuals with diabetes have these data available to assist with self-management and their health care professionals' assessment of glycemic status. Reports generated from CGM will allow the health care professional and person with diabetes to view TIR and a calculated glucose management indicator and assess hypoglycemia, hyperglycemia, and glycemic variability. As discussed in a 2019 consensus report, a report formatted as shown in **Fig. 6.1** can be generated (31). Published data from two retrospective studies suggest a strong correlation between TIR and A1C, with a goal of 70% TIR aligning with an A1C of ~7% (53 mmol/mol) (24,27). Note that the goals of therapy next to each metric in **Fig. 6.1** (e.g., low, <4%; very low, <1%) serve as values to guide changes in therapy. For older adults using CGM, the recommended percent time spent in target range of 70–180 mg/dL is 50% (or 12 h per day) and the recommended time spent in hypoglycemia of less than 70 mg/dL should not be more than 1%, or 15 min per day, to minimize hypoglycemia risk (35–38). In this population, more permissive hyperglycemia is allowed (up to 50% of the time in 24 h).

GLYCEMIC GOALS

Recommendations

6.3a An A1C goal of <7% (<53 mmol/mol) is appropriate for many nonpregnant adults without severe hypoglycemia or frequent hypoglycemia affecting health or quality of life. **A**

6.3b A goal time in range of >70% in people using CGM is appropriate for many nonpregnant adults. **B**

6.3c A goal percent time <70 mg/dL (<3.9 mmol/L) of <4% (or <1% for older adults) and a goal percent time <54 mg/dL (<3.0 mmol/L) of <1% are recommended in people using CGM to prevent hypoglycemia. Deintensify or modify therapy if these goals are not met. **B**

6.4 Based on health care professional judgment and the preference of the person with diabetes, achievement of lower A1C levels than the goal of 7% (53 mmol/mol) may be acceptable and even beneficial if it can be achieved safely without frequent or severe hypoglycemia or other adverse effects of treatment. **B**

6.5 Less stringent glycemic goals may be appropriate for individuals with limited life expectancy or where the harms of treatment are greater than the benefits. **B**

6.6 Deintensify hypoglycemia-causing medications (insulin, sulfonylureas, or meglitinides), or switch to a medication class with lower hypoglycemia risk, for individuals who are at high risk for hypoglycemia, within individualized glycemic goals. **B**

6.7 Deintensify diabetes medications for individuals for whom the harms and/or burdens of treatment may be greater than the benefits, within individualized glycemic goals. **B**

6.8 Reassess glycemic goals based on the individualized criteria shown in **Fig. 6.2**. **E**

6.9 Set a glycemic goal during consultations to improve outcomes. **A**

For all populations, it is critical that the glycemic goals be woven into an individualized, person-centered strategy (39). The glycemic goals for many nonpregnant adults are shown in **Table 6.3**, and **Fig. 6.2** summarizes how A1C goals should be individualized by an individual's health, function, and other modifying

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Table 6.2—CGM metrics for clinical care in nonpregnant individuals with type 1 or type 2 diabetes

Metric	Interpretation	Goals
Metrics for valid CGM wear		
Wear time	Number of days CGM device is worn	≥14-day wear for pattern management
Active percentage time	Percent of time CGM device is active	70% of time active out of 14 days
Glycemic metrics		
Mean glucose	Mean of glucose values	*
Glucose management indicator (GMI)	Calculated value approximating A1C (not always equivalent)	*
Glucose coefficient of variation (CV)	Spread of glucose values	≤36%†
TAR >250 mg/dL (>13.9 mmol/L)	Percent of time in level 2 hyperglycemia	<5% (most adults); <10% (older adults)
TAR 181–250 mg/dL (10.1–13.9 mmol/L)	Percent of time in level 1 hyperglycemia	<25% (most adults); <50% (older adults)‡
TIR 70–180 mg/dL (3.9–10.0 mmol/L)	Percent of time in range	>70% (most adults); >50% (older adults)
TBR 54–69 mg/dL (3.0–3.8 mmol/L)	Percent of time in level 1 hypoglycemia	<4% (most adults); <1% (older adults)§
TBR <54 mg/dL (<3.0 mmol/L)	Percent of time in level 2 hypoglycemia	<1%

CGM, continuous glucose monitoring; TAR, time above range; TBR, time below range; TIR, time in range. *Goals for these values are not standardized. †Some studies suggest that lower coefficient of variation targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas. ‡Goals are for level 1 and level 2 hyperglycemia combined. §Goals are for level 1 and level 2 hypoglycemia combined. Adapted from Battelino et al. (31).

factors. For example, less stringent A1C goals are appropriate for individuals with significant functional and cognitive impairments. For more details regarding glycemic goals in older adults, please refer to Section 13, "Older Adults." For glycemic goals in children, please refer to Section 14, "Children and Adolescents." For glycemic goals during pregnancy, please refer to Section 15, "Management of Diabetes in Pregnancy."

Health care professionals should engage in shared decision-making with the individual (as well as with family members and caregivers) and should consider adjusting goals for simplifying the treatment plan if this change is needed to improve safety and medication-taking behavior. Setting specific glycemic (and other) goals during consultations has been demonstrated to improve glycemic outcomes for individuals with diabetes (40).

Glucose Lowering and Microvascular Complications

Hyperglycemia defines diabetes, and achieving glycemic goals is fundamental to diabetes management. The level of chronic hyperglycemia is the best-established concomitant risk factor associated with microvascular complications (i.e., diabetic retinopathy, nephropathy, and neuropathy). This is best understood by the fact that nerve, retinal, and kidney cells do not require insulin for intracellular glucose entry. Consequently, the exposure of these cells to elevated ambient glucose levels even in the presence of insulin deficiency (absolute or relative) will result in intracellular metabolic dysfunction and increased risk of microvascular complications.

The Diabetes Control and Complications Trial (DCCT) (41), a prospective randomized controlled trial of intensive (mean A1C ~7% [~53 mmol/mol]) versus standard (mean A1C ~9% [~75 mmol/mol]) glycemic management in people with type 1 diabetes, showed definitively that better glycemic status is associated with 50–76% reductions in rates of development and progression of microvascular complications (retinopathy, neuropathy, and diabetic kidney disease). Follow-up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (42,43) demonstrated persistence of these microvascular benefits over two decades despite the fact that the glycemic separation between the treatment groups diminished and disappeared during follow-up.

The Kumamoto study (44) and UK Prospective Diabetes Study (UKPDS) (45,46) examined the effects of "intensive glycemic control" among people with short-duration type 2 diabetes, although glycemic lowering in these studies was not intensive by current standards (mean A1C was 7.1% vs. 9.4% in Kumamoto and 7.0% vs. 7.9% in UKPDS). These trials found lower rates of microvascular complications in the intervention arms, with long-term follow-up of the UKPDS cohorts showing enduring effects on most microvascular complications (47). These studies highlight the long-term benefits of early glycemic lowering in type 2 diabetes.

Therefore, improved glycemia has been shown to reduce microvascular complications of type 1 and type 2 diabetes when instituted early in the course of disease (2,48). The DCCT (41) and UKPDS (49) studies demonstrated a curvilinear relationship between attained A1C level and microvascular complications. Such results suggest that, on a population level, the greatest number of complications will be averted by taking individuals with diabetes from very high to moderate A1C levels. These analyses also suggest that further lowering of A1C from 7% to 6% (53 mmol/mol to 42 mmol/mol) is associated with further reduction in the risk of microvascular complications, although the absolute risk reductions become much smaller. The implication of these findings is that there is no need to deintensify therapy for an individual with an A1C between 6% and 7% in the setting of low hypoglycemia risk with a long life expectancy. There are newer pharmacologic agents that do not cause hypoglycemia, making it possible to maintain glycemic status without the risk of hypoglycemia (see Section 9, "Pharmacologic Approaches to Glycemic Treatment"). Moreover, CGM use was not as common when these trials were conducted and automated insulin delivery systems were not available; these have been shown to improve glucose levels without increasing hypoglycemia.

Among individuals with type 2 diabetes, three landmark trials (Action to Control

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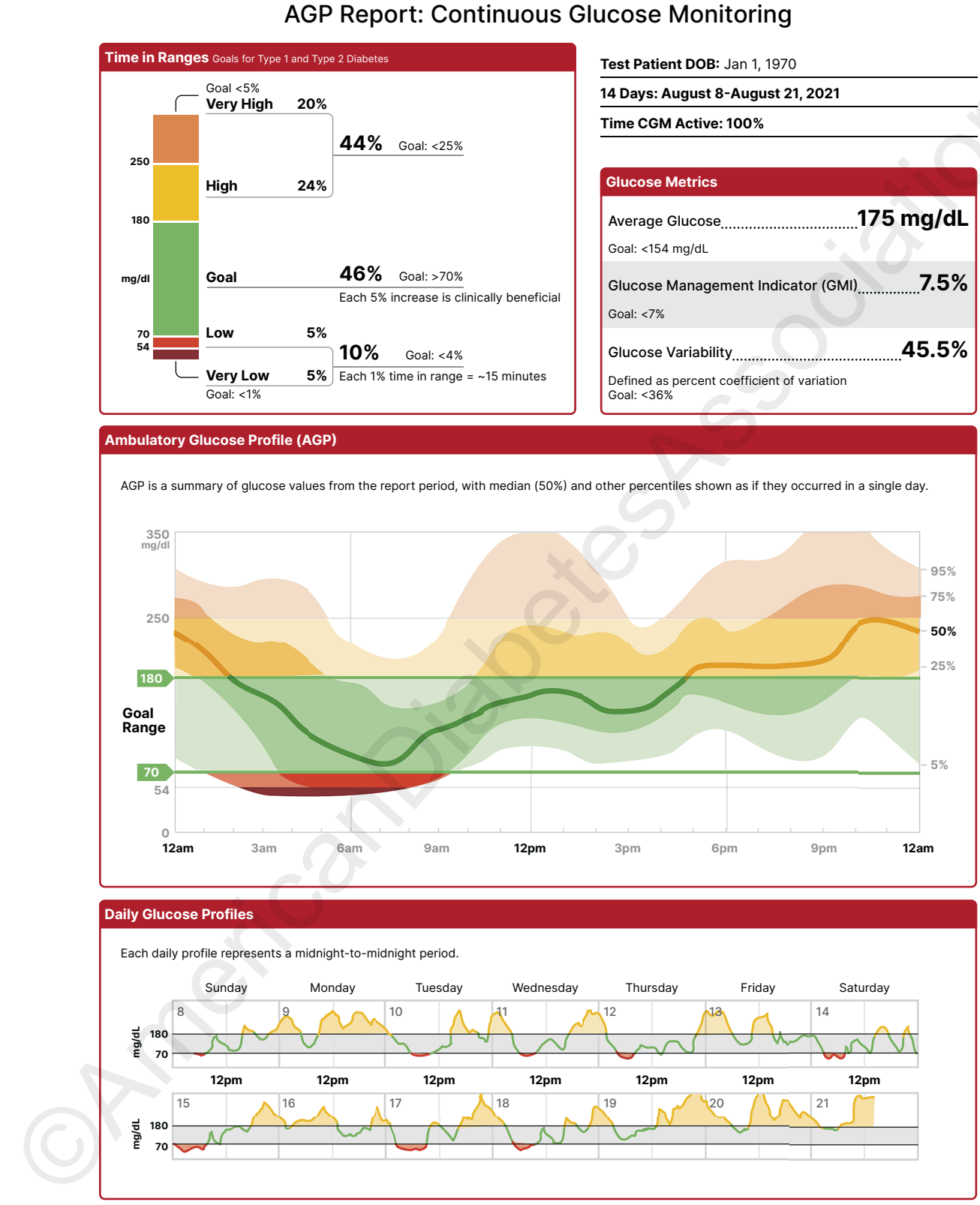

Figure 6.1—Key points included in a standard ambulatory glucose profile (AGP) report. Adapted from Holt et al. (20).

Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], and Veterans Affairs Diabetes Trial [VADT]) were conducted to test the effects of near normalization of blood glucose on cardiovascular outcomes. The ADVANCE and VADT trials found modest reduction in nephropathy with intensive glycemic management; ACCORD was stopped after a median of 3.5 years due to higher mortality in the

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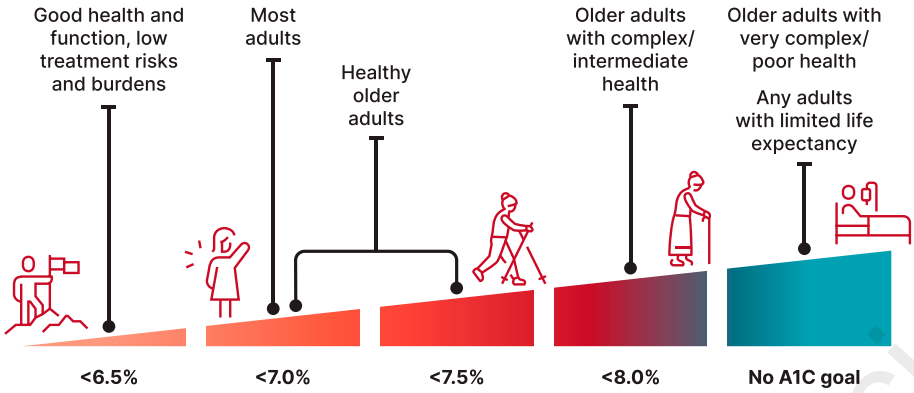

Modifying Factors

Favor more stringent goal	Favor less stringent goal
Short diabetes duration	Long diabetes duration
Low hypoglycemia risk	High hypoglycemia risk
Low treatment risks and burdens	High treatment risks and burdens
Pharmacotherapy with cardiovascular, kidney, weight, or other benefits	Pharmacotherapy without nonglycemic benefits
No cardiovascular complications	Established cardiovascular complications
Few or minor comorbidities	Severe, life-limiting comorbidities

Figure 6.2—Individualized A1C goals for nonpregnant adults. Select the glycemic goal based on individual health and function as described at the top of the figure. Consider modifying to a more or less stringent goal according to the factors listed in the table. Older adults are classified as healthy (few coexisting chronic illnesses, intact cognitive and functional status), as having complex/intermediate health (multiple coexisting chronic illnesses, two or more instrumental impairments to activities of daily living, or mild to moderate cognitive impairment), or as having very complex/ poor health (long-term care or end-stage chronic illnesses, moderate to severe cognitive impairment, or two or more impairments to activities of daily living). Select glycemic goals that avoid symptomatic hypoglycemia and hyperglycemia in all individuals. Consider individuals' resources and support systems to safely achieve glycemic goals. Incorporate the preferences and goals of people with diabetes through shared decision-making.

intervention arm (50–54). Importantly, these landmark studies were conducted prior to the approval of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and sodium–glucose cotransporter 2 (SGLT2) inhibitors, and intensive glycemic management was achieved predominantly through greater use of insulin. Findings from these studies, including the concerning increase in mortality in the intensive treatment arm of ACCORD, suggest caution is needed in treating diabetes to near-normal A1C goals in people with long-standing type 2 diabetes using medications with a high risk for hypoglycemia.

Glucose Lowering and Cardiovascular Disease Outcomes

Cardiovascular disease (CVD) is a more common cause of death than microvascular complications in populations with diabetes. The modern multifaceted management of diabetes, with a focus on the treatment of hypertension and the use of statins, has reduced the prevalence of atherosclerotic CVD to around double compared with that of people without diabetes (55).

The DCCT in individuals with type 1 diabetes and the UKPDS, ACCORD, ADVANCE, and VADT studies in type 2 diabetes all attempted to address whether intensive glycemic management reduced CVD events (41,50,51,53). ACCORD, ADVANCE, and VADT were conducted in relatively older participants with a longer duration of diabetes (mean duration 8–11 years) and either CVD or multiple cardiovascular risk factors. Details of these studies are reviewed extensively in the joint ADA position statement "Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials" (56).

No significant reduction in composite CVD events was demonstrated at the end of the intervention in any of these studies, and ACCORD was stopped prematurely at 3.5 years because of an increase in total mortality, particularly sudden CVD deaths. Serious concerns with the intensive glycemic treatment plan used in

Table 6.3—Summary of glycemic goals for many nonpregnant adults with diabetes

A1C	<7.0% (<53 mmol/mol)*†
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose‡	<180 mg/dL* (<10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for certain individuals. †CGM may be used to assess glycemic status as noted in Recommendations 6.3b and 6.3c and **Fig. 6.1**. Goals should be individualized based on duration of diabetes, age and life expectancy, comorbid conditions, known cardiovascular disease or advanced microvascular complications, impaired awareness of hypoglycemia, and individual considerations (per **Fig. 6.2**). ‡Postprandial glucose may warrant special attention if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, which is generally the timing for peak levels in people with diabetes.

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ACCORD included the rapid escalation of therapies, the early use of large doses of insulin, substantial weight gain, and frequent hypoglycemia. These overall negative results were not unexpected, as blood glucose has subsequently been shown to be a relatively weak CVD risk factor in isolation compared with other CVD risk factors, such as hypertension or hypercholesterolemia. Consequently, even if a wide separation in A1C could be safely obtained, it would take a long time for the CVD benefit to accrue. However, a meta-analysis of individual participant data from UKPDS, ACCORD, ADVANCE, and VADT demonstrated a significant reduction in myocardial infarctions and major CVD events but no difference in stroke, heart failure, or mortality between intensive and less intensive glycemic management (57).

Longer-term epidemiological follow-up has been performed in these studies, and a clear pattern of CVD benefit has emerged (58–60). In the post-DCCT follow-up of the EDIC cohort, participants previously randomized to the intensive arm had a significant 57% reduction in the risk of nonfatal myocardial infarction, stroke, or cardiovascular death compared with those previously randomized to the standard arm (58). The benefit of intensive glycemic management in this cohort with type 1 diabetes has been shown to persist for several decades (59) and to be associated with a modest reduction in all-cause mortality (61).

UKPDS post-trial monitoring, with 20 years of total follow-up, has shown reductions in myocardial infarctions and total mortality both in the group of overweight individuals treated with metformin and in the group previously treated intensively with sulfonylureas or insulin (47). Shorter overall follow-up of the VADT (10 years) has shown a significant reduction in the primary outcome of major CVD events, with myocardial infarctions and heart failure being the commonest outcomes (60). In contrast, shorter follow-up of the ADVANCE study in the Action in Diabetes and Vascular Disease Preterax and Diamicron MR Controlled Evaluation Post Trial Observational Study (ADVANCE-ON) demonstrated no significant effect on CVD events (62). Even in the epidemiological follow-up of ACCORD in the Action to Control Cardiovascular Risk in Diabetes Follow-On Study (ACCORDION), the excess increase in total mortality that was seen during 3.5 years of intensive treatment was reduced by returning to conventional management, and therefore there was no difference in total mortality after a total of 9 years of follow-up (63). Collectively, the results of these studies confirm that long-term intensive glycemic management reduces CVD events, particularly myocardial infarctions.

As discussed above, these landmark studies in individuals with type 2 diabetes need to be considered with the important caveat that GLP-1 RAs and SGLT2 inhibitors were not yet in clinical use. These agents with established cardiovascular and kidney benefits appear to be safe and beneficial in this group of individuals at high risk for cardiovascular and kidney complications. Randomized clinical trials examining these agents for cardiovascular safety were not designed to test higher versus lower A1C; therefore, beyond post hoc analysis of these trials, we do not have evidence that it is the glucose lowering per se by these agents that confers the CVD and kidney benefits (64). Additional beneficial pleotropic effects of these agents may include weight loss, hemodynamic effects, blood pressure lowering, and anti-inflammatory changes.

As discussed further below, severe hypoglycemia is a potent marker of high absolute risk of cardiovascular events and mortality (65). Therefore, health care professionals should be vigilant in preventing hypoglycemia and should not aggressively attempt to achieve near-normal A1C levels in people in whom such goals cannot be safely and reasonably achieved. As discussed in Section 9, "Pharmacologic Approaches to Glycemic Treatment," addition of specific SGLT2 inhibitors or GLP-1 RAs that have demonstrated CVD benefit is recommended in individuals with established CVD, chronic kidney disease, and heart failure. As outlined in more detail in Section 9, "Pharmacologic Approaches to Glycemic Treatment," and Section 10, "Cardiovascular Disease and Risk Management," the cardiovascular benefits of SGLT2 inhibitors or GLP-1 RAs are not contingent upon A1C lowering; therefore, initiation can be considered in people with type 2 diabetes and CVD independent of the current A1C, A1C goal, or metformin therapy. Based on these considerations, the following two strategies are offered (66):

1. If already on dual therapy or multiple glucose-lowering therapies and not on an SGLT2 inhibitor or a GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit.
2. Introduce SGLT2 inhibitors or GLP-1 RAs in people with CVD at A1C goal (independent of metformin) for cardiovascular benefit, independent of baseline A1C or individualized A1C goal.

Setting and Modifying Glycemic Goals

Glycemic goals and management should be individualized and not one size fits all. To prevent both microvascular and macrovascular complications of diabetes, there is a major call to overcome therapeutic inertia and treat to individualized goals (56,67).

Numerous factors must be considered when setting a glycemic goal. The ADA proposes general goals that are appropriate for many people but emphasizes the importance of individualization based on key person characteristics. Glycemic goals must be individualized in the context of shared decision-making to address individual needs and preferences and consider characteristics that influence risks and benefits of therapy; this approach may optimize engagement and self-efficacy.

The factors to consider in individualizing goals are depicted in **Fig. 6.2**. This figure is not designed to be applied rigidly in the care of a given individual but to be used as a broad framework to guide clinical decision-making (39) and engage people with type 1 and type 2 diabetes in shared decision-making. More aggressive goals may be recommended if they can be achieved safely and with an acceptable burden of therapy and if life expectancy is sufficient to reap the benefits of stringent goals. Less stringent goals (e.g., A1C up to 8% [64 mmol/mol]) may be recommended if the individual's life expectancy is such that the benefits of an intensive goal may not be realized or if the risks and burdens outweigh the potential benefits. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment plans, including setting higher glycemic goals.

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Diabetes is a chronic disease that progresses over decades. Thus, a goal that might be appropriate for an individual early in the course of their diabetes may change over time. Newly diagnosed individuals and/or those without comorbidities that limit life expectancy may benefit from intensive glycemic goals proven to prevent microvascular complications. Both DCCT/EDIC and UKPDS suggested that there is metabolic memory, or a legacy effect, in which a finite period of intensive glucose lowering yielded benefits that extended for decades after that period ended. However, there are few recent data on the effects of long-term glucose lowering using modern treatment strategies. Thus, a finite period of intensive treatment to near-normal A1C may yield enduring benefits even if treatment is subsequently deintensified as characteristics change. Over time, comorbidities may emerge, decreasing life expectancy and thereby decreasing the potential to reap benefits from intensive treatment. Also, with longer disease duration, diabetes may become more difficult to manage, with increasing risks and burdens of therapy. Thus, glycemic goals should be reevaluated over time to balance the risks and benefits.

Accordingly, clinicians should continue to evaluate the balance of risks and benefits of diabetes medications for individuals who have achieved individualized glycemic goals, and they should deintensify (decrease the dose or stop) diabetes medications where their risks exceed their benefits. Hypoglycemia is the major risk to individuals treated with insulin, sulfonylureas, or meglitinides, and it is appropriate to deintensify these medications where there is a high risk for hypoglycemia (see HYPOGLYCEMIA RISK ASSESSMENT, below). Switching a high-hypoglycemia-risk medication to lower-hypoglycemia-risk therapy (see Section 9, "Pharmacologic Approaches to Glycemic Treatment") should be considered if needed to achieve individualized glycemic goals or where individuals have evidence-based indications for alternative medications (e.g., use of SGLT2 inhibitors in the setting of heart failure or diabetic kidney disease and use of GLP-1 RAs in the setting of CVD or obesity). Clinicians should also consider medication burdens other than hypoglycemia, including tolerability, difficulties of administration, impact on education or employment, and financial cost. These factors should be balanced against benefits from glycemic lowering and disease-specific benefits of newer medications that may be independent of glycemic lowering (Section 9, "Pharmacologic Approaches to Glycemic Treatment"). Multiple trials have shown that deintensification of diabetes treatment can be achieved successfully and safely (68–70). It is important to partner with people with diabetes during the deintensification process to understand their goals of diabetes treatment and agree upon appropriate glycemic monitoring, glucose levels, and goals of care (71).

HYPOGLYCEMIA ASSESSMENT, PREVENTION, AND TREATMENT

Recommendations

6.10 Review history of hypoglycemia at every clinical encounter for all individuals at risk for hypoglycemia, and evaluate hypoglycemic events as indicated. **C**

6.11 Screen individuals at risk for hypoglycemia for impaired hypoglycemia awareness at least annually and when clinically appropriate. **E** Refer to a trained health care professional for evidence-based intervention to improve hypoglycemia awareness. **A**

6.12 Screen individuals at high risk for hypoglycemia or with severe and/or frequent hypoglycemia for fear of hypoglycemia at least annually and when clinically appropriate. **E** Refer to a trained health care professional for evidence-based intervention. **A**

6.13 Clinicians should consider an individual's risk for hypoglycemia (see **Table 6.5**) when selecting diabetes medications and glycemic goals. **E**

6.14 Use of CGM is beneficial and recommended for individuals at high risk for hypoglycemia. **A**

6.15 Glucose is the preferred treatment for the conscious individual with glucose <70 mg/dL (<3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Avoid using foods or beverages high in fat and/or protein for initial treatment of hypoglycemia. Fifteen minutes after initial treatment, repeat the treatment if hypoglycemia persists. **B**

6.16 Glucagon should be prescribed for all individuals taking insulin or at high risk for hypoglycemia. **A** Family, caregivers, school personnel, and others providing support to these individuals should know its location and be educated on how to administer it. Glucagon preparations that do not have to be reconstituted are preferred. **B**

6.17 All individuals taking insulin **A** or at risk for hypoglycemia **C** should receive structured education for hypoglycemia prevention and treatment, with ongoing education for those who experience hypoglycemic events.

6.18 One or more episodes of level 2 or 3 hypoglycemia should prompt reevaluation of the treatment plan, including deintensifying or switching diabetes medications if appropriate. **E**

6.19 Regularly assess cognitive function; if impaired or declining cognition is found, the clinician, person with diabetes, and caregiver should increase vigilance for hypoglycemia. **B**

Hypoglycemia Definitions and Event Rates

Hypoglycemia is often the major limiting factor in the glycemic management of type 1 and type 2 diabetes. Recommendations regarding the classification of hypoglycemia are outlined in **Table 6.4** (72). Level 1 hypoglycemia is defined as a measurable glucose concentration <70 mg/dL (<3.9 mmol/L) and ≥54 mg/dL (≥3.0 mmol/L). A blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as a threshold for adrenergic responses to falling glucose in people without diabetes. Symptoms of hypoglycemia include, but are not limited to, shakiness, irritability, confusion, tachycardia, sweating, and hunger (73). Because many people with diabetes demonstrate impaired counterregulatory responses to hypoglycemia and/or experience impaired hypoglycemia awareness, a measured glucose level <70 mg/dL (<3.9 mmol/L) is considered clinically important, regardless of symptoms. Level 2 hypoglycemia (defined as a blood glucose concentration <54 mg/dL [<3.0 mmol/L]) is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event. If an individual has level 2 hypoglycemia without adrenergic or neuroglycopenic symptoms, they likely have impaired

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Table 6.4—Classification of hypoglycemia

	Glycemic criteria/description
Level 1	Glucose <70 mg/dL (<3.9 mmol/L) and ≥54 mg/dL (≥3.0 mmol/L)
Level 2	Glucose <54 mg/dL (<3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia, irrespective of glucose level

Adapted from Agiostratidou et al. (72).

hypoglycemia awareness (discussed further in HYPOGLYCEMIA RISK ASSESSMENT, below). This clinical scenario warrants investigation and review of the treatment plan (74,75). Lastly, level 3 hypoglycemia is defined as a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery, irrespective of glucose level.

Hypoglycemia has a broad range of negative health consequences (76). Level 3 hypoglycemia may be recognized or unrecognized and can progress to loss of consciousness, seizure, coma, or death. Level 3 hypoglycemia was associated with mortality in both the standard and the intensive glycemia arms of the ACCORD trial, but the relationships between hypoglycemia, achieved A1C, and treatment intensity were not straightforward (77). An association of level 3 hypoglycemia with mortality was also found in the ADVANCE trial and in clinical practice (78,79). Hypoglycemia can cause acute harm to the person with diabetes or others, especially if it causes falls, motor vehicle accidents, or other injury (80). Hypoglycemia may also cause substantial anxiety that can reduce the quality of life of individuals with diabetes and their caregivers and may contribute to problems with diabetes self-management and treatment (81–83). Recurrent level 2 hypoglycemia and/or level 3 hypoglycemia is an urgent medical issue and requires intervention with medical treatment plan adjustment, behavioral intervention, delivery of diabetes self-management education and support, and use of technology to assist with hypoglycemia prevention and identification (75,84–87).

Studies of rates of hypoglycemia predominantly rely on claims data for hospitalizations and emergency department visits (88–91). These studies do not capture the level 1 and level 2 hypoglycemia that represent the vast majority of hypoglycemic events, and they also substantially underestimate level 3 hypoglycemia (88,92,93). Nevertheless, they reveal a substantial burden of hypoglycemia-related hospital utilization in the community (88–91). Level 1 and level 2 hypoglycemia can be ascertained from patient self-report (94) and are strong risk factors for subsequent level 3 hypoglycemia.

Hypoglycemia Risk Assessment

Assessment of an individual's risk for hypoglycemia includes evaluating clinical risk factors as well as relevant social, cultural, and economic factors (**Table 6.5**). Recommendations 6.10–6.19 group individuals with diabetes into two hypoglycemia risk categories with clinical significance. Individuals at risk for hypoglycemia are those treated with insulin, sulfonylureas, or meglitinides; clinically significant hypoglycemia is rare among individuals taking other diabetes medication classes (95,96). Individuals at high risk for hypoglycemia are the subset of individuals at risk for hypoglycemia who either have a major hypoglycemia

Table 6.5—Assessment of hypoglycemia risk among individuals treated with insulin, sulfonylureas, or meglitinides

Clinical and biological risk factors	Social, cultural, and economic risk factors
Major risk factors • Recent (within the past 3–6 months) level 2 or 3 hypoglycemia • Intensive insulin therapy* • Impaired hypoglycemia awareness • End-stage kidney disease • Cognitive impairment or dementia	Major risk factors • Food insecurity • Low-income status§ • Housing insecurity • Fasting for religious or cultural reasons • Underinsurance
Other risk factors • Multiple recent episodes of level 1 hypoglycemia • Basal insulin therapy* • Age ≥75 years† • Female sex • High glycemic variability‡ • Polypharmacy • Cardiovascular disease • Chronic kidney disease (eGFR <60 mL/min/1.73 m^2 or albuminuria) • Neuropathy • Retinopathy • Major depressive disorder • Severe mental illness	Other risk factors • Low health literacy • Alcohol or substance use disorder

Major risk factors are those that have a consistent, independent association with a high risk for level 2 or 3 hypoglycemia. Other risk factors are those with less consistent evidence or a weaker association. These risk factors are identified through observational analyses and are intended to be used for hypoglycemia risk stratification. Individuals considered at high risk for hypoglycemia are those with ≥1 major risk factor or who have multiple other risk factors (determined by the health care professional incorporating clinical judgment) (89,90,95,97–100,120,180). Proximal causes of hypoglycemic events (e.g., exercise and sleep) are not included. eGFR, estimated glomerular filtration rate. *Rates of hypoglycemia are highest for individuals treated with intensive insulin therapy (including multiple daily injections of insulin, continuous subcutaneous insulin infusion, or automated insulin delivery systems), followed by basal insulin, followed by sulfonylureas or meglitinides. Combining treatment with insulin and sulfonylureas further increases hypoglycemia risk. †Accounting for treatment plan and diabetes subtype, the oldest individuals (aged ≥75 years) have the highest risk for hypoglycemia in type 2 diabetes; younger individuals with type 1 diabetes are also at very high risk. ‡Tight glycemic management in randomized trials increases hypoglycemia rates. In observational studies, both low and high A1C are associated with hypoglycemia in a J-shaped relationship. §Includes factors associated with low income, such as living in a socioeconomically deprived area.

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risk factor or have multiple other risk factors (determined by the health care professional incorporating clinical judgment) (**Table 6.5**). This risk stratification is based on epidemiologic studies of hypoglycemia risk (89,90,95,97–101). Validated tools have been developed to estimate hypoglycemia risk using predominantly electronic health record data (102–104). However, these tools do not include all of the important hypoglycemia risk factors, and more research is needed to determine how they can best be incorporated into clinical care.

Among individuals at risk for hypoglycemia, prior hypoglycemic events, especially level 2 or 3 events, are the strongest risk factors for hypoglycemia recurrence (96,99,105–107). Hypoglycemia history should be assessed at every clinical encounter and should include hypoglycemic event frequency, severity, precipitants, symptoms (or lack thereof), and approach to treatment. It is essential to correlate home glucose readings, both from glucose meters and CGM systems, with symptoms and treatment, as individuals may experience and treat hypoglycemic symptoms without checking their glucose level (108), treat normal glucose values as hypoglycemic, or tolerate hypoglycemia without treatment either because of lack of symptoms or to avoid hyperglycemia.

Individuals at risk for hypoglycemia should also be screened for impaired hypoglycemia awareness (also called hypoglycemia unawareness or hypoglycemia-associated autonomic failure) at least yearly. Impaired hypoglycemia awareness is defined as not experiencing the typical counterregulatory hormone release at low glucose levels or the associated symptoms, which often occurs in individuals with long-standing diabetes or recurrent hypoglycemia (109). Individuals with impaired hypoglycemia awareness may experience confusion as the first sign of hypoglycemia, which can create fear of hypoglycemia and severely impact quality of life (110). Impaired hypoglycemia awareness dramatically increases the risk for level 3 hypoglycemia (111). Validated questionnaires for assessing impaired hypoglycemia awareness include the single-question Pedersen-Bjergaard (112) and Gold (113) tools; the Clarke (114) and HypoA-Q (115) tools are longer questionnaires that evaluate multiple domains of impaired hypoglycemia awareness. Comparisons between these tools largely yield good agreement (116,117). To efficiently screen for impaired hypoglycemia awareness in clinical practice, clinicians can ask a single question based on these tools such as "Can you always feel when your blood sugar is low?" and follow up "No" responses with a more detailed evaluation.

Other notable clinical and biological risk factors for hypoglycemia are older age, multimorbidity, cognitive impairment, chronic kidney disease and end-stage kidney disease in particular, CVD, depression, and neuropathy (95,96). Female sex has also been found to be an independent risk factor for hypoglycemia in multiple studies, although the mechanisms of this relationship are unclear and require further research (95). Cognitive impairment has a strong bidirectional association with hypoglycemia, and recurrent severe hypoglycemic episodes were associated with a greater decline in psychomotor and mental efficiency after long-term follow-up of the DCCT/EDIC cohort (118). Therefore, cognitive function should be routinely assessed among older adults with diabetes.

There are a number of important social, cultural, and economic hypoglycemia risk factors that should be considered. Food insecurity is associated with increased risk of hypoglycemia-related emergency department visits and hospitalizations in low-income households, and this was shown to be mitigated by increased federal nutrition program benefits (119). In general, individuals with low annual household incomes (96), individuals who live in socioeconomically deprived areas (99), and individuals who are underinsured (100) or experiencing housing instability (120) experience higher rates of emergency department visits and hospitalizations for hypoglycemia. Clinicians should also be aware of cultural practices that may influence glycemic management (which are discussed in detail in Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes"), such as fasting as part of religious observance. Fasting may increase the risk for hypoglycemia among individuals treated with insulin or insulin secretagogues if not properly planned for, so clinicians need to engage these individuals to codevelop a diabetes treatment plan that is safe and respectful of their traditions (121).

Young children with type 1 diabetes and older adults, including those with type 1 and type 2 diabetes (122,123), are noted as being particularly vulnerable to hypoglycemia because of their reduced ability to recognize hypoglycemic symptoms and effectively communicate their needs. Individualized glycemic goals, education, nutrition intervention (e.g., bedtime snack to prevent overnight hypoglycemia when specifically needed to treat low blood glucose), physical activity management, medication adjustment, glucose monitoring, and routine clinical surveillance may improve outcomes (109). Insulin pumps with automated low-glucose suspend and automated insulin delivery systems have been shown to be effective in reducing hypoglycemia in type 1 diabetes (124). For people with type 1 diabetes with level 3 hypoglycemia and hypoglycemia unawareness that persists despite medical treatment, pancreas transplant alone or human islet transplantation may be an option, but these approaches remain experimental (125,126).

Hypoglycemia Treatment

Health care professionals should counsel individuals with diabetes to treat hypoglycemia with fast-acting carbohydrates at the hypoglycemia alert value of 70 mg/dL (3.9 mmol/L) or less (127–129). Individuals should be counseled to recheck their glucose 15 min after ingesting carbohydrates and to repeat carbohydrate ingestion and seek care for ongoing hypoglycemia. These instructions should be reviewed at each clinical visit.

For most individuals, 15 g carbohydrates should be ingested. Individuals using automated insulin delivery systems should ingest 5–10 g carbohydrates unless there is hypoglycemia in conjunction with exercise or there has been significant overestimation of a carbohydrate/meal bolus (130). The acute glycemic response to food correlates better with the glucose content than with the total carbohydrate content. Pure glucose is the preferred initial treatment, but any form of carbohydrate that contains glucose will raise blood glucose. Added fat may slow and then prolong the acute glycemic response. Dietary protein intake may increase insulin secretion and should not be used to treat hypoglycemia (131). Ongoing insulin activity or insulin secretagogues may lead to recurrent hypoglycemia unless more food is ingested after recovery.

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Glucagon

The use of glucagon is indicated for the treatment of hypoglycemia in people unable or unwilling to consume carbohydrates by mouth. All individuals treated with insulin or who are at high risk of hypoglycemia as discussed above should be prescribed glucagon. For these individuals, clinicians should routinely review their access to glucagon, as appropriate glucagon prescribing is very low in current practice (132–134). An individual does not need to be a health care professional to safely administer glucagon. Those in close contact with, or having custodial care of, these individuals (family members, roommates, school personnel, childcare professionals, correctional institution staff, or coworkers) should be instructed on the use of glucagon, including where the glucagon product is kept and when and how to administer it. It is essential that they be explicitly educated to never administer insulin to individuals experiencing hypoglycemia. Glucagon was traditionally dispensed as a powder that requires reconstitution prior to injection. However, intranasal and ready-to-inject glucagon preparations are now widely available and are preferred due to their ease of administration resulting in more rapid correction of hypoglycemia (135–137). Although the physical and chemical stability of glucagon has improved with newer formulations, care should be taken to replace glucagon products when they reach their expiration date and to store glucagon based on specific product instructions to ensure safe and effective use. For currently available glucagon products and associated costs, see **Table 6.6**. Health insurance providers may prefer only select glucagon products, so it is important to check individuals' insurance coverage and prescribe formulary products whenever possible.

Hypoglycemia Prevention

A multicomponent hypoglycemia prevention plan (**Table 6.7**) is critical to caring for individuals at risk for hypoglycemia. Hypoglycemia prevention begins by establishing an individual's hypoglycemia history and risk factors, as discussed in HYPOGLYCEMIA RISK ASSESSMENT above. Structured education for hypoglycemia prevention and treatment is critical and has been shown to improve hypoglycemia outcomes (138,139). Education should ideally be provided through a diabetes self-management education and support program or by a trained diabetes care and education specialist, although these services are not available in many areas (140,141). If structured education is not available, clinicians should educate individuals at risk for hypoglycemia on hypoglycemia definitions, situations that may precipitate hypoglycemia (fasting, delayed meals, physical activity, and illness), blood glucose self-monitoring, avoidance of driving with hypoglycemia, step-by-step instructions on hypoglycemia treatment as discussed above, and glucagon use as appropriate (138).

CGM can be a valuable tool for detecting and preventing hypoglycemia in many individuals with diabetes, and it is recommended for insulin-treated individuals, especially those using multiple daily insulin injections or continuous subcutaneous insulin infusion. There is clinical trial evidence that CGM reduces rates of hypoglycemia in these populations. CGM can reveal asymptomatic hypoglycemia and help identify patterns and precipitants of hypoglycemic events (142,143). Real-time CGM can provide alarms that can warn individuals of falling glucose so that they can intervene (142,143). For more information on using BGM and CGM for hypoglycemia prevention, see Section 7, "Diabetes Technology."

An essential component of hypoglycemia prevention is appropriate modification to diabetes treatment in the setting of intercurrent illness (discussed in detail below) or to prevent recurrent hypoglycemic events. Level 2 or 3 hypoglycemic events especially should trigger a reevaluation of the individual's diabetes treatment plan, with consideration of deintensification of therapy within individualized glycemic goals.

Individuals with impaired awareness should be offered training to reestablish awareness of hypoglycemia. Fear of hypoglycemia and hypoglycemia unawareness often co-occur, so interventions aimed at treating one often benefit both (144). Several evidence-based training programs have been developed for this purpose and have been demonstrated to reduce rates of hypoglycemia and improve quality of life among people with type 1 diabetes and impaired hypoglycemia awareness (75,145,146). However, these programs are not currently available for clinical use. Similar training can be provided through qualified behavioral health professionals, diabetes care and education specialists, or other professionals with experience in this area, although this approach has not been evaluated in clinical trials. In addition, several weeks of avoidance of hypoglycemia, typically accomplished through a temporary relaxation of glycemic goals, can improve counterregulation and hypoglycemia awareness in many people with diabetes (147). Hence, individuals with impaired hypoglycemia awareness and recurrent hypoglycemic episodes may benefit from short-term relaxation of glycemic goals.

Table 6.6—Median monthly (30-day) AWP and NADAC of glucagon formulations in the U.S.

Product	Form	Median AWP* (min, max)	Median NADAC* (min, max)	Dosage
Glucagon	Injection powder with diluent for reconstitution	$206 ($194, $337)	$235 ($199, $295)	1 mg
Glucagon	Nasal powder	$347	$269	3 mg
Glucagon	Prefilled pen, prefilled syringe	$379	$295	0.5 mg, 1 mg
Dasiglucagon	Prefilled pen, prefilled syringe	$371	$298	0.6 mg

AWP, average wholesale price; max, maximum; min, minimum; NADAC, National Average Drug Acquisition Cost. AWP and NADAC prices are as of 1 July 2024. *Calculated per unit (AWP [181,182] or NADAC [183]; median AWP or NADAC is listed alone when only one product and/or price is described).

INTERCURRENT ILLNESS

Stressful events (e.g., illness, trauma, and surgery) increase the risk for both hyperglycemia and hypoglycemia among individuals with diabetes. In severe cases, they may precipitate diabetic ketoacidosis or a nonketotic hyperglycemic hyperosmolar state, which are life-threatening

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Table 6.7—Components of hypoglycemia prevention for individuals at risk for hypoglycemia at initial, follow-up, and annual visits

Hypoglycemia prevention action	Initial visit	Every follow-up visit	Annual visit
Hypoglycemia history assessment	✓	✓	✓
Hypoglycemia awareness assessment	✓		✓
Cognitive function and other hypoglycemia risk factor assessment	✓		✓
Structured patient education for hypoglycemia prevention and treatment	✓	✓*	✓*
Consideration of continuous glucose monitoring needs	✓	✓	✓
Reevaluation of diabetes treatment plan with deintensification, simplification, or agent modification as appropriate	✓	✓†	✓†
Glucagon prescription and training for close contacts for insulin-treated individuals or those at high hypoglycemic risk	✓		✓
Training to reestablish awareness of hypoglycemia	✓‡		✓‡

The listed frequencies are the recommended minimum; actions for hypoglycemia prevention should be taken more often as needed based on clinical judgment. *Indicated with recurrent hypoglycemic events or at initiation of medication with a high risk for hypoglycemia. †Indicated with any level 2 or 3 hypoglycemia, intercurrent illness, or initiating interacting medications. ‡Indicated when impaired hypoglycemia awareness is detected.

conditions that require immediate medical care. Any individuals with diabetes experiencing illness or other stressful events should be assessed for the need for more frequent monitoring of glucose; ketosis-prone individuals also require urine or blood ketone monitoring. Clinicians should reevaluate diabetes treatment during these events and make adjustments as appropriate. Clinicians should be aware of medication interactions that may precipitate hypoglycemia. Notably, sulfonylureas interact with a number of commonly used antimicrobials (fluoroquinolones, clarithromycin, sulfamethoxazole-trimethoprim, metronidazole, and fluconazole) that can dramatically increase their effective dose, leading to hypoglycemia (148–150). Clinicians should consider temporarily decreasing or stopping sulfonylureas when these antimicrobials are prescribed.

For further information on management of hyperglycemia in the hospital, see Section 16, "Diabetes Care in the Hospital."

HYPERGLYCEMIC CRISES: DIAGNOSIS, MANAGEMENT, AND PREVENTION

Recommendations

6.20 Review history of hyperglycemic crises (i.e., diabetic ketoacidosis and hyperglycemic hyperosmolar state) at every clinical encounter for all individuals with diabetes at risk for these events. **C**

6.21 Provide structured education on the recognition, prevention, and management of hyperglycemic crisis to all individuals with type 1 diabetes, those with type 2 diabetes who have experienced these events, and people at high risk for these events. **B**

Diabetic ketoacidosis (DKA) and the hyperglycemic hyperosmolar state (HHS) are serious, acute, and life-threatening hyperglycemic emergencies in individuals with diabetes (151) that incur substantial morbidity, mortality, and costs (152). Approximately 1% of all hospitalizations in people with diabetes are for hyperglycemic crises. The diagnostic criteria for DKA and HHS are summarized in **Table 6.8**; all criteria must be met to establish these diagnoses. Importantly, approximately 10% of people experiencing DKA present with euglycemic DKA (plasma glucose <200 mg/dL [11.1 mmol/L]); therefore, DKA diagnosis requires either the presence of hyperglycemia or prior history of diabetes (151). Euglycemic DKA requires insulin deficiency and can be associated with a variety of factors including reduced food intake, pregnancy, alcohol use, liver failure, and/or SGLT2 inhibitor therapy (153). Additionally, DKA and HHS often present concurrently (154), though few studies have examined mixed DKA-HHS events.

There has been a concerning rise in the rate of hyperglycemic crises in people with both type 1 diabetes and type 2 diabetes over the past decade (91,155–161). Recent data suggest hyperglycemic crisis rates of up to 44.5–82.6 per 1,000 person-years among people with type 1 diabetes (91,159) and up to 3.2 per 1,000 person-years among people with type 2 diabetes (91). While DKA mortality decreased in the first decade of the 21st century (156), these improvements have

Table 6.8—Diagnostic criteria for DKA and HHS

DKA	
Diabetes/hyperglycemia	Glucose ≥200 mg/dL (11.1 mmol/L) or prior history of diabetes
Ketosis	β-Hydroxybutyrate concentration ≥3.0 mmol/L or urine ketone strip 2+ or greater
Metabolic acidosis	pH <7.3 and/or bicarbonate concentration <18 mmol/L
HHS	
Hyperglycemia	Plasma glucose ≥600 mg/dL (33.3 mmol/L)
Hyperosmolarity	Calculated effective serum osmolality >300 mOsm/kg (calculated as [2×Na^+ (mmol/L) + glucose (mmol/L)] or total serum osmolality >320 mOsm/kg [2×Na^+ (mmol/L) + glucose (mmol/L) + urea (mmol/L)]
Absence of significant ketonemia	β-Hydroxybutyrate concentration <3.0 mmol/L OR urine ketone strip less than 2+
Absence of acidosis	pH ≥7.3 and bicarbonate concentration ≥15 mmol/L

Adapted from Umpierrez et al. (151).

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plateaued in the past decade (155, 159,162). Most recently available data for inpatient mortality during hospital admission for DKA ranges from 0.2% in type 1 diabetes (163) to 1.0% in type 2 diabetes (156,164). Inpatient mortality among people with type 2 diabetes hospitalized for HHS decreased from 1.44% in 2008 to 0.77% in 2018 (165). The only study to have examined inpatient mortality for mixed DKA-HHS found it to be higher than mortality for HHS or DKA alone (154). Mortality rates reported in low- and middle-income countries are much higher than those in developed countries, potentially because of delayed diagnosis and treatment (151). People discharged after an episode of DKA have a 1-year age-corrected mortality rate that is 13 times higher than the general population (166).

There are a number of clinical factors associated with an increased risk of hyperglycemic crises (**Table 6.9**). In addition, several studies have reported DKA at the presentation of newly diagnosed type 1 diabetes during or after a coronavirus disease 2019 (COVID-19) infection. The precise mechanisms for new-onset diabetes in people with COVID-19 are not known, but several complex interrelated processes may be involved. Some drug classes can affect carbohydrate metabolism and precipitate the development of DKA and HHS, including glucocorticoids, antipsychotic medications, checkpoint inhibitors, and SGLT2 inhibitors. The risk of DKA in people with type 1 diabetes using SGLT2 inhibitors can be 5–17 times higher than that in nonusers. In contrast, observational studies and randomized controlled trials have shown that DKA is uncommon in people with type 2 diabetes treated with SGLT2 inhibitors (0.6–4.9 events per 1,000 patient-years) (167). A meta-analysis of four randomized controlled trials found the relative risk of DKA in participants with type 2 diabetes treated with SGLT2 inhibitors versus placebo or active comparator arm to be 2.46 (95% CI 1.16–5.21), while a meta-analysis of five observational studies found the relative risk to be 1.74 (95% CI 1.07–2.83) (168). Risk factors for DKA in individuals with type 2 diabetes treated with SGLT2 inhibitors include very-low-carbohydrate diets and prolonged fasting, dehydration, excessive alcohol intake, and the presence of autoimmunity, in addition to typical precipitating factors (168,169). Up to 2% of pregnancies with pregestational diabetes (most often type 1 diabetes) are complicated by DKA. The incidence of DKA in gestational diabetes is low (<0.1%) (170). Pregnant individuals may present with euglycemic DKA (glucose <200 mg/dL [11.1 mmol/L]), and the diagnosis of DKA may be hindered by the presence of mixed acid-based disturbances, particularly in the setting of hyperemesis. Due to significant risk of feto-maternal harm, pregnant individuals at risk for DKA should be counseled on the signs and symptoms suggestive of DKA and seek immediate medical attention if concern for DKA is present.

Table 6.9—Risk factors for hyperglycemic crises

Type 1 diabetes/absolute insulin deficiency
Younger age
Prior history of hyperglycemic crises
Prior history of hypoglycemic crises
Presence of other diabetes complications
Presence of other chronic health conditions (particularly in people with type 2 diabetes)
Presence of behavioral health conditions (e.g., depression, bipolar disorder, and eating disorders)
Alcohol and/or substance use
High A1C level
Social determinants of health

Data are from McCoy et al. (184), Gibb et al. (185), Randall et al. (186), and Thomas et al. (187).

Hyperglycemic crisis should be considered in all individuals presenting with polyuria, polydipsia, weight loss, vomiting, dehydration, and change in cognitive state (**Table 6.10**). Individuals at risk for DKA should be counseled on the early signs and symptoms of DKA, provided with appropriate tools for accurate ketone measurement (urine and/or blood ketone tests), and educated on timely self-management of hyperglycemia and ketonemia ("sick day advice") (171–173) to prevent clinical deterioration and need for acute care. Individuals treated with intensive insulin therapy should not stop or hold their basal insulin even if not eating, and clinicians should provide detailed instructions on insulin dose adjustments in the setting of illness or fasting to prevent DKA occurrence and worsening. Individuals concerned about or experiencing DKA should be encouraged to contact their diabetes care team immediately. Readily available clinical support can help individuals self-manage hyperglycemia during illness and prevent emergency department and hospital care (174). Individuals at risk for DKA should measure urine or blood ketones in the presence of symptoms and potential precipitating factors (e.g., illness, missed insulin doses), particularly if glucose levels exceed 200 mg/dL (11.1 mmol/L). When hemodynamically and cognitively intact, able to tolerate oral hydration, and able to administer subcutaneous insulin, individuals may treat mild DKA with frequent blood glucose and urine or blood ketone monitoring, noncaloric hydration, and subcutaneous insulin administration. However, individuals should seek immediate medical attention if unable to tolerate oral hydration, blood glucose levels do not improve with insulin administration, altered mental status is present, or any signs of worsening illness occur. Because HHS is associated with greater volume depletion and is typically triggered by an acute illness, individuals with suspected HHS should be immediately evaluated and treated in the inpatient setting.

A substantial proportion of individuals hospitalized with DKA experience recurrent episodes (175,176), which underscores the importance of engaging individuals experiencing these events to identify triggers and prevent recurrence. Structured diabetes self-management education and support that includes problem-solving is effective at reducing DKA admissions, as are psychological interventions, peer

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Table 6.10—Clinical presentation in people with diabetes with DKA and HHS

DKA	HHS
Develops over hours to days	Develops over days to a week
Usually alert	Change in cognitive state common
Polyuria, polydipsia, weight loss, and dehydration	
Nausea, vomiting, and abdominal pain	Often copresenting with other acute illness
Kussmaul respiration	
One-third of hyperglycemic emergencies have a hybrid DKA-HHS presentation	

Adapted from Umpierrez et al. (151).

support, individual coaching, and behavioral family systems therapy (177,178). Individuals who have experienced DKA or HHS should be screened for social determinants of health that can contribute to or trigger these complications, including inadequate access to insulin, other glucose-lowering medications, and diabetes durable medical equipment (i.e., glucose monitoring and insulin administration devices), and referred to appropriate health care and/or community services to mitigate these barriers to care (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for additional details). Access to CGM may also decrease risk of DKA recurrence (179).

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7. Diabetes Technology: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Diabetes technology is the term used to describe the hardware, devices, and software that people with diabetes use to assist with self-management, ranging from lifestyle modifications to glucose monitoring and therapy adjustments. Historically, diabetes technology has been divided into two main categories: insulin administered by syringe, pen, patch devices, or pump (also called continuous subcutaneous insulin infusion) and glucose as assessed by blood glucose monitoring (BGM) or continuous glucose monitoring (CGM). Diabetes technology now includes automated insulin delivery (AID) systems that use CGM-informed algorithms to modulate insulin delivery. It also encompasses connected insulin pens and diabetes self-management support software that serve as medical devices. Diabetes technology, coupled with education, follow-up, pharmacotherapy if needed, and support, can improve the lives and health of people with diabetes; however, the complexity and rapid evolution of the diabetes technology landscape can also be a barrier to implementation for people with diabetes, their care partners, and the health care team.

GENERAL DEVICE PRINCIPLES

Recommendations

7.1 Diabetes devices should be offered to people with diabetes. **A**

7.2 Initiation of continuous glucose monitoring (CGM) should be offered to people with type 1 diabetes early in the disease, even at time of diagnosis. **A**

7.3 The type(s) and selection of devices should be individualized based on a person's specific needs, circumstances, preferences, and skill level. In the setting of an individual whose diabetes is partially or wholly managed by someone else (e.g., a young child or a person with cognitive impairment or dexterity, psychosocial issues, and/or physical limitations), the caregiver's skills and preferences are integral to the decision-making process. **E**

7.4 When prescribing a device, ensure that people with diabetes and caregivers receive initial and ongoing education and training, either in person or remotely, and ongoing evaluation of technique, results, and the ability to utilize data, including uploading or sharing data (if applicable), to monitor and adjust therapy. **C**

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.*

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7.5 Health care professionals working with diabetes technology should ensure that competencies are established within the health care team based on their specific roles and within specific settings. **E**

7.6 People with diabetes who have been using CGM, continuous subcutaneous insulin infusion (CSII), and/or automated insulin delivery (AID) for diabetes management should have continued access across third-party payors, regardless of age or A1C levels. **E**

7.7 Students should be supported at school in the use of diabetes technology, such as CGM systems, CSII, connected insulin pens, and AID systems, as recommended or prescribed by their health care team. **E**

7.8 Recommend early initiation, including at diagnosis, of CGM, CSII, and AID depending on a person's or caregiver's needs and preferences. **C**

7.9 Standardized reports for all CGM, CSII, AID, and connected insulin devices with a minimum of a single-page report, such as the ambulatory glucose profile and weekly summary, should be available and utilized. Options for daily and weekly reports and raw data should be available. **E**

Technology is rapidly changing, but there is no one-size-fits-all approach to technology use in people with diabetes. Insurance coverage can lag behind device availability, people's interest in devices and willingness for adoption can vary, and health care teams may have challenges in keeping up with newly released technology. An American Diabetes Association resource, which can be accessed at diabetes.org/living-with-diabetes/treatment-care/diabetes-technology-guide, can help health care professionals and people with diabetes make decisions on the initial choice of device(s). Other sources, including health care professionals and device manufacturers, can help people troubleshoot when difficulties arise (1–10).

Education and Training

In general, no device used in diabetes management works optimally without education, training, and ongoing support. There are multiple resources, including online tutorials and training videos as well as written material, on the use of devices. People with diabetes vary in comfort level with technology, and some prefer in-person training and support. Those with more education regarding device use have better outcomes (1,2); therefore, the need for additional education should be periodically assessed, particularly if outcomes are not being met. Better outcomes cannot be achieved, however, without the training and education of health care professionals. The assessment of competencies in diabetes technology is crucial for prescribers, certified diabetes and education specialists, pharmacists, nurses, and anyone involved in the care of people with diabetes. These competencies are described as basic, fundamental, intermediate, and advanced and are specific to the role of each health care team member (11). In addition, the health care team's knowledge and competency are even more relevant when people with diabetes are started on advanced diabetes technologies, such as AID systems. In such situations, training is vital and should include a discussion about realistic expectations for the ability of the initiated system to achieve glucose goals, the system's features and limitations, and the best way to use the new system to maximize the benefits it can offer (12).

Use in Schools

Instructions for device use should be outlined in the student's diabetes medical management plan (DMMP). A backup plan should be included in the DMMP for potential device failure (e.g., BGM, CGM, and/or insulin delivery devices). School nurses and designees should complete training to stay up to date on diabetes technologies prescribed for use in the school setting. Updated resources to support diabetes care at school, including training materials and a DMMP template, can be found online at diabetes.org/safe-at-school-state-laws.

Initiation of Device Use

The use of CGM and BGM devices should be considered from the outset of the diagnosis of diabetes that requires insulin management (3,4). CGM use allows for close tracking of glucose levels with adjustments of insulin dosing and lifestyle modifications and removes the burden of frequent BGM. In addition, early CGM initiation after diagnosis of type 1 diabetes in youth has been shown to decrease A1C levels and is associated with high parental satisfaction and reliance on this technology for diabetes management (5,6). Training on alarm/alert settings when initiating CGM is crucial to avoid alarm overload. Early initiation of AID systems or insulin pumps should be considered, especially in youth. In an open-label, multicenter, randomized, parallel clinical trial enrolling youth with newly diagnosed type 1 diabetes, initiation of an AID system within 21 days from diagnosis showed 10% higher time in range (TIR) (70–180 mg/dL [3.9–10.0 mmol/L]) and lower A1C at 12 months versus usual care (13). In addition, use of diabetes technology overall improves A1C and increases the number of people achieving an A1C $<7\%$ (14). Interruption of access to CGM is associated with a worsening of outcomes (7,15); therefore, it is important for individuals on CGM to have consistent access to devices.

BLOOD GLUCOSE MONITORING

Recommendations

7.10 People with diabetes should be provided with blood glucose monitoring (BGM) devices as indicated by their circumstances, preferences, and treatment. People using CGM devices must also have access to BGM at all times. **A**

7.11 People who are taking insulin and using BGM should be encouraged to check their blood glucose levels when appropriate based on their insulin therapy. This may include checking when fasting, prior to meals and snacks, after meals, at bedtime, in the middle of the night, prior to, during, and after exercise, when hypoglycemia is suspected, after treating low blood glucose levels until they are normoglycemic, when hyperglycemia is suspected, and prior to and while performing critical tasks such as driving. **B**

7.12 Health care professionals should be aware of the differences in accuracy among blood glucose meters. Only meters approved by the U.S. Food and Drug Administration (FDA) (or comparable regulatory agencies for other geographical locations) with proven accuracy should be used, with unexpired test strips purchased from a pharmacy or licensed distributor and properly stored. **E**

7.13 Although BGM in people on noninsulin therapies has not consistently shown clinically significant reductions in A1C levels, it may be helpful when modifying meal plans, physical activity plans, and/or medications (particularly medications that can cause hypoglycemia) in conjunction with a treatment adjustment program. **E**

7.14 Consider potential interference of medications and substances on glucose

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levels measured by blood glucose meters. **B**

Major clinical trials of insulin-treated people with diabetes have included BGM as part of multifactorial interventions to demonstrate the benefit of intensive glycemic management on diabetes complications (16). BGM is thus an integral component of effective therapy for individuals using insulin. In recent years, CGM has emerged as a method for the assessment of glucose levels (discussed below). Glucose monitoring allows people with diabetes to evaluate their individual responses to therapy and assess whether glycemic goals are being safely achieved. Integrating results into diabetes management can be a useful tool for guiding medical nutrition therapy and physical activity, preventing hypoglycemia, or adjusting medications (particularly prandial insulin doses or correction bolus doses). The specific needs and goals of the person with diabetes should dictate BGM frequency and timing or the consideration of CGM use. As recommended by the device manufacturers and the U.S. Food and Drug Administration (FDA), people with diabetes using CGM must have access to BGM for multiple reasons, including whenever there is suspicion that the CGM is inaccurate, while waiting for warm-up, when there is a disruption in CGM transmission, for calibration (if needed) or if a warning message appears, when CGM supplies are delayed, and in any clinical setting where glucose levels are changing rapidly (>2 mg/dL/min), which could cause a discrepancy between CGM and blood glucose values.

Meter Standards

Glucose meters meeting FDA guidance for meter accuracy provide the most reliable data for diabetes management. There are several current standards for the accuracy of blood glucose meters, but the two most used are those of the International Organization for Standardization (ISO) (ISO 15197:2013) and the FDA. The current ISO and FDA standards are compared in **Table 7.1**. In Europe, currently marketed meters must meet current ISO standards. In the U.S., currently marketed meters must meet the standard under which they were approved, which may not be the current standard. Moreover, the monitoring of current accuracy postmarketing is left to the manufacturer and not routinely checked by an independent source.

People with diabetes assume their glucose meter is accurate because it is FDA cleared, but that may not be the case. There is substantial variation in the accuracy of widely used BGM systems (17,18). The Diabetes Technology Society Blood Glucose Monitoring System Surveillance Program provides information on the performance of devices used for BGM (diabetestechnology.org/surveillance/). In one analysis, 6 of the top 18 best-selling glucose meters met the accuracy standard (19). In a subsequent analysis with updated glucose meters, 14 of 18 glucose meters met the minimum accuracy requirements (20). There are single-meter studies in which benefits have been found with individual meter systems, but few studies have compared meters head-to-head. Certain meter system characteristics, such as the use of lancing devices that are less painful (21) and the ability to reapply blood to a strip with an insufficient initial sample, or meters with integrated speech that can read aloud glucose levels for visually impaired individuals (22), may also be beneficial to people with diabetes (23) and may make BGM less burdensome to perform.

Counterfeit Strips

People with diabetes should be advised against purchasing or reselling preowned or secondhand test strips, as these may give incorrect results. Only unopened and unexpired vials of glucose test strips should be used to ensure BGM accuracy.

Optimizing Blood Glucose Monitoring Device Use

Optimal use of BGM devices requires proper review and interpretation of data by both the person with diabetes and the health care professional to ensure that data are used in an effective and timely manner. In people with type 1 diabetes, there is a correlation between greater BGM frequency and lower A1C levels (24). Among those who check their blood glucose at least once daily, many report taking no action when results are high or low (25). Some meters now provide advice to the user in real time when monitoring glucose levels (26), whereas others can be used as a part of integrated health platforms (27). People with diabetes should be taught how to use BGM data to adjust food intake, physical activity, or pharmacologic therapy to achieve specific goals. The ongoing need for and frequency of BGM should be reevaluated at each routine visit to ensure its effective use (24,28).

People With Diabetes on Intensive Insulin Therapies

BGM is especially important for people with diabetes treated with insulin to monitor for and prevent hypoglycemia and hyperglycemia. Most individuals on intensive insulin therapies (multiple daily injections [MDI] or insulin pump therapy) should be encouraged to assess glucose levels using BGM (and/or CGM) prior to meals and snacks, at bedtime, occasionally postprandially, prior

Table 7.1—Comparison of ISO 15197:2013 and FDA blood glucose meter accuracy standards

Setting	FDA*	ISO 15197:2013*
Hospital use	95% within 12% for BG ≥75 mg/dL 95% within 12 mg/dL for BG <75 mg/dL 98% within 15% for BG ≥75 mg/dL 98% within 15 mg/dL for BG <75 mg/dL	95% within 15% for BG ≥100 mg/dL 95% within 15 mg/dL for BG <100 mg/dL 99% in A or B region of consensus error grid‡
Home use	95% within 15% for all BG in the usable BG range† 99% within 20% for all BG in the usable BG range†	

BG, blood glucose; FDA, U.S. Food and Drug Administration; ISO, International Organization for Standardization. To convert mg/dL to mmol/L, see endmemo.com/medical/unitconvert/Glucose.php. *Data shown in the FDA column are from the FDA (298). Data shown in the ISO column are from the FDA (299). †The range of blood glucose values for which the meter has been proven accurate and will provide readings (other than low, high, or error). ‡Values outside of the "clinically acceptable" A and B regions are considered "outlier" readings and may be dangerous to use for therapeutic decisions (300).

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to, during, and after physical activity, when they suspect hypoglycemia or hyperglycemia, after treating hypoglycemia until they are normoglycemic, and prior to and while performing critical tasks such as driving. For many individuals using BGM, this requires checking up to 6–10 times daily, although individual needs may vary. A database study of almost 27,000 children and adolescents with type 1 diabetes showed that, after adjusting for multiple confounders, increased daily frequency of BGM was significantly associated with lower A1C levels (−0.2% per additional check per day) and with fewer acute complications (29).

People With Diabetes Using Basal Insulin and/or Oral Agents and Noninsulin Injectables

The evidence is insufficient regarding when to prescribe BGM and how often monitoring is needed for insulin-treated people with diabetes who do not use intensive insulin therapy, such as those with type 2 diabetes taking basal insulin with or without oral agents and/or noninsulin injectables. However, for those taking basal insulin, assessing fasting glucose with BGM to inform dose adjustments to achieve blood glucose goals results in lower A1C levels (30).

In people with type 2 diabetes not taking insulin, routine glucose monitoring may be of limited additional clinical benefit. By itself, even when combined with education, this practice has shown limited improvement in outcomes (31). However, for some individuals, glucose monitoring can provide insight into the impact of nutrition, physical activity, and medication management on glucose levels. Glucose monitoring may also be useful in assessing hypoglycemia, glucose levels during intercurrent illness, or discrepancies between measured A1C and glucose levels when there is concern an A1C result may not be reliable in specific individuals (for more details, see Section 2, "Diagnosis and Classification of Diabetes"). It may be useful when coupled with a treatment adjustment program. In a year-long study of insulin-naive people with diabetes with suboptimal initial glycemic outcomes, a group trained in structured BGM (a paper tool was used at least quarterly to collect and interpret seven-point BGM profiles taken on three consecutive days) reduced their A1C levels by 0.3% more than the control group (32). A trial of once-daily BGM that included enhanced feedback from people with diabetes through messaging found no clinically or statistically significant change in A1C levels at 1 year (31). Meta-analyses have suggested that BGM can reduce A1C levels by 0.25–0.3% at 6 months (33–35), but the effect was attenuated at 12 months in one analysis (33). Reductions in A1C levels were greater (−0.3%) in trials where structured BGM data were used to adjust medications, but A1C levels were not changed significantly without such structured diabetes therapy adjustment (35). A key consideration is that performing BGM alone does not lower blood glucose levels. To be useful, the information must be integrated into clinical and self-management treatment plans.

Glucose Meter Inaccuracy

Although many meters function well under various circumstances, health care professionals and people with diabetes must be aware of factors that impair meter accuracy. A meter reading that seems discordant with the clinical picture needs to be retested or tested in a laboratory. Health care professionals in intensive care unit settings need to be particularly aware of the potential for incorrect meter readings during critical illness, and laboratory-based values should be used if there is any doubt. Some meters give error messages if meter readings are likely to be false (36).

Oxygen. Currently available glucose monitors use an enzymatic reaction linked to an electrochemical reaction, either glucose oxidase or glucose dehydrogenase (37). Glucose oxidase monitors are sensitive to the oxygen available and should only be used with capillary blood in people with normal oxygen saturation. Higher oxygen tensions (i.e., arterial blood or oxygen therapy) may result in false low-glucose readings, and low oxygen tensions (i.e., high altitude, hypoxia, or venous blood readings) may lead to falsely elevated glucose readings. Glucose dehydrogenase–based monitors are generally not sensitive to oxygen.

Temperature. Because the reaction is sensitive to temperature, all monitors have an acceptable temperature range (37). Most will show an error if the temperature is unacceptable, but a few will provide a reading and a message indicating that the value may be incorrect. Humidity and altitude may also alter glucose readings.

Interfering Substances. There are several physiologic and pharmacologic factors that interfere with glucose readings measured with either personal blood glucose meters or professional blood glucose meters used in various inpatient settings (neonatal intensive care unit, hospital wards, and intensive care unit) (37). They are listed in **Table 7.2**.

CONTINUOUS GLUCOSE MONITORING DEVICES

See **Table 7.3** for definitions of types of CGM devices.

Recommendations

7.15 Recommend real-time CGM (rtCGM) **A** or intermittently scanned CGM (isCGM) for diabetes management to youth **C** and adults **B** with diabetes on any type of insulin therapy. The choice of CGM device should be made based on the individual's circumstances, preferences, and needs.

7.16 Consider using rtCGM and isCGM in adults with type 2 diabetes treated with glucose-lowering medications other than insulin to achieve and maintain individualized glycemic goals. The choice of device should be made based on the individual's circumstances, preferences, and needs. **B**

7.17 In people with diabetes on insulin therapy, rtCGM devices should be used as close to daily as possible for maximal benefit. **A** isCGM devices should be scanned frequently, at minimum once every 8 h, to avoid gaps in data. **A** People with diabetes should have uninterrupted access to their supplies to minimize gaps in CGM. **A**

7.18 CGM can help achieve glycemic goals (e.g., time in range and time above range) **A** and A1C goal **B** in type 1 diabetes and pregnancy and may be beneficial for other types of diabetes in pregnancy. **E**

7.19 In circumstances when consistent use of CGM is not feasible, consider periodic use of personal or professional CGM to adjust medication and/or lifestyle. **C**

7.20 Skin reactions, either due to irritation or allergy, should be assessed and addressed to aid in successful use of devices. **E**

7.21 People who wear CGM devices should be educated on potential interfering substances and other factors that may affect accuracy. **C**

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Table 7.2—Common interfering substances and/or conditions that affect glucose meters (for inpatient and outpatient use)

Substance or condition	Effects on glucose values measured by blood glucose meters
Maltose*	Falsely higher blood glucose values
Galactose	Falsely higher blood glucose values
Xylose	Falsely higher blood glucose values
N-Acetylcysteine†	Falsely higher blood glucose values
Acetaminophen	Falsely higher blood glucose values at low blood glucose levels
Dopamine	Falsely higher blood glucose values at low blood glucose levels
Furosemide	Falsely lower blood glucose values
Vitamin C	Falsely lower or higher blood glucose values
Uric acid	Falsely higher blood glucose values at very low or very high glucose levels
Hematocrit (high)	Falsely higher blood glucose values
Hematocrit (low)	Falsely lower blood glucose values

*Unmodified glucose dehydrogenase method only. †Glucose dehydrogenase monitors using pyrroloquinoline quinone cofactor (GDH/PQQ).

CGM measures interstitial glucose (which correlates well with plasma glucose, although at times, it can lag if glucose levels are rising or falling rapidly). There are two basic types of CGM devices. The first type includes those that are owned by the user, unblinded, and intended for frequent or continuous use, including real-time CGM (rtCGM), intermittently scanned CGM (isCGM), and over-the-counter CGM devices. The second type is professional CGM devices that are owned by practices and applied in the clinic, which provide data that are blinded or unblinded for a discrete period of time. The types of sensors currently available are either disposable (rtCGM and isCGM) or implantable (rtCGM). **Table 7.3** provides definitions for the types of CGM devices. For people with type 1 diabetes using CGM, frequency of sensor use is an important predictor of A1C lowering for all age-groups (38,39). The frequency of scanning with isCGM devices is also correlated with improved outcomes (40–43).

Few real-time systems require calibration by the user, which varies in frequency depending on the device. CGM systems are generally nonadjunctive, meaning they do not require BGM confirmation for treatment decisions like insulin dosing or treating hypoglycemia, except in certain clinical situations (see BLOOD GLUCOSE MONITORING, above) (44–46).

Most CGM systems are designated as integrated CGM (iCGM), a higher standard set by the FDA for integration with other digitally connected devices. Dexcom G6 rtCGM (no generic form available), Dexcom G7 rtCGM (no generic form available), FreeStyle Libre 2 Plus (no generic form available), FreeStyle Libre 3 Plus (no generic form available), and Eversense E3 (no generic form available) are FDA approved for use with AID systems. Similarly, Dexcom G6 rtCGM, Dexcom G7 rtCGM, FreeStyle Libre 2 isCGM (no generic form available), and Medtronic Simplera rtCGM (no generic form available) are approved for use with connected insulin pens (47). Currently, Dexcom G6 and Dexcom G7 are integrated with four AID systems (t:slim X2 with Control-IQ, Omnipod 5, iLet, and Mobi). Similarly, at this time in the U.S., the FreeStyle Libre 2 Plus is integrated with one AID system (t:slim X2 with Control-IQ) and the FreeStyle Libre 3 Plus with another AID system (iLet). Finally, the Medtronic Guardian 3 rtCGM (no generic form available) and the Medtronic Guardian 4 rtCGM (no generic form available) are FDA approved for use with the 670/770G and 780G AID systems, respectively.

Benefits of Continuous Glucose Monitoring

Data From Randomized Controlled Trials

Multiple randomized controlled trials (RCTs) have been performed using rtCGM devices, and the results have largely been positive in terms of reducing A1C levels and/or episodes of hypoglycemia if participants regularly wore the devices (38–41,48–51). The initial studies were done primarily in adults and youth with type 1 diabetes on insulin pump therapy and/or MDI (38,39,48,49, 52). The primary outcome was met and showed benefit in adults of all ages (38,53,54), including seniors (55–57). Data in children show that rtCGM use in young children with type 1 diabetes reduced hypoglycemia; in addition, behavioral support of parents of young

Table 7.3—Continuous glucose monitoring devices

Type of CGM	Description
rtCGM	CGM systems that measure and display glucose levels continuously
isCGM with and without alarms	CGM systems that measure glucose levels continuously but require scanning for visualization and storage of glucose values
Professional CGM	CGM devices that are placed on the person with diabetes in the health care professional's office and worn for a discrete period of time (generally 7–14 days). Data may be blinded or visible to the person wearing the device. The data are used to assess glycemic patterns and trends. Unlike rtCGM and isCGM devices, these devices are clinic-based and not owned by the person with diabetes.
Over-the-counter CGM	CGM devices called biosensors, which measure glucose continuously and display the levels at various times, have insights rather than alarms and are indicated for people with prediabetes or with diabetes not on insulin.

CGM, continuous glucose monitoring; isCGM, intermittently scanned CGM; rtCGM, real-time CGM.

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children with diabetes using rtCGM showed the benefits of reducing hypoglycemia concerns and diabetes distress (38,49,58). Similarly, A1C level reduction was seen in adolescents and young adults with type 1 diabetes using rtCGM (48). RCT data on rtCGM use in individuals with type 2 diabetes on MDI (59), mixed therapies (10, 60), and basal insulin (61,62) have consistently shown reductions in A1C levels and increases in TIR (70–180 mg/dL [3.9–10 mmol/L]) but not a reduction in rates of hypoglycemia (63). Although short-term use of rtCGM in youth with type 2 diabetes did not impact short-term glucose changes or A1C improvement, users reported behavioral changes with increased blood glucose measurements, increased insulin administration, and overall improved diabetes management and quality of life (64,65). The improvements in type 2 diabetes have largely occurred without changes in insulin doses or other diabetes medications. CGM discontinuation in individuals with type 2 diabetes on basal insulin caused partial reversal of A1C reduction and TIR improvements, suggesting that continued CGM use achieves the greatest benefits (15).

RCT data for rtCGM benefits in people with type 2 diabetes not using insulin are increasing and generally have shown greater benefits of CGM compared with BGM for A1C, TIR, time below range (TBR), and time above range (TAR) as well as greater user-reported satisfaction (66). These benefits were initially reported in a study where the intermittent use of rtCGM for either one session or two sessions (3 months apart) versus control treatment showed improvement of A1C at 3 months. At 6 months, the two-session rtCGM group achieved significant A1C reduction. For both rtCGM groups, participants who measured BGM at least 1.5 times per day achieved greater A1C improvement compared with the control group (67).

In addition, rtCGM benefits were reported in a mixed population (including people not using insulin) of adults with type 2 diabetes with reduction in A1C levels, increase in TIR, and reduction of time in hyperglycemia (>180 mg/dL [>10 mmol/L] and >250 mg/dL [>13.9 mmol/L]) (10).

RCT data for isCGM are fewer but increasing. One study was performed in adults with type 1 diabetes and met its primary outcome of a reduction in rates of hypoglycemia (68). In adults with type 2 diabetes using insulin, two studies were done: one study did not meet its primary end point of A1C level reduction (69) but achieved a secondary end point of a reduction in hypoglycemia, and the other study met its primary end point of an improvement in the Diabetes Treatment Satisfaction Questionnaire score as well as a secondary end point of A1C level reduction (70). In a study of individuals with type 1 or type 2 diabetes taking insulin, the primary outcome of a reduction in severe hypoglycemia was not met and the incidence of severe hypoglycemia was not significantly different between isCGM users and the BGM group (71). One study in youth with type 1 diabetes did not show a reduction in A1C levels (72); however, the device was well received and was associated with an increased frequency of testing and improved diabetes treatment satisfaction (72). A randomized trial of adults with type 1 diabetes showed that the use of isCGM with optional alerts and alarms resulted in reduction of A1C levels compared with BGM use (9).

The benefits of isCGM for adults with type 2 diabetes not using insulin were initially reported in a multicenter, open-label, randomized (1:1), parallel-group study. At 12 weeks, A1C was significantly reduced from baseline in both groups without difference. However, at 24 weeks, the isCGM group showed a greater A1C reduction than the control group. Furthermore, there were no between-group differences in change of antihyperglycemic drugs (73). In a subsequent post hoc analysis, the isCGM group showed that the effects of isCGM were present 1 week after isCGM initiation for weekly mean glucose, glucose management indicator (GMI), percentage of TIR, percentage of TAR, and mean amplitude glucose excursion and remained stable from baseline to 12 weeks (74). Additionally, benefits of isCGM were also reported in an RCT where the use of isCGM plus diabetes education versus diabetes education alone showed decreased A1C levels and increased TIR as well as increased time in tight target range (70–140 mg/dL [3.9–7.8 mmol/L]) in the isCGM-plus-education group (8).

Observational and Real-world Studies

CGM systems are widely available in many countries for people with diabetes, and this allows for the collection of large amounts of data across groups of people with diabetes.

Data for isCGM in adults with diabetes include results from observational studies, retrospective studies, and analyses of registry and population data (75,76). In individuals with type 1 diabetes wearing isCGM devices, studies have shown improvement in A1C levels (41,77), TIR (70–180 mg/dL [3.9–10.0 mmol/L]), and hypoglycemia (41,43,75,78,79). Reductions in acute diabetes complications, such as diabetic ketoacidosis (DKA), episodes of severe hypoglycemia or diabetes-related coma, and hospitalizations for hypoglycemia and hyperglycemia, have been observed in adults with type 1 or type 2 diabetes (43,78,80), with persistent effects observed even after 2 years of CGM initiation (81). Similar reductions of acute diabetes events and all-cause inpatient hospitalizations were seen in a retrospective review of adults with type 2 diabetes treated with basal insulin or with noninsulin therapy 6 months after initiation of isCGM (82). Prospective observational as well as retrospective studies in adults with type 2 diabetes treated with MDI showed significant reduction of A1C and hypoglycemia (83) after 12 weeks of isCGM use, with increased user satisfaction (83). Similar results were seen in a retrospective study with adults with type 2 diabetes on basal insulin at 3–6 months (84). Furthermore, retrospective observational data in adults with type 2 diabetes treated with either basal insulin or noninsulin therapy have shown an improvement in A1C levels (85). Finally, a retrospective study of continued use of isCGM in adults with nonintensively treated type 2 diabetes showed reduction of A1C and GMI, increase in TIR, and reduction of TAR (>180 mg/dL) (86). Results of self-reported outcomes varied, but, where measured, people with diabetes had an increase in treatment satisfaction with isCGM compared with BGM. In an observational study in youth with type 1 diabetes, a slight increase in A1C levels and weight was seen, but the device was associated with a high user satisfaction rate (76).

Retrospective data from rtCGM use in adults (87) with type 1 or type 2 diabetes treated with insulin showed that the use of rtCGM significantly lowered A1C levels and reduced rates of emergency department visits or hospitalizations for hypoglycemia but did not significantly lower overall rates of emergency department visits, hospitalizations, or hyperglycemia.

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Recent data have emerged from a real-world observational analysis of rtCGM use in adults with type 2 diabetes not treated with insulin. In this study, rtCGM benefits were observed at 6 month and 12 months versus baseline, with reduction of mean glucose levels, reduction of GMI, increase in TIR, increase in time in tight target range (70–140 mg/dL [3.9–7.8 mmol/L]), and reduction in TAR >180 and >250 mg/dL (88).

Real-time Continuous Glucose Monitoring Compared With Intermittently Scanned Continuous Glucose Monitoring

In adults with type 1 diabetes, three RCTs have been conducted comparing isCGM (without predictive alerts/alarms) and rtCGM (with predictive alerts/alarms) (84,89,90). In two of the studies, the primary outcome was a reduction in time spent in hypoglycemia, and rtCGM showed greater benefits compared with isCGM (89,90). In the other study, the primary outcome was improved TIR, and rtCGM also showed greater benefits compared with isCGM (84). A retrospective analysis also showed improvement in TIR with rtCGM compared with isCGM (91). A more recent 12-month real-world nonrandomized study compared rtCGM with isCGM in adults with type 1 diabetes. At 12 months, A1C levels, time in level 1 hypoglycemia (<70 mg/dL [<3.9 mmol/L]), and time in level 2 hypoglycemia (<54 mg/dL [<3.0 mmol/L]) were all lower in the rtCGM group than in the isCGM group; similarly, the TIR was higher in the rtCGM group than in the isCGM group (92).

Data Analysis

The abundance of data provided by CGM offers opportunities to analyze data for people with diabetes more granularly than previously possible, providing additional information to aid in achieving glycemic goals. A variety of metrics have been proposed (93) and are discussed in Section 6, "Glycemic Goals and Hypoglycemia." CGM is essential for creating an ambulatory glucose profile (AGP) and providing data on TIR, percentage of time spent above and below range, and glycemic variability (94). Standardized reports for CGM, AID, and connected insulin pens include multiple reports, each providing different degrees of information. These reports, whether single page or with raw data, should be used in clinical practice to identify CGM trends and patterns; in the setting of AID systems, these reports provide important information on insulin delivery and its suspension or modulation as well as information on automated bolus delivery that can assist the clinician in making therapy adjustments (12,94,95). However, data analysis can be burdensome without a systematic approach to its review, and CGM and AID manufacturers should aim to make device data reports as standardized as possible to reduce the burden of data analysis (12). Several efforts have been made to streamline the interpretation of CGM reports to assist health care professionals in their daily practice. These have various, but overall similar, approaches. The initial steps are focused on assessing the sufficiency and quality of data; subsequent recommendations include reviewing the presence and trends or patterns of hypoglycemia, followed by hyperglycemia patterns and trends. Some authors also suggest approaches to changing therapy plans based on the data reviewed that enable health care professionals to make a simple yet comprehensive review and plan of care even within the time constraints of office visits (96–100).

Real-time Continuous Glucose Monitoring Device Use in Pregnancy

CGM indication is now expanded to include pregnancy for Dexcom G7, FreeStyle Libre 2, and FreeStyle Libre 3, which will enhance care in this population (101,102). Prior data from one well-designed RCT showed a reduction in A1C levels in pregnant adults with type 1 diabetes on MDI or insulin pump therapy and using rtCGM in addition to standard care; CGM users experienced more pregnancy-specific TIR (63–140 mg/dL [3.5–7.8 mmol/L]) and less time in hyperglycemia (103). This study demonstrated the value of rtCGM in pregnancy complicated by type 1 diabetes by showing a mild improvement in A1C levels and a significant improvement in the maternal glucose TIR for pregnancy (63–140 mg/dL [3.5–7.8 mmol/L]), without an increase in hypoglycemia, as well as reductions in large-for-gestational-age births, infant hospital length of stay, and severe neonatal hypoglycemia (103). An observational cohort study that evaluated the glycemic variables reported using rtCGM and isCGM found that lower mean glucose, lower SD, and higher percentage of TIR were associated with lower risks of large-for-gestational-age births and other adverse neonatal outcomes (104). Another observational study in pregnancies with and without gestational diabetes mellitus (GDM) wearing blinded CGM found higher mean glucose, more time spent at >120 mg/dL and >140 mg/dL, and less time spent at 63–120 mg/dL were associated with large-for-gestational-age births and gestational hypertensive disorders, while lower mean glucose and more time spent at <63 mg/dL and <54 mg/dL were associated with small-for-gestational-age birth (105). Data from one study suggested that the use of rtCGM-reported mean glucose is superior to use of the glucose management indicator and other calculations to estimate A1C levels given the changes to A1C levels that occur in pregnancy (106). Two studies employing intermittent use of rtCGM showed no difference in neonatal outcomes in individuals with type 1 diabetes (107) or gestational diabetes mellitus (108). At this time, data are insufficient to recommend the use of CGM in all pregnant people with type 2 diabetes or GDM (109,110). The decision of whether to use CGM in pregnant individuals with type 2 diabetes or GDM should be individualized based on treatment plan, circumstances, preferences, and needs.

Although CGM systems for use in pregnancy do not require calibrations and are approved for nonadjunctive use, when using CGM in diabetes and pregnancy, determination of glucose levels by finger stick may be necessary in certain circumstances, such as in the setting of hypoglycemia or hyperglycemia outside the recommended CGM goal ranges (63–140 mg/dL [3.5–7.8 mmol/L]) during pregnancy.

Use of Professional Continuous Glucose Monitoring and Intermittent Use of Continuous Glucose Monitoring

Professional CGM devices, which provide retrospective data, either blinded or unblinded, for analysis can be used to identify patterns of hypoglycemia and hyperglycemia (111,112). Professional CGM can be helpful to evaluate an individual's glucose levels when either rtCGM or isCGM is not available to the individual or they prefer a blinded analysis or a shorter experience with unblinded data. It can be particularly useful in individuals using agents that can cause hypoglycemia, as the data can be used to evaluate periods of hypoglycemia and make medication dose adjustments if needed. It can also be useful to evaluate periods of hyperglycemia.

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Some data have shown the benefit of intermittent use of CGM (rtCGM or isCGM) in individuals with type 2 diabetes on noninsulin and/or basal insulin therapies (60,73). In these RCTs, people with type 2 diabetes not on intensive insulin therapy used CGM intermittently compared with those randomized to BGM. Both early (60) and late improvements in A1C levels were found (60,73).

Furthermore, in a real-world study, the use of professional CGM in individuals with type 2 diabetes not on insulin at baseline and at 6 months of follow-up resulted in lower A1C at 6 months as well as a shift toward greater use of glucose-lowering medications with cardiometabolic benefits, such as sodium–glucose transporter 2 inhibitors and glucagon-like peptide 1 receptor agonists (113). Use of professional or intermittent CGM should always be coupled with analysis and interpretation for people with diabetes along with education, as needed, to adjust medication and change lifestyle behaviors (114–116).

Side Effects of Continuous Glucose Monitoring Devices

Contact dermatitis (both irritant and allergic) has been reported with all devices that attach to the skin (20,117,118). In some cases, this has been linked to the presence of isobornyl acrylate, a skin sensitizer that can cause an additional spreading allergic reaction (119–121). It is important to ask CGM users periodically about adhesive reactions, as tape formulations may change over time. Patch testing can sometimes identify the cause of contact dermatitis (122). Identifying and eliminating tape allergens is important to ensure the comfortable use of devices and promote self-care (123–126). The PANTHER Program offers resources in English and Spanish at www.pantherprogram.org/skin-solutions. In some instances, using an implanted sensor can help avoid skin reactions in those sensitive to tape (127,128).

Substances and Factors Affecting Continuous Glucose Monitoring Accuracy

Sensor interference due to several medications/substances is a known potential source of CGM sensor measurement errors (**Table 7.4**). While several of these substances have been reported in the various CGM brands' user manuals, additional interferences have been discovered after the market release of these products. Hydroxyurea, used for myeloproliferative disorders and hematologic conditions, is one of the most recently identified interfering substances that cause a temporary increase in sensor glucose values discrepant from actual glucose values (129–134). Similarly, substances such as mannitol and sorbitol, when administered intravenously or as a component of peritoneal dialysis solution, may increase blood mannitol or sorbitol concentrations and cause falsely elevated readings of sensor glucose (135). Therefore, it is crucial to routinely review the medications and supplements used by the person with diabetes to identify possible interfering substances and advise them accordingly on the need to use additional BGM if sensor values are unreliable due to these substances.

INSULIN DELIVERY

Insulin Syringes and Pens

Recommendations

7.22 For people with insulin-requiring diabetes on multiple daily injections (MDI), insulin pens are preferred in most cases. Still, insulin syringes may be used for insulin delivery considering individual and caregiver preference, insulin type, availability in vials, dosing therapy, cost, and self-management capabilities. **C**

7.23 Insulin pens or insulin injection aids are recommended for people with dexterity issues or vision impairment or when decided by shared decision-making to facilitate the accurate dosing and administration of insulin. **C**

7.24 Offer connected insulin pens for people with diabetes taking multiple daily insulin injections. **B**

7.25 FDA-approved insulin dose calculators/decision support systems may be helpful for calculating insulin doses. **B**

Injecting insulin with a syringe or pen (136–147) is the insulin delivery method used by most people with diabetes (142,148), although inhaled insulin is also available. Others use insulin pumps or AID devices (see INSULIN PUMPS AND AUTOMATED INSULIN DELIVERY SYSTEMS, below). For people with diabetes who use insulin, insulin syringes and pens both can deliver insulin safely and effectively for the achievement of glycemic goals. Individual preferences, cost, insulin type, dosing therapy, and self-management capabilities should be considered when choosing among delivery systems. Trials with insulin pens generally show equivalence or small improvements in glycemic outcomes compared with using a vial and syringe. Many individuals with diabetes prefer using a pen because of its simplicity and convenience. It is important to note that while many insulin types are available for purchase as either pens or vials, others may be

Table 7.4—Continuous glucose monitoring device interfering substances

Medication	Systems affected	Effect
Acetaminophen		
>4 g/day	Dexcom G6, Dexcom G7	Higher sensor readings than actual glucose
Any dose	Medtronic Guardian	Higher sensor readings than actual glucose
Ascorbic acid (vitamin C), >500 mg/day	FreeStyle Libre 14 day, FreeStyle Libre 2, FreeStyle Libre 3	Higher sensor readings than actual glucose
Ascorbic acid (vitamin C), >1,000 mg/day	FreeStyle Libre 2 Plus, FreeStyle Libre 3 Plus	Higher sensor readings than actual glucose
Hydroxyurea	Dexcom G6, Dexcom G7, Medtronic Guardian	Higher sensor readings than actual glucose
Mannitol (intravenously or as peritoneal dialysis solution)	Senseonics Eversense	Higher sensor readings than actual glucose
Sorbitol (intravenously or as peritoneal dialysis solution)	Senseonics Eversense	Higher sensor readings than actual glucose

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available in only one form or the other, and there may be significant cost differences between pens and vials (see **Table 9.4** for a list of insulin product costs with dosage forms). Insulin pens may allow people with vision impairment or dexterity issues to dose insulin accurately (149–151), and insulin injection aids are also available to help with these issues. (For a helpful list of injection aids, see living-with-diabetes/treatment-care/diabetes-technology-guide). Inhaled technosphere insulin can be useful for people with diabetes, providing an alternative method of insulin delivery with very fast onset of action. In a recent randomized clinical trial, the use of technosphere inhaled insulin showed lower postprandial hyperglycemia than subcutaneous rapid-acting analog insulin (152).

The most common syringe sizes are 1 mL, 0.5 mL, and 0.3 mL, allowing doses of up to 100 units, 50 units, and 30 units, respectively, of U-100 insulin. Some 0.3-mL syringes have half-unit markings, whereas other syringes have markings in 1- to 2-unit increments. In a few parts of the world, insulin syringes still have U-80 and U-40 markings for older insulin concentrations and veterinary insulin, and U-500 syringes are available for the use of U-500 insulin. Syringes are generally used once but may be reused by the same individual in resource-limited settings with appropriate storage and cleansing (151).

Insulin pens offer added convenience by combining the vial and syringe into a single device. Insulin pens, allowing push-button injections, come as disposable pens with prefilled cartridges or reusable insulin pens with replaceable insulin cartridges. Pens vary with respect to dosing increment and minimal dose, ranging from half-unit doses to 2-unit dose increments, with the latter available in U-200 insulin pens. U-500 pens come in 5-unit dose increments. Some reusable pens include a memory function, which can recall dose amounts and timing. Insulin pens, once started, can be kept in use for variable durations, based on the type of insulin, usually for 28 days, ranging from 14 to 56 days. Needle thickness (gauge) and length are other considerations. Needle gauges range from 22 to 34, with a higher gauge indicating a thinner needle. A thicker needle can give a dose of insulin more quickly, while a thinner needle may cause less pain. Needle length ranges from 4 to 12.7 mm, with some evidence suggesting that shorter needles (4–5 mm) lower the risk of intramuscular injection with erratic absorption and possibly the development of lipohypertrophy. When reused, needles may be duller and thus injections may be more painful. Proper insulin injection technique is a requisite for receiving the full dose of insulin with each injection. Concerns with technique and use of the proper technique are outlined in Section 9, "Pharmacologic Approaches to Glycemic Treatment."

Connected insulin pens are insulin pens with the capacity to record and/or transmit insulin dose data. Insulin pen caps are also available and are placed on existing insulin pens and may assist with calculating insulin doses and by providing a memory function. Some connected insulin pens and pen caps can be programmed to calculate insulin doses, can be synced with select CGM systems, and can provide downloadable data reports. These pens and pen caps are useful to people with diabetes for real-time insulin dosing and allow clinicians to retrospectively review the insulin delivery times and, in some cases, doses and glucose data to make informed insulin dose adjustments (153). A quantitative study showed that people with diabetes preferred connected pens because of their ability to log insulin doses and glucose levels automatically (153). In a multicenter RCT in people with type 1 diabetes, the use of an insulin pen cap was associated with improved glycemic outcomes at 6 weeks in the insulin cap group, with an increase in TIR and decrease in GMI and TAR (154). A systematic review of connected insulin pens or pen caps showed improvement of glucose outcomes whether as A1C reduction, TIR increase, or hypoglycemia reduction (155). A recent real-world study with multinational data collected from 3,954 adults with diabetes using a connected pen and CGM validated the fact that treatment engagement with a connected insulin pen is positively associated with glycemic outcomes. On the other hand, missing as little as two basal doses or four bolus insulin doses over a 14-day period would be associated with a clinically relevant decrease in TIR of ≥5% (156).

Bolus calculators have been developed to aid dosing decisions (157–162). These systems are subject to FDA approval to ensure safety and efficacy in terms of algorithms used and subsequent dosing recommendations. People interested in using these systems should be encouraged to use those that are FDA approved. Health care professional input and education can be helpful for setting the initial dosing calculations with ongoing follow-up for adjustments as needed.

Insulin Pumps and Automated Insulin Delivery Systems

Recommendations

7.26 AID systems should be the preferred insulin delivery method to improve glycemic outcomes and reduce hypoglycemia and disparities in youth and adults with type 1 diabetes **A** and other types of insulin-deficient diabetes **E** who are capable of using the device (either by themselves or with a caregiver). Choice of an AID system should be made based on the individual's circumstances, preferences, and needs. **A**

7.27 Insulin pump therapy, preferably with CGM, should be offered for diabetes management to youth and adults on MDI with type 2 diabetes who can use the device safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs. **A**

7.28 Individuals with diabetes who have been using CSII should have continued access across third-party payors. **E**

Insulin Pumps

Insulin pumps have been available in the U.S. for over 40 years. These devices deliver rapid-acting insulin throughout the day to help manage glucose levels. Most insulin pumps use tubing to deliver insulin through a cannula, while a few attach directly to the skin without tubing (pods or patch pumps), and these systems have been approved for use in type 1 and type 2 diabetes. AID systems, which can adjust insulin delivery rates based on sensor glucose values, are preferred over nonautomated pumps and MDI in people with type 1 diabetes and have largely replaced the use of nonintegrated or standard insulin pumps. Recently, one AID system was approved for use by people with type 2 diabetes.

Historically, studies that compared MDI with insulin pump therapy were relatively small and of short duration. However, a systematic review and meta-analysis concluded that pump therapy has modest advantages for lowering A1C levels (−0.30% [95% CI −0.58 to −0.02]) and for reducing severe hypoglycemia rates in children and adults (163). Real-world data on insulin

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pump use in individuals with type 1 diabetes show benefits in A1C levels and hypoglycemia reductions as well as total daily insulin dose reduction (164). There is no consensus to guide choices on which form of insulin administration is best for a given individual, and research to guide this decision-making process is needed (163). Thus, the choice of MDI or an insulin pump is often based on the characteristics of the person with diabetes and which method is most likely to benefit them. DiabetesWise (diabeteswise.org/), for individuals with diabetes, DiabetesWise Pro (pro.diabeteswise.org/), for health care professionals, and the PANTHER Program (pantherprogram.org/device-comparison-chart) have helpful websites to assist health care professionals and people with diabetes in choosing diabetes devices based on their individual needs and the features of the devices. Newer systems, such as sensor-augmented pumps (SAPs) and AID systems, are discussed below.

Adoption of pump therapy in the U.S. shows geographical variations, which may be related to health care professional preference or center characteristics (165,166) and socioeconomic status, as pump therapy is more common in individuals of higher socioeconomic status, as reflected by private health insurance, family income, and education (165,166). Given the additional barriers to optimal diabetes care observed in disadvantaged groups (167), addressing the differences in access to insulin pumps and other diabetes technologies may contribute to fewer health disparities.

Pump therapy can be successfully started at the time of diagnosis (168). Practical aspects of pump therapy initiation include assessment of readiness of the person with diabetes and their family, if applicable (although there is no consensus on which factors to consider in adults [169] or children and adolescents with diabetes), selection of pump type and initial pump settings, individual and family education on potential pump complications (e.g., DKA with infusion set failure), transition from MDI, and introduction of advanced pump settings (e.g., temporary basal rates and extended bolus, square-wave bolus, or dual-wave bolus).

Older individuals with type 1 diabetes benefit from ongoing insulin pump therapy. There are no data to suggest that measurement of C-peptide levels or antibodies predicts success with insulin pump therapy (170,171). Additionally, the frequency of follow-up does not influence outcomes. Access to insulin pump therapy, including AID systems, should be allowed or continued in older adults as it is in younger people.

Complications of the pump can be caused by issues with infusion sets (dislodgement and occlusion), which put individuals at risk for ketosis and DKA and thus must be recognized and managed early (172). Other pump skin issues include lipohypertrophy or, less frequently, lipoatrophy (173) and pump site infection. Discontinuation of pump therapy is relatively uncommon today; the frequency has decreased over the past few decades, and its causes have changed (174). Current reasons for attrition are problems with cost or wearability, loss of insurance, dislike of the pump, suboptimal glycemic outcomes, or mood disorders (e.g., anxiety or depression) (175).

Insulin Pumps in Youth

The safety of insulin pumps in youth has been established for over 15 years (176). Studying the effectiveness of insulin pump therapy in lowering A1C levels has been challenging because of the potential selection bias of observational studies. Participants on insulin pump therapy may have a higher socioeconomic status that may facilitate better glycemic outcomes (177) than MDI. In addition, the fast pace of development of new insulins and technologies quickly renders comparisons obsolete. However, RCTs that compared insulin pumps and MDI with rapid-acting insulin analogs demonstrated a modest improvement in A1C levels in participants on insulin pump therapy (178,179). Observational studies, registry data, and meta-analyses have also suggested an improvement in glycemic outcomes in participants on insulin pump therapy (180–182). Data suggest that insulin pumps reduce the rates of severe hypoglycemia compared with MDI (182–185).

There is also evidence that insulin pump therapy may reduce DKA risk (182,186) and diabetes complications, particularly retinopathy and peripheral neuropathy in youth, compared with MDI (169). In addition, treatment satisfaction and quality-of-life measures improved on insulin pump therapy compared with MDI (187). Therefore, insulin pumps can be used safely and effectively in youth with type 1 diabetes to assist with achieving targeted glycemic outcomes while reducing the risk of hypoglycemia and DKA, improving quality of life, and preventing long-term complications. Based on shared decision-making by people with diabetes and health care professionals, insulin pumps may be considered in all children and adolescents with type 1 diabetes. In particular, pump therapy may be the preferred mode of insulin delivery for children under 7 years of age (188). Because of a paucity of data in adolescents and youth with type 2 diabetes, there is insufficient evidence to make recommendations.

Common barriers to pump therapy adoption in children and adolescents are concerns regarding the physical interference of the device, discomfort with the idea of having a device on the body, therapeutic effectiveness, and financial burden (180,189).

Sensor-Augmented Pumps

SAPs (or partial closed-loop systems) consist of three components: an insulin pump, a CGM system, and an algorithm that automates insulin suspension when glucose is low or is predicted to go low within the next 30 min. Predictive low-glucose suspend systems have been shown to reduce time spent with glucose $<$70 mg/dL without rebound hyperglycemia during a 6-week randomized crossover trial (190). Similar results were seen in additional studies in adults and children with reduction of hypoglycemia (191–193). SAPs have now been largely replaced by AID systems, which offer superior benefits for glycemic outcomes; nevertheless, some AID systems can still be used in either low-glucose suspend mode or predictive low-glucose suspend mode.

Automated Insulin Delivery Systems

AID systems consist of mainly three components: an insulin pump, a CGM system, and an algorithm that determines insulin delivery. Based on the model and brand of currently FDA approved AID systems, the algorithm can be hosted in the pump body, in an insulin pod, or on a phone app. All AID systems on the market today integrate with one or more CGM systems and adjust insulin delivery either by modulating the preprogrammed basal rates or by replacing the basal rates with microboluses or microdoses of insulin every 5 min.

The modulation of insulin delivery is done by increasing, decreasing, or pausing insulin based on the CGM feedback, the predicted direction of the glucose levels, and the speed with which the

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glucose levels are changing. Different AID systems modulate insulin based on predicted glucose levels at various times, most commonly 30 min or 1 h. Currently available AID systems have either fixed glucose targets or adjustable glucose targets, generally ranging from 100 to 120 mg/dL, with some exceptions where glucose targets can be adjusted up to 150 mg/dL. Glucose targets are generally set up for 24 h but can also be adjusted in some systems with up to eight segments per day. All current AID systems provide automated correction doses, whether embedded in the microdose adjustments every 5 min or by providing additional correction boluses whose doses are dependent on the various types of algorithms with variable frequency and threshold glucose based on the type of control algorithm. Most AID systems can be used in manual mode, although this is generally not recommended, as the benefits of CGM modulation may be partially or totally lost. However, use of AID in manual mode may be necessary in some circumstances, therefore it is important to review and reassess manual-mode settings periodically. Current AID systems still require manual entry of carbohydrates for meal announcements or qualitative meal estimation announcements to calculate prandial doses.

Adjustments for physical activity are available in most AID systems currently on the market. These can be programmed in various time increments. In general, the glucose target is raised to prespecified levels based on AID systems, and these are often accompanied by more conservative insulin delivery to reduce the risk of hypoglycemia in the setting of increased insulin sensitivity other than physical activity, such as prolonged fasting or NPO status for procedures. Of note, some systems may still give autocorrection boluses if the glucose levels rise above a certain threshold even while the exercise/activity mode has been enabled. Details on the available AID systems and their features can be found at pantherprogram.org/device-type.

AID systems have largely replaced other methods of continuous subcutaneous insulin delivery due to the advantages they offer in insulin modulation and sophistication of algorithms to adjust insulin doses and minimize hypoglycemia and hyperglycemia.

Data From Pivotal Trials

All currently FDA-approved AID systems were tested for safety and efficacy in their pivotal trials in children and adults with type 1 diabetes (194–206). These studies were conducted either as a single arm of manual mode followed by automated mode of a specific AID system or as an RCT comparing the AID system to an SAP and/or usual care. Regardless of the study design, all AID system pivotal trials that examined individuals 2 years old or older, including older adults, have consistently demonstrated superiority to either standard insulin delivery (or manual mode for the single-arm studies) or SAP and/or usual care (for the randomized trials), with consistent improvement in A1C, increase in TIR, especially overnight, as well as reduction of time spent in hypoglycemia (207–219). The greatest improvements were seen with AID when used in individuals with the highest baseline A1C or lowest TIR (220). These systems may also lower the risk of exercise-related hypoglycemia (219) and have been shown to have psychosocial benefits (221–225). A review of the literature on the health and economic value of AID systems in individuals with type 1 diabetes found that AID systems are cost-effective (226). AID is rapidly becoming the standard of care for people with type 1 diabetes and should be the preferred method of insulin delivery in these individuals. The decision to use AID systems should be made based on the preference of the person with diabetes and the selection of individuals (and/or caregivers) who are capable of safely and effectively using the devices.

Data From Real-world Studies

Data from real-world studies on AID systems have become available and continue to increase rapidly. These studies include large numbers of users, at times even 30-fold higher than the number of people studied in AID pivotal trials (227). It is important to emphasize that for some AID systems all data are automatically collected to the database (228), whereas for other systems data are collected based on voluntary sharing to the database by AID users. A recent systematic review of AID real-world studies, with 20 studies representing 171,209 individuals, substantiated the results observed in the pivotal trials and have confirmed the clinical benefits of AID systems in people with type 1 diabetes. Newer systems have shown increased time spent in automation, and the real-world studies have retrospectively analyzed longer duration of system use compared with their respective pivotal trials, with most analyses occurring for more than 6 months and an average duration of 9 months (227).

Benefits include improvement in A1C levels, TIR, and other glucometrics as well as psychosocial benefits (229–234).

Finally, real-world data showed that AID systems provide the same glycemic benefits to Medicare and Medicaid beneficiaries with type 1 and type 2 diabetes, emphasizing that access to this technology should be made available regardless of A1C levels and should be based on the individual's needs (235).

Automated Insulin Delivery Systems in Pregnancy

The use of AID systems in diabetes and pregnancy presents particular challenges, as the current FDA-approved AID systems (except for one that has been FDA approved but is not yet commercially available) have glucose goals that are not pregnancy specific and do not have algorithms designed to achieve pregnancy-specific glucose goals. Initiating or continuing AID systems during pregnancy needs to be assessed carefully. Selected individuals with type 1 diabetes should be evaluated as potential candidates for AID systems in the setting of expert guidance. Recent data have shown the clinical benefits and safety of AID use, even though only one study used an AID system with a pregnancy-specific glycemic target. This study, a multicenter, controlled trial, enrolled pregnant women with type 1 diabetes before 14 weeks' gestation and randomized them by week 16 to the AID system or standard care (MDI with CGM or standard insulin pump therapy with CGM). The primary outcome of time spent in the pregnancy-specific target range of 63–140 mg/dL was found to be 10.5% higher in the AID group versus standard care ($P < 0.001$). The secondary outcomes were also met, with less time spent above range (>140 mg/dL) in the AID group, greater overnight time in target range, and lower A1C (236). There were no differences in the number of preterm births, birth weight, neonatal complications, or admission to the neonatal intensive care unit.

Additional data were reported from a pilot RCT of SAP without automation versus assisted hybrid closed-loop therapy in pregnant women with type 1 diabetes that enrolled participants in the first trimester and randomized them at 14–18 weeks'

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gestation. This system did not have pregnancy-specific glucose targets; however, the results showed that the time in hypoglycemia <54 mg/dL did not differ between groups. Time at <63 mg/dL was lower in the hybrid closed-loop group, whereas percentage of the pregnancy-specific TIR was greater in the SAP group in the third trimester, with similar safety and adverse pregnancy outcomes between groups (237). There were no statistically significant differences in measures of glycemic risk or in measures of glycemic variability between the hybrid closed-loop and the SAP groups at any point during pregnancy or postpartum (238). In another study with an AID system with a lowest glucose target of 100 mg/dL, participants were randomized to AID or standard of care in the first trimester and for the rest of gestation. The 24-h percentage of pregnancy-specific TIR was not different between groups, but the overnight percentage of pregnancy-specific TIR was higher in the AID group while using assistive techniques. Time spent below range was lower over 24 h and overnight in the AID group as well. Quality-of-life metrics were improved in the AID group in this study (239).

Therefore, if the decision is made to use AID systems without pregnancy-specific targets in selected pregnant individuals, then using assistive techniques, such as the combination of SAP mode (or manual mode) and hybrid closed-loop mode at different time points in pregnancy or throughout the day or entering fake carbohydrate boluses, should be considered and applied as needed to achieve intended goals (240). See Section 15, "Diabetes and Pregnancy," for more details.

Insulin Pumps and Automated Insulin Delivery Systems in People With Type 2 and Other Types of Diabetes

Traditional insulin pumps can be considered for the treatment of people with type 2 diabetes who are on MDI as well as those who have other types of diabetes resulting in insulin deficiency, for instance, those who have had a pancreatectomy and/or individuals with cystic fibrosis (241–245). Similar to data on insulin pump use in people with type 1 diabetes, reductions in A1C levels have been reported in some studies (243,246). More recently, real-world reports have shown reduction of A1C levels and reduction of total daily insulin dose in individuals with type 2 diabetes initiating insulin pump therapy (247). Use of insulin pumps in insulin-requiring people with any type of diabetes may improve user satisfaction and simplify therapy (171,241).

For people with diabetes judged to be clinically insulin deficient who are treated with an intensive insulin therapy, the presence or absence of measurable C-peptide levels does not correlate with response to therapy (171). A low C-peptide value should not be required for insulin pump coverage in individuals with type 2 diabetes.

The use of insulin pumps and AID systems in type 2 diabetes is still limited, and at this time only one system is FDA approved for use in type 2 diabetes. Nevertheless, data are increasing; a small, single-arm prospective study in adults with type 2 diabetes who were on MDI and started an AID system revealed improvement of TIR by 15% at 6 weeks (248). Similar findings were reported in a randomized controlled, crossover trial of adults with type 2 diabetes previously treated with conventional insulin pump therapy plus CGM. While on the AID system (5 weeks), the TIR increased by a mean of 15%, with a decrease in TAR (>180 mg/dL and >250 mg/dL) and GMI. Of note, an increase in total daily insulin dose was noted in the subjects while on the AID system (249), whereas other studies have shown either nonsignificant trends for a lower total daily dose of insulin in the AID group (250) or a reduction of total daily insulin in the AID group previously using MDI (251). Finally, a recent RCT of older adults with type 2 diabetes who used MDI but were unable to manage insulin therapy on their own revealed an increase of TIR of 27% over 12 weeks of AID system use in addition to tailored home health care services (250). Real-world studies have also shown benefits of these technologies in adults with type 2 diabetes (235,251).

Alternative insulin delivery options in people with type 2 diabetes include disposable patch-like devices, which provide either a continuous subcutaneous insulin infusion of rapid-acting insulin (basal) with bolus insulin in 2-unit increments at the press of a button or bolus insulin only, delivered in 2-unit increments, used in conjunction with basal insulin injections (242,244, 252,253). Use of an insulin pump as a means of insulin delivery is an individual choice for people with diabetes and should be considered an option in those who are capable of safely using the device.

Open-Source Automated Insulin Dosing

Recommendation

7.29 Support and provide diabetes management advice to people with diabetes who choose to use an open-source closed-loop system. **B**

Open-source automated insulin dosing (OS-AID) algorithms provide the precise code that governs their operation, so health care professionals and people with diabetes can have a more complete understanding of risks and benefits (254). Any commercial entity could provide the source code for their interoperable automated glycemic controller, but most choose not to. OS-AID algorithms are largely designed, maintained, and curated by people with diabetes and their loved ones. Thousands of people with diabetes use these algorithms with cleared CGM systems and insulin pump components. The information on how to set up and manage these systems is freely available online.

OS-AID is the preferred term when referring to any open-source system (commercial or otherwise). It is important to note that the term "DIY" is not reflective of any aspect of these community-driven systems. No individual person has written all the code for these algorithms, and a large percentage of users do not build the software themselves (255). There are two main available algorithms, the OpenAPS algorithm and the Loop algorithm, which have been implemented on a variety of platforms.

The OpenAPS heuristic algorithm (implemented on a system on a chip in OpenAPS, Android smartphones as AndroidAPS, and iPhone as iAPS/Trio) is supported by large real-world studies (256) and a multicenter RCT (257). The OpenAPS algorithm is the only AID system to support unannounced meals. In a single-center study of adolescents with type 1 diabetes randomized to AndroidAPS with quantitative carbohydrate announcements, qualitative announcements, and no announcements, TIR was preserved across groups (258).

Loop, an open-source model predictive control algorithm, is implemented on iPhones as an app. Prospective real-world data from 558 adults and children with type 1 diabetes on this system (255) was used to support the FDA clearance of a variant called Tidepool Loop (259).

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Both the Loop and OpenAPS algorithms offer direct management of algorithm aggressiveness through conventional pump settings. Therefore, it is advisable that health care professionals understand and offer support in tuning settings for these safe and effective technologies (254). This may include, for example, the adjustment of basal rates, insulin-to-carbohydrate ratios, or insulin sensitivity factors. As with any AID system, a backup insulin treatment plan is advisable.

Digital Health Technology

Recommendation

7.30 Consider combining technology (CGM, insulin pump, and/or diabetes apps) with online or virtual coaching to improve glycemic outcomes in individuals with diabetes or prediabetes. **B**

Increasingly, people are turning to the internet for advice, coaching, connection, and health care. Diabetes, partly because it is both common and numeric, lends itself to the development of apps and online programs. Recommendations for developing and implementing a digital diabetes clinic have been published (260). The FDA approves and monitors clinically validated, digital, and usually online health technologies intended to treat a medical or psychological condition; these are known as digital therapeutics, or "digiceuticals" (fda.gov/medical-devices/digital-health-center-excellence/device-software-functions-including-mobile-medical-applications) (261). Other applications, such as those that assist in displaying or storing data, encourage a healthy lifestyle or provide limited clinical data support. Therefore, it is possible to find apps that have been fully reviewed and approved by the FDA and others designed and promoted by people with relatively little skill or knowledge in the clinical treatment of diabetes. There are insufficient data to provide recommendations for specific apps for diabetes management, education, and support in the absence of RCTs and validation of apps unless they are FDA cleared.

An area of particular importance is that of online privacy and security. Established cloud-based data aggregator programs, such as Tidepool, Glooko, and others, have been developed with appropriate data security features and are compliant with the U.S. Health Insurance Portability and Accountability Act of 1996. These programs can help monitor people with diabetes and provide access to their health care teams (262). Consumers should read the policy regarding data privacy and sharing before entering data into an application and learn how they can manage the way their data will be used (some programs offer the ability to share more or less information, such as being part of a registry or data repository or not).

Many online programs offer lifestyle counseling to achieve weight loss and increased physical activity (263). Many include a health coach and can create small groups of similar participants on social networks. Some programs aim to treat prediabetes and prevent progression to diabetes, often following the model of the Diabetes Prevention Program (264,265). Others assist in improving diabetes outcomes by remotely monitoring clinical data (for instance, wireless monitoring of glucose levels, weight, or blood pressure) and providing feedback and coaching (266–271). There are text messaging approaches that tie into a variety of different types of lifestyle and treatment programs, which vary in terms of their effectiveness (272,273). There are limited RCT data for many of these interventions, and long-term follow-up is lacking. However, in a real-world observational study in individuals with type 2 diabetes treated with basal insulin, oral medications, or no medications, the use of a digital health solution and rtCGM resulted in reductions of GMI and TAR >180 and >250 mg/dL as well as an increase in TIR by 15% and participation in a least one engagement activity per week (274). Therefore, even with limited data, for an individual with diabetes, opting in to one of these programs can be helpful in providing support and, for many, is an attractive option.

Inpatient Care

Recommendations

7.31 In people with diabetes wearing personal CGM, the use of CGM should be continued when clinically appropriate during hospitalization, with confirmatory point-of-care glucose measurements for insulin dosing and hypoglycemia assessment and treatment under an institutional protocol. **B**

7.32 Continue use of insulin pump or AID in people with diabetes who are hospitalized when clinically appropriate, with confirmatory point-of-care blood glucose measurements for insulin dose decisions and hypoglycemia assessment and treatment. This is contingent upon availability of necessary supplies, resources, and training, ongoing competency assessments, and implementation of institutional diabetes technology protocols. **C**

Individuals who are comfortable using their diabetes devices, such as insulin pumps and CGM, should be allowed to use them in an inpatient setting if they are well enough to take care of the devices and have brought the necessary supplies (273,275–278). People with diabetes who are familiar with treating their own glucose levels can often adjust insulin doses more knowledgeably than inpatient staff who do not personally know the individual or their management style. It is crucial that, when people with diabetes in the inpatient setting need to temporarily disconnect or interrupt their device use for a procedure or imaging studies, etc., the care team is particularly careful to not discard these devices or stop their use without ensuring that an alternate method of insulin delivery has been initiated, if these are insulin delivery devices, and to ensure that close glucose monitoring is continued by finger stick. Therefore, it is particularly important that the use of diabetes devices while in the inpatient setting should occur based on the hospital's policies for diabetes management and use of diabetes technology, and there should be supervision to ensure that the individual is achieving and maintaining glycemic goals during acute illness in a hospitalized setting where factors such as infection, certain medications, immobility, and changes in nutrition can affect insulin sensitivity and the insulin response (279–281).

With the advent of the coronavirus disease 2019 pandemic, the FDA exercised enforcement discretion by allowing CGM device use temporarily in the hospital for patient monitoring (282). This approach has been taken to reduce the use of personal protective equipment and more closely monitor patients so that health care personnel do not have to go into a patient room solely to measure a glucose level (283–286). Studies have been published assessing the effectiveness of this approach, which may ultimately lead to the approved use of CGM

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for monitoring hospitalized individuals (277,286–295). When used in the setting of a clinical trial or when clinical circumstances (such as during a shortage of personal protective equipment) require it, CGM can be used to manage hospitalized individuals in conjunction with BGM. Point-of-care BGM remains the approved method for glucose monitoring in hospitals, especially for dosing insulin and treating hypoglycemia. Similarly, data are emerging on the inpatient use of AID systems and their challenges (277,296, 297). For more information, see Section 16, "Diabetes Care in the Hospital."

The Future

The pace of development in diabetes technology is extremely rapid. New approaches and tools are available each year. It is difficult for research to keep up with these advances, because newer versions of the devices and digital solutions are already on the market by the time a study is completed. The most important component in all these systems is the person with diabetes. Technology selection must be appropriate for the individual. Simply having a device or application does not change outcomes unless the human being engages with it to create positive health benefits. This underscores the need for the health care team to assist people with diabetes in device and program selection and to support their use through ongoing education and training. Expectations must be tempered by reality—we do not yet have technology that completely eliminates the self-care tasks necessary for managing diabetes, but the tools described in this section can make it easier to manage.

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8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes–2025

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Obesity is a chronic, often relapsing disease with numerous metabolic, physical, and psychosocial complications, including a substantially increased risk for the development and progression of type 2 diabetes (1). There is strong and consistent evidence that obesity management can delay the progression from prediabetes to type 2 diabetes (2–6) and is highly beneficial in treating type 2 diabetes (7–15). In people with type 2 diabetes and overweight or obesity, modest weight loss improves glycemia and reduces the need for glucose-lowering medications (7,16,17), and greater weight loss substantially reduces A1C and fasting glucose and may promote sustained diabetes remission (9,18–22). Metabolic surgery, which results in an average >20% body weight loss, greatly improving glycemia and often leading to remission of diabetes, improved quality of life, improved cardiovascular outcomes, and reduced mortality (23,24). Several therapeutic modalities, including intensive behavioral and lifestyle counseling, weight management pharmacotherapy, and metabolic surgery, may aid in achieving and maintaining meaningful weight loss and reducing obesity-associated health risks. This section aims to provide evidence-based recommendations for obesity management, including behavioral, pharmacologic, and surgical interventions, in people with, or at high risk of, type 2 diabetes. Additional considerations regarding weight management in older individuals and children can be found in Section 13, "Older Adults," and Section 14, "Children and Adolescents."

ASSESSMENT AND MONITORING OF THE INDIVIDUAL WITH OVERWEIGHT OR OBESITY

Recommendations

8.1 Use person-centered, nonjudgmental language that fosters collaboration between individuals and health care professionals, including person-first language (e.g.,

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"person with obesity" rather than "obese person" and "person with diabetes" rather than "diabetic person"). **E**

8.2a To support the diagnosis of obesity, measure height and weight to calculate BMI and perform additional measurements of body fat distribution, like waist circumference, waist-to-hip ratio, and/or waist-to-height ratio if BMI is indeterminant. **E**

8.2b Monitor obesity-related anthropometric measurements at least annually to inform treatment considerations. During active weight management treatment, increase monitoring to at least every 3 months. **E**

8.3 Accommodations should be made to provide privacy during anthropometric measurements. **E**

8.4 In people with type 2 diabetes and overweight or obesity, weight management should represent a primary goal of treatment along with glycemic management. **A**

8.5 Provide weight management treatment, aiming for any magnitude of weight loss. Weight loss of 3–7% of baseline weight improves glycemia and other intermediate cardiovascular risk factors. **A** Sustained loss of >10% of body weight usually confers greater benefits, including disease-modifying effects and possible remission of type 2 diabetes, and may improve long-term cardiovascular outcomes and mortality. **B**

8.6 Individualize initial treatment approaches for obesity (i.e., lifestyle and nutritional therapy, pharmacologic agents, or metabolic surgery) **A** based on the person's medical history, life circumstances, preferences, and motivation. **C** Consider combining treatment approaches if appropriate. **E**

Obesity is defined by the World Health Organization as an abnormal or excessive fat accumulation that presents a risk to health (25). BMI (calculated as weight in kilograms divided by the square of height in meters [kg/m^2]) has been used widely to diagnose and stage obesity (overweight: BMI 25–29.9 kg/m^2; obesity class I: BMI 30–34.9 kg/m^2; obesity class II: BMI 35–39.9 kg/m^2; obesity class III: BMI ≥40 kg/m^2); however, BMI should not be relied on as a sole diagnostic and staging tool (19). Despite its ease of measurement, BMI is at most an imperfect measure of adipose tissue mass and does not measure adipose tissue distribution or function, and it does not factor in the presence of weight-related health or well-being consequences (26,27). BMI is especially prone to misclassification in individuals who are very muscular or frail and in populations with different body composition and cardiometabolic risk (28). A diagnosis of obesity should be made based on an overall assessment of the individual's adipose tissue mass (BMI can be used as a general guide), distribution (using other anthropometric measurements, like waist circumference, waist-to-hip circumference ratio, or waist-to-height ratio), or function and, importantly, the presence of associated health or well-being consequences: metabolic, physical, or psychological (29).

Obesity is a key pathophysiologic driver of diabetes, other cardiovascular risk factors (e.g., hypertension, hyperlipidemia, metabolic dysfunction–associated steatotic liver disease [MASLD], and inflammatory state), and ultimately cardiovascular and kidney disease (30). Diabetes can further exacerbate obesity, including through the use of glucose-lowering therapies that lead to weight gain (e.g., insulin, sulfonylurea, and pioglitazone), and obesity can exacerbate hyperglycemia and diabetes, thereby setting up a vicious cycle that contributes to disease progression and occurrence of microvascular and macrovascular complications. As such, treatment goals for both glycemia and weight are recommended in people with diabetes to address both hyperglycemia and its underlying pathophysiologic driver (obesity) and therefore benefit the person holistically.

Weight stigma, fat bias, and anti-fat bias are ways to describe the bias toward people living in larger bodies. Fat bias is prevalent among health care professionals and the general public. Health care professionals are strongly encouraged to increase their awareness of implicit and explicit weight-biased attitudes (31). Increasing empathy and understanding about the complexity of weight management among health care professionals is a useful avenue to help reduce weight bias (32).

A person-centered communication style that uses inclusive and nonjudgmental language and active listening to elicit individual preferences and beliefs and assesses potential barriers to care should be used to optimize health outcomes and health-related quality of life. Use person-first language (e.g., "person with obesity" rather than "obese person") to avoid defining people by their condition (26,33,34). Measurement of weight and height (to calculate BMI) and other anthropometric measurements should be performed at least annually to aid the diagnosis of obesity. More frequent assessments (at least every 3 months) should be undertaken to monitor response to treatment during active weight management (35). Clinical considerations, such as the presence of comorbid heart failure or unexplained weight change, may warrant more frequent evaluation (36,37). If such measurements are questioned or declined by the individual, the health care professional should be mindful of possible prior stigmatizing experiences and query for concerns, and the value of monitoring should be explained as a part of the medical evaluation process that helps to inform treatment decisions (38,39). Accommodations should be made to ensure privacy during weighing and other anthropometric measurements, particularly for those individuals who report or exhibit a high level of disease-related distress or dissatisfaction. Anthropometric measurements should be performed and reported nonjudgmentally; such information should be regarded as sensitive health information.

Health care professionals should advise individuals with overweight or obesity and those with increasing weight trajectories that, in general, greater fat accumulation increases the risk of diabetes, cardiovascular disease, and all-cause mortality and has multiple adverse health and quality of life consequences. Health care professionals should also assess readiness to engage in behavioral changes for weight loss and jointly determine behavioral and weight loss goals and individualized intervention strategies using shared decision-making (40). Strategies may include nutrition and eating pattern changes, physical activity and exercise, behavioral counseling, pharmacotherapy, medical devices, and metabolic surgery. The initial and subsequent therapeutic choices should be individualized based on the person's medical history, life circumstances, preferences, and motivation (41). Combination treatment approaches may be appropriate in higher-risk individuals.

Among people with type 2 diabetes and overweight or obesity who have inadequate glycemic, blood pressure, and lipid management and/or other obesity-related metabolic complications, modest and

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sustained weight loss (3–7% of body weight) improves glycemia, blood pressure, and lipids and may reduce the need for disease-specific medications (7,16,17,42). In people at risk, 3–7% weight loss reduces progression to diabetes (2,16,17,43,44). Greater weight loss produces additional benefits (20,21). Mounting data have shown that >10% body weight loss usually confers greater benefits on glycemia and diabetes remission and improves other metabolic comorbidities, including cardiovascular outcomes, metabolic dysfunction–associated steatohepatitis (MASH), MASLD, adipose tissue inflammation, and sleep apnea, as well as physical comorbidities and quality of life (6,20,21,30,43,45–54).

With the increasing availability of more effective treatments, individuals with diabetes and overweight or obesity should be informed of the potential benefits of both modest and more substantial weight loss and guided in the range of available treatment options, as discussed in the sections below. Shared decision-making should be used when counseling on behavioral changes, intervention choices, and weight management goals.

NUTRITION, PHYSICAL ACTIVITY, AND BEHAVIORAL THERAPY

Recommendations

8.7 Nutrition, physical activity, and behavioral therapy are recommended for people with type 2 diabetes and overweight or obesity to achieve both weight and health outcome goals. **B**

8.8a Interventions including high frequency of counseling (≥16 sessions in 6 months) with focus on nutrition changes, physical activity, and behavioral strategies to achieve a 500–750 kcal/day energy deficit should be recommended for weight loss and should be considered when available. **A**

8.8b If access to such interventions is limited, consider alternative structured programs delivering behavioral counseling (face-to-face or remote). **E**

8.9 Nutrition recommendations should be individualized to the person's preferences and nutritional needs. Use nutritional plans that create an energy deficit, regardless of macronutrient composition, to achieve weight loss. **A**

8.10 When developing a plan of care, consider systemic, structural, cultural, and socioeconomic factors that may impact nutrition patterns and food choices, such as food insecurity and hunger, access to healthful food options, and other social determinants of health. **C**

8.11 For those who achieve weight loss goals, continue to monitor progress, provide ongoing support, and recommend continuing interventions to maintain weight goals long term. **E** Effective long-term (≥1 year) weight maintenance programs provide monthly contact and support, include frequent self-monitoring of body weight (weekly or more frequently) and other self-monitoring strategies (e.g., food diaries or wearables), and encourage regular physical activity (200–300 min/week). **A**

8.12 Short-term nutrition intervention using structured, very-low-calorie meals (800–1,000 kcal/day) should be prescribed only to carefully selected individuals by trained practitioners in medical settings with close monitoring. Long-term, comprehensive weight maintenance strategies and counseling should be integrated to maintain weight loss. **B**

8.13 Nutritional supplements have not been shown to be effective for weight loss and are not recommended. **A**

For a more detailed discussion of lifestyle management approaches and recommendations, see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes." For a detailed discussion of nutrition-specific interventions, please refer to "Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report" (55).

Behavioral Interventions

Numerous behavioral interventions have demonstrated positive effects from reducing energy intake, increasing physical activity, or some combination of these key lifestyle behaviors (56). The Look AHEAD (Action for Health in Diabetes) trial confirmed the feasibility of achieving and maintaining long-term weight loss in people with type 2 diabetes. Approximately half of intensive lifestyle intervention participants lost and maintained ≥5% of their initial body weight (44). Tailoring behavioral interventions to cultural context could be an additional useful tool for improving the impact of interventions (57–59).

To achieve significant weight loss with lifestyle change programs, creating a 500–750 kcal/day energy deficit is recommended. For most women, this is equal to approximately 1,200–1,500 kcal/day, and for most men, this is equal to approximately 1,500–1,800 kcal/day, with adjustment for the individual's baseline body weight. Clinical benefits of weight loss typically begin upon achieving 3% weight loss (19,60), but these benefits are progressive; more intensive weight loss goals (>7%, >10%, >15%, etc.) can achieve further health improvements if these goals can be feasibly and safely attained. Almost one-third of the Look AHEAD intensive lifestyle group participants lost and maintained ≥10% of their initial body weight at 8 years (44) and required fewer glucose-, blood pressure–, and lipid-lowering medications than those randomly assigned to standard care.

Nutrition interventions can create the necessary energy deficit to promote weight loss in many ways, and no single way is best (19,61–63). Altering macronutrient content and using meal replacement plans prescribed by trained professionals are two commonly used approaches (64). Reducing processed and ultraprocessed food intake is also an encouraging area of ongoing weight loss research. The Preventing Overweight Using Novel Dietary Strategies (POUNDS) Lost trial reported small but significant improvements when ultraprocessed foods were replaced isocalorically by less processed foods, with improved trunk fat loss (β = 3.9, 95% CI −7.01 to −0.70, P = 0.02) (65). The specific nutrition and lifestyle choices should be based on the individual's health status, clinical considerations, social determinants of health, overall preferences, and other cultural and personal circumstances that affect eating and activity patterns (66) (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more discussion on processed and ultraprocessed foods).

Based on evidence from the Diabetes Prevention Program (DPP) and Look AHEAD, proven intensive behavioral interventions generally include ≥16 sessions during an initial 6 months and focus on nutritional changes, physical activity, and behavioral strategies to achieve an ~500–750 kcal/day energy deficit. Such interventions should be provided by trained individuals and can be conducted

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face-to-face or remotely and on an individual or group basis (60,67,68). Assessing a person's motivation level, life circumstances, cultural considerations, socioeconomic factors, and ability to implement behavioral changes to achieve weight loss should be considered along with medical status when such interventions are recommended and initiated (40,69).

People with type 2 diabetes and overweight or obesity who have lost weight should be offered long-term (≥1 year) comprehensive weight loss maintenance programs. Weight loss maintenance programs should be delivered by an interprofessional team with appropriate training and experience in implementing long-term weight maintenance programs. While we acknowledge that most insurers, Medicare, and Medicaid are not currently covering many long-term weight maintenance programs, there is evidence to support their effectiveness and benefits (44,60,70) on both personal and population levels. Weight maintenance programs should include at least monthly contact with trained individuals and focus on ongoing monitoring of body weight (weekly or more frequently) and/or other self-monitoring strategies such as tracking food and beverage intake and steps; continued focus on nutrition and behavioral changes; and participation in high levels of physical activity (200–300 min/week) (71,72). Some commercial and proprietary weight loss programs have shown promising weight loss results; however, results vary across programs, most lack evidence of effectiveness, many do not satisfy guideline recommendations, and some promote unscientific and possibly dangerous practices (73,74).

Structured, very-low-calorie eating patterns, typically 800–1,000 kcal/day, using high-protein foods and meal replacement products, may increase the pace and/or magnitude of initial weight loss and glycemic improvements compared with standard behavioral interventions (20,21). However, such intensive nutritional interventions should be provided only by trained and experienced professionals in medical settings with close ongoing monitoring and integration with behavioral support and counseling, and only for a short term (generally up to 3 months). Furthermore, due to the high risk of complications (electrolyte abnormalities, severe fatigue, cardiac arrhythmias, etc.), such intensive interventions should be prescribed only to carefully selected individuals, such as those requiring weight loss and/or glycemic management before surgery, if benefits exceed potential risks (75–77). As weight regain is common, such interventions should include long-term, comprehensive weight maintenance strategies and counseling to maintain weight loss and behavioral changes (78,79).

Despite widespread marketing and exorbitant claims, there is no clear evidence that nutrition supplements (e.g., herbs, vitamins and minerals, amino acids, enzymes, and antioxidants) are effective for obesity management or weight loss (80–82). Several large systematic reviews show that most trials evaluating nutrition supplements for weight loss are of low quality and at high risk for bias. High-quality published studies show little or no weight loss benefits. In contrast, vitamin and mineral supplementation (e.g., iron, vitamin B12, and vitamin D) may be indicated in cases of documented deficiency (83), and protein supplements may be indicated as adjuncts to medically supervised weight loss therapies (84). See METABOLIC SURGERY, below, for more details on nutrition guidance for people who have undergone metabolic surgery.

Health disparities adversely affect people who have systematically experienced greater obstacles to health based on their race or ethnicity, socioeconomic status, gender identity, disability, or other factors. Overwhelming research shows that these disparities can significantly affect health outcomes, including increasing the risk for obesity, diabetes, and diabetes-related complications. Health care professionals should evaluate systemic, structural, and socioeconomic factors that may impact food choices, access to healthful foods, and nutrition patterns; behavioral patterns, such as neighborhood safety and availability of safe outdoor spaces for physical activity; environmental exposures; access to health care; social contexts; and, ultimately, diabetes risk and outcomes. For a detailed discussion of social determinants of health, refer to "Social Determinants of Health: A Scientific Review" (85).

PHARMACOTHERAPY

Recommendations

8.14 Whenever possible, minimize medications for comorbid conditions that are associated with weight gain. **E**

8.15 When choosing glucose-lowering medications for people with type 2 diabetes and overweight or obesity, prioritize medications with beneficial effect on weight. **B**

8.16 Weight management pharmacotherapy should be considered for people with diabetes and overweight or obesity along with lifestyle changes. Potential benefits and risks must be considered. **A**

8.17 In people with diabetes and overweight or obesity, the preferred pharmacotherapy should be a glucagon-like peptide 1 receptor agonist or dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist with greater weight loss efficacy (i.e., semaglutide or tirzepatide), especially considering their added weight-independent benefits (e.g., glycemic and cardiometabolic). **A**

8.18 Screen people with diabetes and obesity who have lost significant weight for malnutrition, especially those who have undergone metabolic surgery **A** and those treated with weight management pharmacologic therapy. **B**

8.19 Weight management pharmacotherapy indicated for chronic therapy should be continued beyond reaching weight loss goals to maintain the health benefits. Sudden discontinuation of weight management pharmacotherapy often results in weight gain and worsening of cardiometabolic risk factors. **A**

8.20 For those not reaching treatment goals, reevaluate weight management therapies and intensify treatment with additional approaches (e.g., metabolic surgery, additional pharmacologic agents, and structured lifestyle management programs). **A**

Glucose-Lowering Therapy

Numerous effective glucose-lowering medications are currently available. However, to achieve both glycemic and weight management goals for diabetes treatment, health care professionals should prioritize the use of glucose-lowering medications with a beneficial effect on weight. Agents associated with clinically meaningful weight loss include glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) and a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA (tirzepatide). Sodium–glucose

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cotransporter 2 inhibitors, metformin, acarbose, and amylin mimetics are also associated with weight loss, although the magnitude of weight loss is much smaller (<5% body weight loss). Dipeptidyl peptidase 4 inhibitors, centrally acting dopamine agonist (bromocriptine), α-glucosidase inhibitors, and bile acid sequestrants (colesevelam) are considered weight neutral. In contrast, insulin secretagogues (sulfonylureas and meglitinides), thiazolidinediones, and insulin are often associated with weight gain (see Section 9, "Pharmacologic Approaches to Glycemic Treatment").

Concomitant Medications

Health care professionals should carefully review the individual's concomitant medications and, whenever possible, minimize or provide alternatives for medications that promote weight gain (86). Examples of medications associated with weight gain include antipsychotics (e.g., clozapine, olanzapine, and risperidone), some antidepressants (e.g., tricyclic antidepressants, some selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors), glucocorticoids, injectable progestins, some anticonvulsants (e.g., gabapentin and pregabalin), β-blockers (e.g., atenolol, metoprolol, and propranolol), and possibly sedating antihistamines and anticholinergics (87).

Approved Weight Management Pharmacotherapy

The U.S. Food and Drug Administration (FDA) has approved several medications for weight management as adjuncts to a reduced-calorie eating pattern and increased physical activity in individuals with BMI ≥30 kg/m^2 or ≥27 kg/m^2 with one or more obesity-associated comorbid conditions (e.g., type 2 diabetes, hypertension, and/or dyslipidemia). Nearly all FDA-approved weight management medications have been shown to improve glycemia in people with type 2 diabetes and delay progression to type 2 diabetes in at-risk individuals (22), and some of these agents (e.g., liraglutide, semaglutide, and tirzepatide) have an indication for glucose lowering as well as weight management. Phentermine and other older adrenergic agents are approved for short-term treatment (88), while all others are approved for long-term treatment (22) (**Tables 8.1 and 8.2**). (Refer to Section 14, "Children and Adolescents," for medications approved for adolescents with obesity.) In addition, setmelanotide, a melanocortin 4 receptor agonist, is approved for use in cases of rare genetic mutations resulting in severe hyperphagia and extreme obesity, such as leptin receptor deficiency and proopiomelanocortin deficiency.

In people with type 2 diabetes and overweight or obesity, agents with both glucose-lowering and weight loss effects are preferred (refer to Section 9, "Pharmacologic Approaches to Diabetes Treatment") and include agents from the GLP-1 RA class and the dual GIP and GLP-1 RA class (collectively referred to as nutrient-stimulated hormone-based therapeutics, a class that also includes other investigational agents that act on various nutrient-stimulated hormonal pathways, like glucagon and amylin). Should use of these medications not result in achievement of weight management goals, or if they are not tolerated or are contraindicated, other obesity treatment approaches should be considered. In the Effect and Safety of Semaglutide 2.4 mg Once-Weekly in Subjects With Overweight or Obesity and Type 2 Diabetes (STEP 2) trial, semaglutide 2.4 mg resulted in a body weight loss of 6.2% more than placebo and A1C lowering of 1.2% more than placebo after 68 weeks (50). In the Efficacy and Safety of Tirzepatide Once Weekly in Participants With Type 2 Diabetes Who Have Obesity or Are Overweight: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-2), tirzepatide resulted in body weight loss of 9.6% and 11.6% more than placebo and A1C lowering of 1.55% and 1.57% more than placebo after 72 weeks of treatment with the 10 mg and 15 mg doses, respectively, with adverse effects similar to those seen with the GLP-1 RA class (89). The observed weight loss with weight management pharmacotherapy is lower in people with diabetes than in those of similar baseline weight without diabetes; therefore, it is important to appropriately manage expectations of individuals with diabetes and health care professionals.

Weight management pharmacotherapy has demonstrated multiple additional benefits beyond weight loss and improvement in glucose management. Some such examples include improvements or potential improvements in cardiovascular risk factors (e.g., blood pressure and lipids), inflammation, obstructive sleep apnea, MASLD and MASH, and symptoms related to heart failure with preserved ejection fraction (90–93). Liraglutide 1.8 mg and semaglutide 1 mg (doses approved for type 2 diabetes, which are lower than those approved for the treatment of obesity) demonstrated reduction in cardiovascular events in people with type 2 diabetes who are either at high risk for cardiovascular disease or have cardiovascular disease (51,94). Additionally, semaglutide 2.4 mg (dose approved for the treatment of obesity) also demonstrated reduction in cardiovascular events in people with overweight or obesity and preexistent cardiovascular disease but without diabetes (95).

Health care professionals should be knowledgeable about the dosing, benefits, and risks for each treatment option to balance the potential benefits of successful weight loss against the potential risks for each individual. The high risk and prevalence of cardiovascular disease in people with diabetes must be balanced against the lack of long-term cardiovascular outcomes trial data for agents like combination naltrexone and bupropion and combination phentermine and topiramate. The response to all weight management medications is highly heterogeneous; therefore, their weight loss effectiveness should be reevaluated after initiation and therapy adjustments should be considered, if needed. All these medications are contraindicated in individuals who are pregnant or actively trying to conceive and are not recommended for use in individuals who are nursing. Individuals of childbearing potential should receive counseling regarding the use of reliable methods of contraception while using weight loss medications. Tirzepatide in particular may reduce the efficacy of oral hormonal contraceptives due to delayed gastric emptying, an effect that is largest after the first dose and diminishes over time. Individuals using oral hormonal contraceptives should switch to a nonoral contraceptive method or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation. Of note, while weight loss medications are often used in people with type 1 diabetes, clinical trial data in this population are limited.

Incretin pharmacotherapies and metabolic surgery options for weight loss may increase the risk for malnutrition and sarcopenia (96). Health care professionals should encourage resistance training (97) and sufficient protein intake. Individuals with diabetes who are experiencing significant (>20%) or rapid (>4 kg/month) weight loss should be screened for

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Table 8.1—Weight management pharmacotherapy

Medication name	Treatment arm; weight loss from baseline	Time frame for weight loss (weeks)*	Common side effects	Possible safety concerns and considerations
Sympathomimetic amine anorectic: approved for short-term use only				
Phentermine (160,161)†	• 15 mg q.d.; 7.4% • 7.5 mg q.d.; 6.6% • Placebo; 2.3%	28	Dry mouth, insomnia, dizziness, irritability, increased blood pressure, elevated heart rate	• Contraindicated for use in combination with monoamine oxidase inhibitors • Caution with cardiovascular disease • Do not use if at high risk for glaucoma due to risk of acute angle-closure glaucoma
Lipase inhibitor				
Orlistat (4,162)‡	• 120 mg t.i.d.; 9.6% • Placebo; 5.6%	52	Abdominal pain, flatulence, fecal urgency	• Potential malabsorption of fat-soluble vitamins (A, D, E, K) and of certain medications (e.g., cyclosporine, thyroid hormone, anticonvulsants) • Rare cases of severe liver injury reported • Cholelithiasis • Nephrolithiasis
Sympathomimetic amine anorectic/ antiepileptic combination				
Phentermine/topiramate ER (49,163)§	• 15 mg/92 mg q.d.; 9.8% • 7.5 mg/46 mg q.d.; 7.8% • Placebo; 1.2%	56	Constipation, paresthesia, insomnia, nasopharyngitis, xerostomia, increased blood pressure, nephrolithiasis	• Contraindicated for use in combination with monoamine oxidase inhibitors • Birth defects • Cognitive impairment • Caution with cardiovascular disease • Do not use if at high risk for glaucoma due to risk of acute angle-closure glaucoma
Opioid antagonist/antidepressant combination				
Naltrexone/bupropion ER (13,164)	• 16 mg/180 mg b.i.d.; 5% • Placebo; 1.8%	56	Constipation, nausea, headache, xerostomia, insomnia, elevated heart rate and blood pressure	• Contraindicated in people with unmanaged hypertension and/or seizure disorders • Contraindicated for use with chronic opioid therapy • Acute angle-closure glaucoma **Black box warning:** • Risk of suicidal behavior/ideation in people younger than 24 years old who have depression
Glucagon-like peptide 1 receptor agonist				
Liraglutide (14,51,165)‖	• 3.0 mg q.d.; 6% • 1.8 mg q.d.; 4.7% • Placebo; 2%	56	Gastrointestinal side effects (nausea, vomiting, diarrhea, esophageal reflux)	• Hypoglycemia (with concomitant use of insulin or sulfonylurea) • Pancreatitis has been reported in clinical trials, but causality has not been established; discontinue if pancreatitis is suspected. • Use caution in people with kidney disease when initiating or increasing dose due to increased risk of gastrointestinal side effects and potential risk of acute kidney injury from dehydration

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Table 8.1—Continued

Medication name	Treatment arm; weight loss from baseline	Time frame for weight loss (weeks)*	Common side effects	Possible safety concerns and considerations
Semaglutide (50,94)‖	• 2.4 mg weekly; 9.6% • 1.0 mg weekly; 7% • Placebo; 3.4%			• May cause cholelithiasis and gallstone-related complications • Gastrointestinal disorders (severe constipation and small-bowel obstruction/ileus progression) • Monitor for potential consequences of delayed absorption of oral medications • May cause injection site reactions • May cause elevated heart rate **Black box warning:** • Risk of thyroid C-cell tumors in rodents; human relevance not determined; do not use in individuals with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2
Dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist				
Tirzepatide (89,166)	• 15 mg weekly; 14.7% • 10 mg weekly; 12.8% • Placebo; 3.2%	72	Gastrointestinal side effects (nausea, vomiting, diarrhea, esophageal reflux)	• Same as for GLP-1 receptor agonists • Monitor effects of oral medications with narrow therapeutic index (warfarin) or whose efficacy is dependent on threshold concentration • Advise females using oral contraceptives to switch to a nonoral contraceptive method or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation **Black box warning:** • Risk of thyroid C-cell tumors in rodents; human relevance not determined; do not use in individuals with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2

Select safety and side effect information is provided; for a comprehensive discussion of safety considerations, please refer to the prescribing information for each agent. b.i.d., twice daily; ER, extended release; q.d., every day; Rx, prescription; t.i.d., three times daily, p.o., by mouth. *Time frames used in clinical trials. Medications approved for long-term use should be continued as indicated beyond reaching weight loss goals. †Phentermine was evaluated in a general adult population with obesity. As monotherapy, phentermine is only approved for short-term use. Use lowest effective dose; maximum appropriate dose is 37.5 mg. ‡Enrolled participants had normal (79%) or impaired (21%) glucose tolerance. §Maximum dose, depending on response, is 15 mg/92 mg q.d. Approximately 68% of enrolled participants had type 2 diabetes or impaired glucose tolerance. ‖Agent has indication for reduction of cardiovascular events (51,94).

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Table 8.2—Median monthly (30-day) AWP and NADAC of maximum or maintenance dose of weight management pharmacotherapies

Medication name	Typical adult maintenance dose	AWP (median and range for 30-day supply)	NADAC (median and range for 30-day supply)
Sympathomimetic amine anorectic: approved for short-term use only			
Phentermine	8–37.5 mg q.d.	$43 ($9–$98)*	$3 ($3, $79)*
Lipase inhibitor			
Orlistat	60 mg t.i.d. (OTC) 120 mg t.i.d. (Rx)	$58 ($41–$82) $843 ($781–$904)	NA $677 ($629–$724)
Sympathomimetic amine anorectic/antiepileptic combination			
Phentermine/topiramate ER	7.5 mg/46 mg q.d.	$237	NA
Opioid antagonist/antidepressant combination			
Naltrexone/bupropion ER	16 mg/180 mg b.i.d.	$750	NA
Glucagon-like peptide 1 receptor agonist			
Liraglutide†	3 mg q.d.	$1,619	$1,296
Semaglutide	2.4 mg once weekly	$1,619	$1,296
Dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist			
Tirzepatide	5, 10, or 15 mg once weekly	$1,272	$1,017

The costs listed in this table are representative of costs at a national level. These costs may not be representative of an individual's cost and do not account for medication coverage or available discounts. AWP, average wholesale price; b.i.d., twice daily; ER, extended release; NA, data not available; NADAC, National Average Drug Acquisition Cost; OTC, over the counter; q.d., every day; Rx, prescription; t.i.d., three times daily. AWP and NADAC prices are for a 30-day supply of maximum or maintenance dose as of 1 July 2024 (167,168). *Data are for 37.5 mg q.d. dose. †New generic liraglutide pricing was not available on 1 July 2024.

malnutrition. While no single method is best to screen for both malnutrition and sarcopenia, instruments are available to screen for each condition, including the Simplified Nutritional Appetite Questionnaire (SNAQ) and the Malnutrition Universal Screening Tool (MUST) (98–100). For a more detailed discussion of malnutrition in the context of diabetes and weight loss, see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes."

Thus, choice of therapy should be guided by person-centered treatment factors, including comorbidities, considerations of adverse effects and treatment burden, treatment cost and accessibility, and the individual's therapeutic goals and preferences. Medication cost and insurance coverage considerations often influence treatment decisions, and payors should cover evidence-based obesity treatments for people with diabetes and prediabetes to reduce barriers to treatment access. It is also essential that health care teams are knowledgeable about insurance coverage requirements and establish systems to support clinicians in prescribing evidence-based weight management medications and to reduce financial hardship of treatment for individuals, including formulary and medication coverage requirements, eligibility for medication assistance programs, and availability of copayment reduction cards (see Section 1, "Improving Care and Promoting Health in Populations").

Assessing Efficacy and Safety of Weight Management Pharmacotherapy

Upon initiating medications for obesity, assess their effectiveness and safety at least monthly for the first 3 months and at least quarterly thereafter. Modeling from published clinical trials consistently shows that early responders have improved long-term outcomes (101,102); however, it is notable that the response rate with the latest generation of weight management pharmacotherapies is much higher (50,89). Unless clinical circumstances (such as poor tolerability) or other considerations (such as financial expense or individual preference) suggest otherwise, those who achieve sufficient early weight loss upon starting a chronic weight management medication (typically defined as >5% weight loss after 3 months of use) should continue the medication long-term. When early weight loss results are modest (typically <5% weight loss after 3 months of use), the benefits of ongoing treatment need to be examined in the context of the glycemic response, the availability of other potential treatment options, treatment tolerance, and overall treatment burden. Ongoing monitoring of the achievement and maintenance of weight management goals is recommended. Sudden discontinuation of semaglutide and tirzepatide results in regain of one-half to two-thirds of the weight loss within 1 year (103–105). Shared decision-making should be used to determine the best long-term weight management approach, such as continuing pharmacotherapy on the lowest effective dose, using intermittent therapy, or stopping medication followed by close weight monitoring.

For those not reaching or maintaining weight-related treatment goals, avoid treatment inertia by reevaluating ongoing weight management therapies and intensify treatment with additional approaches (e.g., metabolic surgery, additional pharmacologic agents, and structured lifestyle management programs).

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MEDICAL DEVICES FOR WEIGHT LOSS

While gastric banding devices have fallen out of favor due to their limited long-term efficacy and high rate of complications, several minimally invasive medical devices have been approved by the FDA for short-term weight loss, including implanted gastric balloons, a vagus nerve stimulator, and gastric aspiration therapy (106). High cost, limited insurance coverage, and limited data supporting the efficacy of these devices in the treatment of individuals with diabetes has created uncertainty for their current use and led to the voluntary removal of several of these medical devices from the U.S. market (107).

METABOLIC SURGERY

Recommendations

8.21 Consider metabolic surgery as a weight and glycemic management approach in people with diabetes with BMI ≥30.0 kg/m^2 (or ≥27.5 kg/m^2 in Asian American individuals) who are otherwise good surgical candidates. **A**

8.22 Metabolic surgery should be performed in high-volume centers with interprofessional teams knowledgeable about and experienced in managing obesity, diabetes, and gastrointestinal surgery (www.facs.org/quality-programs/accreditation-and-verification/metabolic-and-bariatric-surgery-accreditation-and-quality-improvement-program/). **E**

8.23 People being considered for metabolic surgery should be evaluated for comorbid psychological conditions and social and situational circumstances that have the potential to interfere with surgery outcomes. **B**

8.24 People who undergo metabolic surgery should receive long-term medical and behavioral support and routine micronutrient, nutritional, and metabolic status monitoring. **B**

8.25 If post–metabolic surgery hypoglycemia is suspected, clinical evaluation should exclude other potential disorders contributing to hypoglycemia, and management should include education, medical nutrition therapy with a registered dietitian nutritionist experienced in post–metabolic surgery hypoglycemia, and medication treatment, as needed. **A** In individuals with post–metabolic surgery hypoglycemia, use continuous glucose monitoring to improve safety. **C**

8.26 In people who undergo metabolic surgery, routinely screen for psychosocial and behavioral health changes and refer to a qualified behavioral health professional as needed. **C**

8.27 Monitor individuals who have undergone metabolic surgery for insufficient weight loss or weight recurrence at least every 6–12 months. **E** In those who have insufficient weight loss or experience weight recurrence, assess for potential predisposing factors and, if appropriate, consider additional weight loss interventions (e.g., weight management pharmacotherapy). **C**

Surgical procedures for obesity treatment—often referred to interchangeably as bariatric surgery, weight loss surgery, metabolic surgery, or metabolic/bariatric surgery—can promote significant and durable weight loss and improve glycemic management and long-term outcomes in those with type 2 diabetes. Given the magnitude and rapidity of improvement of hyperglycemia and glucose homeostasis, these procedures have been suggested as treatments for type 2 diabetes even in the absence of severe obesity, hence the current preferred terminology of "metabolic surgery" (108).

A substantial body of evidence, including data from large cohort studies and randomized controlled (nonblinded) clinical trials, demonstrates that metabolic surgery achieves superior glycemic management and reduction of cardiovascular risk in people with type 2 diabetes and obesity compared with nonsurgical intervention (47). In addition to improving glycemia, metabolic surgery reduces the incidence of microvascular disease (109), improves quality of life (47,110,111), decreases cancer risk, improves cardiovascular disease risk factors and long-term cardiovascular events (111–119), and decreases all-cause mortality (120). Cohort studies that match surgical and nonsurgical subjects strongly suggest that metabolic surgery reduces all-cause mortality (121,122). Studies have also shown that metabolic surgery can improve liver outcomes among individuals with MASH, including biopsy-proven disease (123–125).

The overwhelming majority of procedures performed in the U.S. are vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB). Both procedures result in a smaller stomach pouch and often robust changes in enteroendocrine hormones. In VSG, ∼80% of the stomach is removed, leaving behind a long, thin sleeve-shaped pouch. RYGB creates a much smaller stomach pouch (roughly the size of a walnut), which is then attached to the distal small intestine, thereby bypassing the duodenum and jejunum.

Metabolic surgery has been demonstrated to have beneficial effects on type 2 diabetes irrespective of the presurgical BMI (126). The American Society for Metabolic and Bariatric Surgery recommends metabolic surgery for people with type 2 diabetes and a BMI ≥30 kg/m^2(or ≥27.5 kg/m^2 for Asian American individuals) in surgically eligible individuals. A real-world data analysis through the National Patient-Centered Outcomes Research Network (PCORnet) in the U.S. compared surgical outcomes between 6,233 individuals with type 2 diabetes who underwent RYGB and 3,477 who underwent VSG. At 1 year after surgery, those who had RYGB lost on average 29.1% of their total body weight, while those who had VSG lost on average 22.8% of their total body weight. At 5 years after surgery, the total body weight loss was 24.1% for those who had RYGB and 16.1% for those who had VSG, with 86.1% of individuals experiencing type 2 diabetes remission after RYGB and 83.5% of individuals experiencing type 2 diabetes remission after VSG. Among the 6,141 individuals who experienced type 2 diabetes remission, the subsequent type 2 diabetes relapse rate was lower for those who had RYGB than for those who had VSG (hazard ratio 0.75 [95% CI 0.67–0.84]). Estimated relapse rates for those who had RYGB and VSG were 33.1% and 41.6%, respectively, at 5 years after surgery. At 5 years, compared with baseline, A1C was reduced, on average, 0.4 percentage points more for individuals who had RYGB than for individuals who had VSG (127). Most notably, the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, which randomized 150 participants with type 2 diabetes, A1C >7.0%, and BMI 27–43 kg/m^2 to receive either metabolic surgery or medical treatment for type 2 diabetes using glucose-lowering agents, found that 29% of those treated with RYGB and 23% of those treated with VSG achieved A1C of ≤6.0% after 5 years (47). Available data suggest an erosion of diabetes remission over time (48); 35–50% of individuals

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who initially achieve remission of diabetes eventually experience recurrence. Still, the median disease-free period among such individuals following RYGB is 8.3 years (128,129), and the majority of those who undergo surgery maintain substantial improvement of glycemia from baseline for at least 5–15 years (47,110,111,113).

Exceedingly few presurgical predictors of diabetes remission have been identified. However, younger age, shorter duration of diabetes (e.g., <8 years) (101), and lesser severity of diabetes (better glycemic management, not using insulin) are associated with higher rates of diabetes remission (47,111,130,131). Greater baseline visceral fat area may also predict diabetes remission, especially among Asian American people with type 2 diabetes (132).

A review of case series and reports suggests that metabolic surgery also improves the metabolic profiles and cardiovascular risk of people with type 1 diabetes, but larger and longer-term studies with better designs are needed to determine the role of metabolic surgery in such individuals (133).

Whereas metabolic surgery has greater initial costs than nonsurgical obesity treatments, retrospective analyses and modeling studies suggest that surgery may be cost-effective or even cost-saving for individuals with type 2 diabetes. However, these results largely depend on assumptions about the long-term effectiveness and safety of the procedures, the specific medications being compared, the time horizon for cost-effectiveness assessments, and the population examined (e.g., duration and severity of diabetes) (134,135).

The safety of metabolic surgery has improved significantly with continued refinement of minimally invasive (laparoscopic) approaches, enhanced training and credentialing, and involvement of interprofessional teams. Perioperative mortality rates are typically 0.1–0.5%, similar to those for common abdominal procedures such as cholecystectomy and hysterectomy (136,137). Major complications occur in 2–6% of those undergoing metabolic surgery, which compares favorably with the rates for other commonly performed elective operations (137). Postsurgical recovery times and morbidity have also dramatically declined. Minor complications and need for operative reintervention occur in up to 15% (136,138–143). Empirical data suggest that the proficiency of the operating surgeon and surgical team is a key determinant of mortality, complications, reoperations, and readmissions (144). Accordingly, metabolic surgery should be performed in high-volume centers with interprofessional teams experienced in managing diabetes, obesity, and gastrointestinal surgery. Refer to the American College of Surgeons website for information on accreditation and locations of accredited programs (https://www.facs.org/quality-programs/accreditation-and-verification/metabolic-and-bariatric-surgery-accreditation-and-quality-improvement-program/).

Beyond the perioperative period, longer-term risks include vitamin and mineral deficiencies, anemia, osteoporosis, dumping syndrome, and severe hypoglycemia (145). Nutritional and micronutrient deficiencies and related complications occur with variable frequency depending on the type of surgical procedure and require routine monitoring of micronutrient and nutritional status and lifelong vitamin/nutritional supplementation (145). Dumping syndrome usually occurs shortly (10–30 min) after a meal and may present with diarrhea, nausea, vomiting, palpitations, and fatigue; hypoglycemia is usually not present at the time of symptoms but, in some cases, may develop several hours later. Post–metabolic surgery hypoglycemia can occur with RYGB, VSG, and other gastrointestinal procedures and may severely impact quality of life (146–148). Post–metabolic surgery hypoglycemia is driven in part by altered gastric emptying of ingested nutrients, leading to rapid intestinal glucose absorption and excessive postprandial secretion of GLP-1 and other gastrointestinal peptides. As a result, overstimulation of insulin release and a sharp drop in plasma glucose occur, most commonly 1–3 h after a high-carbohydrate meal. Symptoms range from sweating, tremor, tachycardia, and increased hunger to impaired cognition, loss of consciousness, and seizures. In contrast to dumping syndrome, which often occurs soon after surgery and improves over time, post–metabolic surgery hypoglycemia typically presents >1 year after surgery. Diagnosis is primarily made by a thorough examination of history, detailed records of food intake, physical activity, and symptom patterns, and exclusion of other potential causes of hypoglycemia (e.g., malnutrition, side effects of medications or supplements, dumping syndrome, and insulinoma). Initial management includes education to facilitate reduced intake of rapidly digested carbohydrates while ensuring adequate intake of protein, healthy fats, and vitamin and nutrient supplements. When available, individuals should be offered medical nutrition therapy with a registered dietitian nutritionist experienced in post–metabolic surgery hypoglycemia and the use of continuous glucose monitoring (ideally real-time continuous glucose monitoring, which can detect dropping glucose levels before severe hypoglycemia occurs), especially for those with impaired hypoglycemia awareness. Medication treatment, if needed, is primarily aimed at slowing carbohydrate absorption (e.g., acarbose) or reducing GLP-1 and insulin secretion (e.g., diazoxide, octreotide) (149).

People who undergo metabolic surgery may be at increased risk for substance use, worsening or new-onset depression and/or anxiety disorders, and suicidal ideation (150–154). Candidates for metabolic surgery should be assessed by a behavioral health professional with expertise in obesity management prior to consideration for surgery (155). Surgery should be postponed in individuals with alcohol or substance use disorders, severe depression, suicidal ideation, or other significant behavioral health conditions until these conditions have been sufficiently addressed. Individuals with preoperative or new-onset psychopathology should be assessed regularly following surgery to optimize behavioral health and postsurgical outcomes.

Finally, no definitive evidence supports the pre– and post–metabolic surgery use of nutrient-stimulated hormone-based therapeutics for chronic obesity. Existing studies suggest that among individuals with a BMI >50 kg/m^2, GLP-1 RAs are associated with significant weight loss prior to surgery with no increase in complications or time to surgery (156). Nutrient-stimulated hormone-based therapeutics can be considered as adjuvants after metabolic surgery to augment initial weight loss either shortly after surgery or when weight loss has plateaued (157). Studies have also shown that GLP-1 RAs can effectively treat weight regain after metabolic surgery and therefore could be considered as an alternative to revisional surgery (158). Long-term outcomes, however, are lacking in terms of durability of weight loss, effect on weight regain when medications are stopped, and long-term side

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effects with use and after discontinuation (159).

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9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 1 DIABETES

Recommendations

9.1 Treat most adults with type 1 diabetes with continuous subcutaneous insulin infusion or multiple daily doses of prandial (injected or inhaled) and basal insulin. **A**

9.2 For most adults with type 1 diabetes, insulin analogs (or inhaled insulin) are preferred over injectable human insulins to minimize hypoglycemia risk. **A**

9.3 Early use of continuous glucose monitoring is recommended for adults with type 1 diabetes to improve glycemic outcomes and quality of life and to minimize hypoglycemia. **B**

9.4 Automated insulin delivery systems should be offered to all adults with type 1 diabetes. **A**

9.5 To improve glycemic outcomes and quality of life and to minimize hypoglycemia risk, most adults with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake and fat and protein intake. They should also be taught how to modify the insulin dose (correction dose) based on concurrent glycemia, glycemic trends (if available), sick-day management, and anticipated physical activity. **B**

9.6 Insulin treatment plan and insulin-taking behavior should be reevaluated at regular intervals (e.g., every 3–6 months) and adjusted to incorporate specific factors that impact choice of treatment and ensure achievement of individualized glycemic goals. **E**

Insulin Therapy

Insulin treatment is essential for individuals with type 1 diabetes because the hallmark of type 1 diabetes is absent or near-absent β-cell function. In addition to hyperglycemia,

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insulinopenia can contribute to other metabolic disturbances like hypertriglyceridemia and ketoacidosis as well as tissue catabolism that can be life threatening. Severe metabolic decompensation can be, and was, mostly prevented with once- or twice-daily insulin injections for the six or seven decades after the discovery of insulin. Over the past four decades, evidence has accumulated supporting more intensive insulin replacement, using multiple daily injections of insulin or continuous subcutaneous administration through an insulin pump, as providing the best combination of effectiveness and safety for people with type 1 diabetes.

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion (CSII) reduced A1C and was associated with improved long-term outcomes (1–3). The study was carried out with short-acting (regular) and intermediate-acting (NPH) human insulins. In this landmark trial, lower A1C with intensive management (7%) led to ∼50% reductions in microvascular complications over 6 years of treatment. However, intensive therapy was associated with a higher rate of severe hypoglycemia than conventional treatment (62 compared with 19 episodes per 100 person-years of therapy) (1). Follow-up of participants from the DCCT demonstrated fewer macrovascular and microvascular complications in the group that received intensive treatment. Achieving intensive glycemic goals during the active treatment period of the study had a persistent beneficial impact over the 20 years after the active treatment component of the study ended (1–3).

Insulin replacement plans typically consist of basal insulin, mealtime insulin, and correction insulin (**Fig. 9.1**) (4). Basal insulin includes NPH insulin, long-acting insulin analogs, and continuous delivery of rapid-acting insulin via an insulin pump. Basal insulin analogs have longer duration of action with flatter, more constant and consistent plasma concentrations and activity profiles than NPH insulin; rapid-acting analogs (RAA) have a quicker onset and peak and shorter duration of action than regular human insulin. In people with type 1 diabetes, treatment with analog insulins is associated with less hypoglycemia and weight gain and lower A1C compared with injectable human insulins (5–7). Two injectable ultra-rapid-acting analog (URAA) insulin formulations are available that contain excipients that accelerate absorption and provide more activity in the first portion of their profile compared with the other RAA (8,9). Inhaled human insulin has a rapid peak and shortened duration of action compared with RAA (10) (see also subsection ALTERNATIVE INSULIN ROUTES IN PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES). These newer formulations may cause less hypoglycemia while improving postprandial glucose excursions and administration flexibility (in relation to prandial intake) compared with RAA (10–12). In addition, longer-acting basal analogs (U-300 glargine or degludec) may confer a lower hypoglycemia risk compared with U-100 glargine in individuals with type 1 diabetes (13,14).

Despite the advantages of insulin analogs in individuals with type 1 diabetes, the expense and/or complexity of treatment required for their use may be prohibitive (**Table 9.1**). There are multiple approaches to insulin treatment. The central precept in the management of type 1 diabetes is that some form of insulin be given in a defined treatment plan tailored to the individual to prevent diabetic ketoacidosis (DKA) and minimize clinically relevant hypoglycemia while achieving the individual's glycemic goals. The impact of the introduction of interchangeable biosimilars and unbranded versions of some analog products as well as current and upcoming price reductions on insulin access need to be evaluated. Reassessment of insulin-taking behavior and adjustment of treatment plans to account for specific factors, including cost, that impact choice of treatment is recommended at regular intervals (every 3–6 months).

Most studies comparing multiple daily injections with CSII have been relatively small and of short duration. A systematic review and meta-analysis concluded that CSII via pump therapy has modest advantages for lowering A1C (−0.30% [95% CI −0.58 to −0.02]) and for reducing severe hypoglycemia rates in children and adults (15). Use of CSII is associated with improvement in quality of life, particularly in areas related to fear of hypoglycemia and diabetes distress, compared with multiple

Representative relative attributes of insulin delivery approaches in people with type 1 diabetes

Injected insulin plans	Greater flexibility	Lower risk of hypoglycemia	Higher costs
MDI with LAA + RAA or URAA	+++	+++	$$$
Less-preferred, alternative injected insulin plans			
MDI with NPH + RAA or URAA	++	++	$$
MDI with NPH + short-acting (regular) insulin	++	+	$
Two daily injections with NPH + short-acting (regular) insulin or premixed	+	+	$

Continuous insulin infusion plans	Greater flexibility	Lower risk of hypoglycemia	Higher costs
Automated insulin delivery systems	+++++	+++++	$$$$$
Insulin pump with threshold/ predictive low-glucose suspend	++++	++++	$$$$$
Insulin pump therapy without automation	+++	+++	$$$$

Figure 9.1—Choices of insulin plans in people with type 1 diabetes. Continuous glucose monitoring improves outcomes with injected or infused insulin and is superior to blood glucose monitoring. Inhaled insulin may be used in place of injectable prandial insulin in the U.S. The number of plus or dollar signs is an estimate of relative association of the plan with greater flexibility, lower risk of hypoglycemia, and higher costs between the different plans. LAA, long-acting insulin analog; MDI, multiple daily injections; RAA, rapid-acting insulin analog; URAA, ultra-rapid-acting insulin analog. Adapted from Holt et al. (4).

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Table 9.1—Examples of subcutaneous insulin treatment plans

Plans	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Plans that more closely mimic normal insulin secretion				
Insulin pump therapy (also including AID systems: hybrid closed-loop, low-glucose suspend, CGM-augmented open-loop, BGM-augmented open-loop)	Basal delivery of URAA or RAA; generally 30–50% of TDD. Mealtime and correction: URAA or RAA by bolus based on ICR and/or ISF and target glucose, with premeal insulin ~15 min before eating.	Can adjust basal rates for varying insulin sensitivity by time of day, for exercise, and for sick days. Flexibility in meal timing and content. Pump can deliver insulin in increments of fractions of units. Potential for integration with CGM for AID systems. TIR % highest and TBR % lowest with: hybrid closed-loop > low-glucose suspend > CGM-augmented open-loop > BGM-augmented open-loop.	Most expensive plan. Must continuously wear one or more devices. Risk of rapid development of ketosis or DKA with interruption of insulin delivery. Potential reactions to adhesives and site infections. Most technically complex approach (harder for people with lower numeracy or literacy skills).	Mealtime insulin: if carbohydrate counting is accurate, change ICR if glucose after meal consistently out of target. Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range. Basal rates: adjust based on overnight, fasting or daytime glucose outside of activity of URAA/RAA bolus. AID systems: carbohydrate ratio, insulin on board, targets, and/or ISF may be adjusted, depending on the system. Make sure to review and adjust manual mode settings, if available.
MDI: LAA + flexible doses of URAA or RAA at meals	LAA once daily (insulin detemir or insulin glargine may require twice-daily dosing); generally 30–50% of TDD. Mealtime and correction: URAA or RAA based on ICR and/or ISF and target glucose.	Can use pens for all components. Flexibility in meal timing and content. Insulin analogs cause less hypoglycemia than human insulins.	At least four daily injections. Most costly insulins. Smallest increment of insulin is 1 unit (0.5 unit with some pens). LAAs may not cover strong dawn phenomenon (rise in glucose in early morning hours) as well as pump therapy.	Mealtime insulin: if carbohydrate counting is accurate, change ICR if glucose after meal consistently out of target. Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range. LAA: based on overnight or fasting glucose or daytime glucose outside of activity time course, or URAA or RAA injections.
MDI plans with less flexibility				
Four injections daily with fixed doses of N and RAA	Pre-breakfast: RAA ~20% of TDD. Pre-lunch: RAA ~10% of TDD. Pre-dinner: RAA ~10% of TDD. Bedtime: N ~50% of TDD.	May be feasible if unable to carbohydrate count. All meals have RAA coverage. N is less expensive than LAAs.	Shorter duration RAA may lead to basal deficit during day; may need twice-daily N. Greater risk of nocturnal hypoglycemia with N. Requires relatively consistent mealtimes and carbohydrate intake.	Pre-breakfast RAA: based on BGM after breakfast or before lunch. Pre-lunch RAA: based on BGM after lunch or before dinner. Pre-dinner RAA: based on BGM after dinner or at bedtime. Evening N: based on fasting or overnight BGM.

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Table 9.1—Continued

Plans	Timing and distribution	Advantages	Disadvantages	Adjusting doses
Four injections daily with fixed doses of N and R	Pre-breakfast: R ∼20% of TDD. Pre-lunch: R ∼10% of TDD. Pre-dinner: R ∼10% of TDD. Bedtime: N ∼50% of TDD.	May be feasible if unable to carbohydrate count. R can be dosed based on ICR and correction. All meals have R coverage. Least expensive insulins.	Greater risk of nocturnal hypoglycemia with N. Greater risk of delayed post-meal hypoglycemia with R. Requires relatively consistent mealtimes and carbohydrate intake. R must be injected at least 30 min before meal for better effect.	Pre-breakfast R: based on BGM after breakfast or before lunch. Pre-lunch R: based on BGM after lunch or before dinner. Pre-dinner R: based on BGM after dinner or at bedtime. Evening N: based on fasting or overnight BGM.
Plans with fewer daily injections				
Three injections daily: N + R or N + RAA	Pre-breakfast: N ∼40% TDD + R or RAA ∼15% TDD. Pre-dinner: R or RAA ∼15% TDD. Bedtime: N ∼30% TDD.	Morning insulins can be mixed in one syringe. May be appropriate for those who cannot take injection in middle of day. Morning N covers lunch to some extent. Same advantages of RAAs over R. Least (N + R) or less expensive insulins than MDI with analogs.	Greater risk of nocturnal hypoglycemia with N than LAAs. Greater risk of delayed post-meal hypoglycemia with R than RAAs. Requires relatively consistent mealtimes and carbohydrate intake. Coverage of post-lunch glucose often suboptimal. R must be injected at least 30 min before meal for better effect.	Morning N: based on pre-dinner BGM. Morning R: based on pre-lunch BGM. Morning RAA: based on post-breakfast or pre-lunch BGM. Pre-dinner R: based on bedtime BGM. Pre-dinner RAA: based on post-dinner or bedtime BGM. Evening N: based on fasting BGM.
Twice-daily "split-mixed": N + R or N + RAA	Pre-breakfast: N ∼40% TDD + R or RAA ∼15% TDD. Pre-dinner: N ∼30% TDD + R or RAA ∼15% TDD.	Least number of injections for people with strong preference for this. Insulins can be mixed in one syringe. Least (N + R) or less (N + RAA) expensive insulins vs. analogs. Eliminates need for doses during the day.	Risk of hypoglycemia in afternoon or middle of night from N. Fixed mealtimes and meal content. Coverage of post-lunch glucose often suboptimal. Difficult to reach targets for blood glucose without hypoglycemia.	Morning N: based on pre-dinner BGM. Morning R: based on pre-lunch BGM. Morning RAA: based on post-breakfast or pre-lunch BGM. Evening R: based on bedtime BGM. Evening RAA: based on post-dinner or bedtime BGM. Evening N: based on fasting BGM.

AID, automated insulin delivery; BGM, blood glucose monitoring; CGM, continuous glucose monitoring; ICR, insulin-to-carbohydrate ratio; ISF, insulin sensitivity factor; LAA, long-acting analog; MDI, multiple daily injections; N, NPH insulin; R, short-acting (regular) insulin; RAA, rapid-acting analog; TBR, time below range; TDD, total daily insulin dose; TIR, time in range; URAA, ultra-rapid-acting analog (inhaled insulin may be considered if appropriate). Adapted from Holt et al. (4).

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daily injections of insulin (16,17). However, there is no consensus to guide the choice of injection or pump therapy in a given individual, and research to guide this decision-making is needed (4). Integration of continuous glucose monitoring (CGM) into the treatment plan soon after diagnosis improves glycemic outcomes, decreases hypoglycemic events, and improves quality of life for individuals with type 1 diabetes (18–23). Its use is now considered standard of care for most people with type 1 diabetes (4) (see Section 7, "Diabetes Technology"). Reduction of nocturnal hypoglycemia in individuals with type 1 diabetes using insulin pumps with CGM is improved by automatic suspension of insulin delivery at a preset glucose level, with further improvements when using devices with predictive low-glucose insulin delivery suspension (24,25).

Automated insulin delivery (AID) systems are safe and effective for people with type 1 diabetes. Randomized controlled trials and real-world studies have demonstrated the ability of commercially available systems to improve achievement of glycemic goals while reducing the risk of hypoglycemia (26–31). Data are emerging on the safety and effectiveness of do-it-yourself systems (32,33). Evidence suggests that an AID hybrid closed-loop system is superior to AID sensor-augmented pump therapy for increased percentage of time in range and reduction of hypoglycemia (34,35).

Intensive insulin management using a version of CSII and CGM should be considered in individuals with type 1 diabetes whenever feasible. AID systems are preferred and should be considered for individuals with type 1 diabetes who are capable of using the device safely (either by themselves or with a caregiver) to improve time in range and reduce A1C and hypoglycemia (26,28–31,36–42). When choosing among insulin delivery systems, individual preferences, cost, insulin type, dosing plan, and self-management capabilities should be considered. See Section 7, "Diabetes Technology," for a full discussion of insulin delivery devices.

In general, individuals with type 1 diabetes require approximately 30–50% of their daily insulin as basal and the remainder as prandial (43). This proportion depends on several factors, including but not limited to carbohydrate consumption, age, pregnancy status, and puberty stage (4,44–48). Total daily insulin requirements can be estimated based on weight, with typical doses ranging from 0.4 to 1 unit/kg/day. Higher amounts may be required during puberty, menses, and medical illness. The *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook* notes 0.5 units/kg/day as a typical starting dose in adults with type 1 diabetes who are metabolically stable, with approximately one-half administered as prandial insulin given to manage blood glucose after meals and the remaining portion as basal insulin to manage glycemia in the periods between meal absorption (49). Starting doses and those soon after diagnosis may be higher, if an individual presents with ketoacidosis, or lower (0.2–0.6 units/kg), particularly in young children and those with continued endogenous insulin production (during the partial remission phase or "honeymoon period," or in people who present with type 1 diabetes in adulthood) (49–51). This guideline provides detailed information on intensification of therapy to meet individualized needs. In addition, the American Diabetes Association (ADA) position statement "Type 1 Diabetes Management Through the Life Span" provides a thorough overview of type 1 diabetes treatment (52).

Typical multidose treatment plans for individuals with type 1 diabetes combine premeal use of prandial insulins with a longer-acting formulation. The long-acting basal dose is titrated to regulate overnight and fasting glucose. Postprandial glucose excursions are best managed by a well-timed injection or inhalation of prandial insulin. Prandial insulin should ideally be administered prior to meal consumption; however, the optimal time to administer varies based on the pharmacokinetics of the formulation (regular, RAA, or inhaled), the premeal blood glucose level, and carbohydrate consumption. Recommendations for prandial insulin dose administration should therefore be individualized. Physiologic insulin secretion varies with glycemia, meal size, meal composition, and tissue demand for glucose. To address this variability in people treated with insulin, strategies have evolved to adjust prandial doses based on predicted needs. Thus, education on how to adjust prandial insulin to account for nutritional intake and the correction dose based on premeal glucose levels, anticipated activity, and sick-day management can be effective and should be offered to most individuals (53–58). Education regarding adjustment of prandial insulin dose for glycemic trends should be provided to individuals who are using CGM alone or an AID system (59–62). Further adjustment of prandial insulin doses for nutritional intake of protein and fat, in addition to carbohydrates, is recommended but may be more feasible for individuals using CSII than for those using multiple daily injections (55). With some AID systems, use of a simplified meal announcement method may be an alternative for prandial insulin dosing (31,63). Assessment and education tailored to improve health literacy and numeracy may be necessary for individuals to effectively use various insulin dosing strategies and tools (64,65) (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," and Section 7, "Diabetes Technology").

The 2021 ADA/European Association for the Study of Diabetes (EASD) consensus report on the management of type 1 diabetes in adults summarizes different insulin plans and glucose monitoring strategies in individuals with type 1 diabetes (**Fig. 9.1** and **Table 9.1**) (4).

Insulin Administration Technique

Ensuring that individuals and/or caregivers understand correct insulin administration technique is important to optimize glycemic management and insulin use safety. Recommendations have been published elsewhere outlining best practices for insulin administration (66). Proper insulin administration technique includes the following: injection, insertion of patch or infusion (for CSII or AID systems) into appropriate body areas, or oral inhalation (inhaled human insulin); injection or infusion site rotation; appropriate care of injection or infusion sites to avoid infection or other complications; avoidance of intramuscular (IM) insulin delivery; and filling of the reservoir (for bolus patch, CSII, or AID systems) or inhaler (for inhaled human insulin) depending on the method of administration. Selection of method of administration (vial and syringe, insulin pen, insulin patch, inhaled insulin, connected insulin pens/devices, or insulin pumps) will depend on a variety of individual-specific factors and needs, cost and coverage, and individual preferences. Reassessment of the appropriate administration technique should be completed during routine follow-up.

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Exogenously delivered insulin should be injected or infused into subcutaneous tissue, not intramuscularly. Recommended sites for insulin administration include the abdomen, thigh, buttock, and upper arm. Insulin absorption from IM sites differs from that in subcutaneous sites and is also influenced by the activity of the muscle. Inadvertent IM injection can lead to unpredictable insulin absorption and variable effects on glucose and is associated with frequent and unexplained hypoglycemia. Risk for IM insulin delivery is increased in younger, leaner individuals when injecting into the limbs rather than truncal sites (abdomen and buttocks) and when using longer needles. Recent evidence supports the use of short needles (e.g., 4-mm pen needles) as effective and well tolerated compared with longer needles, including a study performed in adults with obesity (67).

Injection or infusion site rotation is additionally necessary to avoid lipohypertrophy, an accumulation of subcutaneous fat in response to the adipogenic actions of insulin at a site of multiple injections. Lipohypertrophy appears as soft, smooth raised areas several centimeters in breadth and can contribute to erratic insulin absorption, increased glycemic variability, and unexplained hypoglycemic episodes. People treated with insulin and/or caregivers should receive education about proper injection or infusion site rotation and how to recognize and avoid injecting in areas of lipohypertrophy. As noted in **Table 4.1**, examination of insulin administration sites for the presence of lipohypertrophy, as well as assessment of administration device use and injection technique, are key components of a comprehensive diabetes medical evaluation and treatment plan. Proper insulin injection, infusion, or inhalation technique may lead to more effective use of this therapy and, as such, holds the potential for improved clinical outcomes.

Noninsulin Treatments for Type 1 Diabetes

Injectable and oral noninsulin glucose-lowering medications have been studied for their efficacy as adjuncts to insulin treatment of type 1 diabetes. Pramlintide is based on the naturally occurring β-cell peptide amylin and is approved for use in adults with type 1 diabetes. Clinical trials have demonstrated a modest reduction in A1C (0.3–0.4%) and modest weight loss (∼1 kg) with pramlintide (68). Similar results have been reported for several agents currently approved only for the treatment of type 2 diabetes. The addition of metformin in adults with type 1 diabetes was associated with small reductions in body weight, insulin dose, and lipid levels but did not sustainably improve A1C (69,70). The largest clinical trials of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in type 1 diabetes have been conducted with liraglutide 1.8 mg daily, and results showed modest A1C reductions (∼0.4%), decreases in weight (∼5 kg), and reductions in insulin doses (71,72). Liraglutide was also assessed for impact on C-peptide in individuals with type 1 diabetes and residual β-cell function. During treatment there was no impact, and with liraglutide discontinuation there was worsening of C-peptide loss compared with placebo (73). Retrospective case series have revealed potential benefits on body weight and glycemic metrics with addition of semaglutide or tirzepatide for individuals with type 1 diabetes and obesity (74,75). Prospective studies using semaglutide are ongoing (76,77).

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been studied in clinical trials in people with type 1 diabetes, and results showed improvements in A1C, reduced body weight, and improved blood pressure (78); however, SGLT2 inhibitor use in type 1 diabetes was associated with an increased rate of DKA (79). The SGLT1/2 inhibitor sotagliflozin has been studied in clinical trials in people with type 1 diabetes, and results showed improvements in A1C and body weight (80); however, sotagliflozin use was associated with an eightfold increase in DKA compared with placebo (81). The studies that led to the approved indication for heart failure (HF) excluded individuals with type 1 diabetes or a history of DKA (82,83). See SGLT INHIBITION AND RISK OF KETOSIS, later in this section, and PREVENTION AND TREATMENT OF HEART FAILURE in Section 10, "Cardiovascular Disease and Risk Management," for information on risk mitigation with the use of SGLT inhibitors in those with type 1 diabetes. The risks and benefits of adjunctive agents continue to be evaluated, with consensus statements providing guidance on selection of candidates for treatment and precautions (84).

There are currently no approved therapies for preservation of C-peptide or delaying the progression of symptomatic type 1 diabetes. Higher C-peptide levels have been associated with better A1C, lower risk of retinopathy, lower risk of nephropathy, and lower risk of severe hypoglycemia (85). Various therapies, including verapamil, menin inhibitors, Janus kinase inhibitors, antithymocyte globulin, several monoclonal antibodies including teplizumab, and cell therapies, are currently under active investigation.

SURGICAL TREATMENT OF TYPE 1 DIABETES

Pancreas and Islet Transplantation

Successful pancreas and islet transplantation can normalize glucose levels and mitigate microvascular complications of type 1 diabetes. However, people receiving these treatments require lifelong immunosuppression to prevent graft rejection and/or recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for people with type 1 diabetes undergoing simultaneous kidney transplantation, following kidney transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite optimized glycemic management (86). In much of the world, allogenic islet transplantation is regulated as an organ transplant. However, in the U.S., allogenic islet transplantation is regulated as a cell therapy, and the first such allogeneic islet cell therapy, donislecel-jujn, was approved in 2023. Donislecel is indicated for the treatment of adults with type 1 diabetes who are unable to reach their A1C goals because of repeated episodes of severe hypoglycemia despite intensive diabetes management and education (87). Alternative islet sources are currently under active investigation.

The 2021 ADA/EASD consensus report on the management of type 1 diabetes in adults offers a simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes (**Fig. 9.2**) (4).

PHARMACOLOGIC THERAPY FOR ADULTS WITH TYPE 2 DIABETES

Recommendations

9.7 Healthy behaviors, diabetes self-management education and support, avoidance of therapeutic inertia, and social determinants of health should

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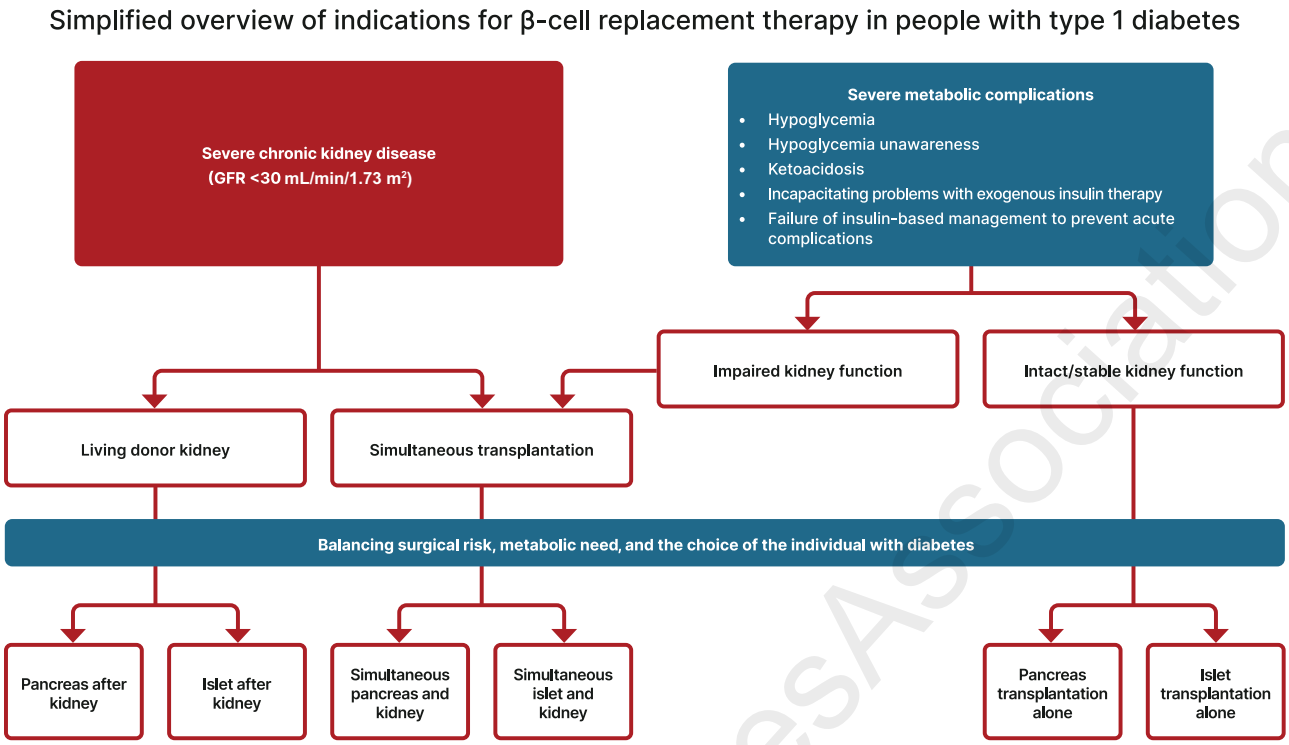

Figure 9.2—Simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes. The two main forms of β-cell replacement therapy are whole-pancreas transplantation and islet cell transplantation. β-Cell replacement therapy can be combined with kidney transplantation if the individual has end-stage kidney disease, which may be performed simultaneously or after kidney transplantation. All decisions about transplantation must consider the surgical risk, metabolic need, and the choices of the individual with diabetes. GFR, glomerular filtration rate. Adapted from Holt et al. (4).

be included in the glucose-lowering management of type 2 diabetes. **A**

9.8 A person-centered shared decision-making approach should guide the choice of glucose-lowering medications for adults with type 2 diabetes. Use medications that provide sufficient effectiveness to achieve and maintain intended treatment goals with consideration of the effects on cardiovascular, kidney, weight, and other relevant comorbidities; hypoglycemia risk; cost and access; risk for adverse reactions and tolerability; and individual preferences (**Fig. 9.3** and **Table 9.2**). **E**

9.9 Combination therapy can be considered in adults with type 2 diabetes at treatment initiation to shorten time to attainment of individualized treatment goals. **A**

9.10 In adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease, the treatment plan should include medications with demonstrated benefits to reduce cardiovascular events (e.g., glucagon-like peptide 1 receptor agonist [GLP-1 RA] and/or sodium–glucose cotransporter 2 [SGLT2] inhibitor) for glycemic management and comprehensive cardiovascular risk reduction (irrespective of A1C) (**Fig. 9.3** and **Table 9.2**). **A**

9.11 In adults with type 2 diabetes who have heart failure (HF) (with either reduced or preserved ejection fraction), an SGLT2 inhibitor is recommended for both glycemic management and prevention of HF hospitalizations (irrespective of A1C) (**Fig. 9.3**). **A**

9.12 In adults with type 2 diabetes and symptomatic heart failure with preserved ejection fraction (HFpEF) and obesity, a GLP-1 RA with demonstrated benefits for both glycemic management and reduction of HF-related symptoms (irrespective of A1C) is recommended. **A**

9.13 In adults with type 2 diabetes who have CKD (with confirmed estimated glomerular filtration rate [eGFR] 20–60 mL/min/1.73 m^2 and/or albuminuria), an SGLT2 inhibitor or GLP-1 RA with demonstrated benefit in this population should be used for both glycemic management (irrespective of A1C) and for slowing progression of CKD and reduction in cardiovascular events (**Fig. 9.3**). The glycemic benefits of SGLT2 inhibitors are reduced at eGFR <45 mL/min/1.73 m^2. **A**

9.14 In adults with type 2 diabetes and advanced CKD (eGFR <30 mL/min/1.73 m^2), a GLP-1 RA is preferred for glycemic management due to lower risk of hypoglycemia and for cardiovascular event reduction. **B**

9.15 In adults with type 2 diabetes, metabolic dysfunction–associated steatotic liver disease (MASLD), and overweight or obesity, consider using a GLP-1 RA or a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA with potential benefits in metabolic dysfunction–associated steatohepatitis (MASH) for glycemic management and as an adjunctive to healthy interventions for weight loss. **B**

9.16a In adults with type 2 diabetes and biopsy-proven MASH or those at high risk for liver fibrosis (based on noninvasive tests), pioglitazone, a GLP-1 RA, or a dual GIP and GLP-1 RA is preferred for glycemic management due to potential beneficial effects on MASH. **B**

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9.16b Combination therapy with pioglitazone plus a GLP-1 RA can be considered for the treatment of hyperglycemia in adults with type 2 diabetes with biopsy-proven MASH or those at high risk of liver fibrosis (identified with noninvasive tests) due to potential beneficial effects on MASH. **B**

9.17 Medication plan and medication-taking behavior should be reevaluated at regular intervals (e.g., every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment (**Fig. 4.1** and **Table 9.2**). **E**

9.18 Treatment modification (intensification or deintensification) for adults not meeting individualized treatment goals should not be delayed. **A**

9.19 Choice of glucose-lowering therapy modification should take into consideration individualized glycemic and weight goals, presence of comorbidities (cardiovascular, kidney, liver, and other metabolic comorbidities), and the risk of hypoglycemia. **A**

9.20 When initiating a new glucose-lowering medication, reassess the need for and/or dose of medications with higher hypoglycemia risk (i.e., sulfonylureas, meglitinides, and insulin) to minimize the risk of hypoglycemia and treatment burden. **A**

9.21 Concurrent use of dipeptidyl peptidase 4 (DPP-4) inhibitors with a GLP-1 RA or a dual GIP and GLP-1 RA is not recommended due to lack of additional glucose lowering beyond that of a GLP-1 RA alone. **B**

9.22 In adults with type 2 diabetes who have not achieved their individualized weight goals, additional weight management interventions (e.g., intensification of lifestyle modifications, structured weight management programs, pharmacologic agents, or metabolic surgery, as appropriate) are recommended. **A**

9.23 In adults with type 2 diabetes, initiation of insulin should be considered regardless of background glucose-lowering therapy or disease stage if symptoms of hyperglycemia are present or when A1C or blood glucose levels are very high (i.e., A1C >10% [>86 mmol/mol] or blood glucose ≥300 mg/dL [≥16.7 mmol/L]). **E**

9.24 In adults with type 2 diabetes and no evidence of insulin deficiency, a GLP-1 RA, including a dual GIP and GLP-1 RA, is preferred to insulin (**Fig. 9.4**). **A**

9.25 If insulin is used, combination therapy with a GLP-1 RA, including a dual GIP and GLP-1 RA, is recommended for greater glycemic effectiveness as well as beneficial effects on weight and hypoglycemia risk for adults with type 2 diabetes. Insulin dosing should be reassessed upon addition or dose escalation of a GLP-1 RA or dual GIP and GLP-1 RA. **A**

9.26 In adults with type 2 diabetes who are initiating insulin therapy, continue glucose-lowering agents (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits (i.e., weight, cardiometabolic, or kidney benefits). **A**

A holistic, multifaceted, person-centered approach that accounts for the complexity of managing type 2 diabetes and its complications across the life span is recommended. Person-specific factors that affect choice of treatment include individualized glycemic goals (see Section 6, "Glycemic Goals and Hypoglycemia"), individualized weight goals (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes"), the individual's risk for hypoglycemia, and the individual's history of or risk factors for cardiovascular, kidney, liver, and other comorbidities and complications of diabetes (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management"). In addition, treatment decisions must consider the tolerability and side effect profiles of medications, complexity of the medication plan and the individual's capacity to implement it given their specific situation and context, and the access, cost, and availability of medications. Lifestyle modifications and health behaviors that improve health (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes") should be emphasized along with any pharmacologic therapy. Section 13, "Older Adults," and Section 14, "Children and Adolescents," have recommendations specific for older adults and for children and adolescents with type 2 diabetes, respectively. Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management," have recommendations for the use of glucose-lowering drugs in the management of cardiovascular disease and kidney disease, respectively.

Choice of Glucose-Lowering Therapy

Healthy lifestyle behaviors, diabetes self-management education and support (DSMES), avoidance of therapeutic inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities, considerations of adverse effects (including hypoglycemia) and treatment burden, and treatment goals and preferences. Shared decision-making can be facilitated during clinical encounters through use of decision aides and has been shown to improve A1C in adults with type 2 diabetes, though in clinical trials the benefits of shared decision-making were limited to face-to-face discussions (not online encounters) and to individuals with elevated A1C (>8%) (88). Pharmacotherapy should be started at the time type 2 diabetes is diagnosed, without delay, unless there are contraindications. Medication plans should have adequate efficacy to achieve and maintain individualized treatment goals with respect to glucose lowering, reduction of cardiovascular and kidney disease risks, weight management, and impacts on other health conditions and treatment burden. In adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease (ASCVD), HF, and/or chronic kidney disease (CKD), the treatment plan should include agents that reduce cardiovascular and kidney disease risk (**Fig. 9.3** and **Table 9.2**) (see also Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management").

In individuals without ASCVD, HF, or CKD, choice of therapy should be informed by considerations of weight management (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes"), mitigation of

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metabolic dysfunction–associated liver disease (MASLD) or metabolic dysfunction–associated steatohepatitis (MASH) risk (see Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities"), and achievement and maintenance of individualized glycemic goals. In general, higher-efficacy approaches, including combination therapy, have greater likelihood of achieving treatment goals. Weight management is a distinct treatment goal, along with glycemic management, as it has multifaceted benefits, including reduction of A1C, reduction in hepatic steatosis, and improvement in cardiovascular risk factors (89–91). For individuals with type 2 diabetes who require initiation or intensification of glucose-lowering therapy to achieve and/or maintain individualized glycemic goals and who do not have additional considerations informing choice of therapy beyond need for glucose lowering, metformin is a commonly used medication that historically has been the first-line treatment for type 2 diabetes (92,93). Metformin is effective and safe, is inexpensive and widely available, and reduces risks of microvascular complications, cardiovascular events, and death (92,94,95). Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, is weight neutral, does not cause hypoglycemia, and reduces cardiovascular mortality (96). Metformin is also more effective than dipeptidyl peptidase 4 (DPP-4) inhibitors in lowering A1C and weight when used as monotherapy (97).

The principal side effects of metformin are gastrointestinal intolerance due to bloating, abdominal discomfort, and diarrhea; these can be mitigated by gradual dose titration and/or using extended-release formulation. The drug is cleared by kidney filtration, and metformin may be safely used in people with estimated glomerular filtration rate $\geq$30 mL/min/1.73 m^2 (98). Very high circulating levels (e.g., as a result of overdose or acute kidney injury) have been associated with lactic acidosis (99). However, the occurrence of this complication is very rare (100) and primarily occurs when the estimated glomerular filtration rate (eGFR) is $<$30 mL/min/1.73 m^2 (101). For people with an eGFR of 30–45 mL/min/1.73 m^2, there is an increased risk for periodic decreases of eGFR to $\leq$30 mL/min/1.73 m^2 which heightens the risk of lactic acidosis. Metformin use is also associated with increased risk of vitamin B12 deficiency and worsening of symptoms of neuropathy (102,103), suggesting periodic testing of vitamin B12 levels (see Section 3, "Prevention or Delay of Diabetes and Associated Comorbidities").

The comparative glucose-lowering efficacy of different pharmacologic agents has been examined primarily in network meta-analyses, as few prospective clinical trials have compared multiple drug classes head-to-head. In general, the largest reductions in A1C levels are achieved by treatment plans that include insulin, select GLP-1 RAs (particularly semaglutide), and tirzepatide, while DPP-4 inhibitors resulted in the smallest reductions in A1C (104–106). In A Diabetes Outcome Progression Trial (ADOPT), rosiglitazone monotherapy was more effective than metformin and glyburide monotherapies in achieving and maintaining fasting plasma glucose below 180 mg/dL (10 mmol/L) among recently diagnosed individuals with type 2 diabetes whose baseline fasting plasma glucose was 126–180 mg/dL (7–10 mmol/L), while glyburide was least effective (107). More recently, the Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) trial compared use of insulin glargine U-100, liraglutide, sitagliptin, and glimepiride as add-on treatments to metformin monotherapy among individuals with type 2 diabetes and baseline A1C 6.8–8.5% (108). It found that at 5 years, all therapies decreased A1C levels but glargine and liraglutide were modestly more effective in achieving and maintaining A1C below 7%, while sitagliptin was least effective. Severe hypoglycemia was significantly more common in those prescribed glargine or glimepiride. An observational study that emulated many of GRADE's design features and included canagliflozin as a comparator arm, but did not include insulin glargine, found that liraglutide was more effective at achieving and maintaining A1C below 7% than sitagliptin, canagliflozin, or glimepiride, which all had comparable effectiveness (108).

Thus, when choosing a glucose-lowering medication to achieve individualized glycemic goals, we recommend engaging in shared decision-making and considering factors such as glucose-lowering efficacy, the side effect profile, and medication accessibility and affordability (108). In all cases, treatment plans need to be continuously reviewed for efficacy, side effects, hypoglycemia, and treatment burden (**Table 9.2**).

When A1C is $\geq$1.5% above the individualized glycemic goal (see Section 6, "Glycemic Goals and Hypoglycemia," for appropriate goals), many individuals will require dual-combination therapy or a more potent glucose-lowering agent to achieve and maintain their goal A1C level (89) (**Fig. 9.3** and **Table 9.2**). Insulin should be considered as part of any combination medication plan when hyperglycemia is severe, especially if catabolic features (weight loss, hypertriglyceridemia, and ketosis) are present. It is common practice to initiate insulin therapy for people who present with blood glucose levels $\geq$300 mg/dL ($\geq$16.7 mmol/L) or A1C $>$10% ($>$86 mmol/mol) or if the individual has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (unexpected weight loss) (**Fig. 9.4**). As glucose toxicity resolves, simplifying the medication plan and/or changing to noninsulin agents is possible. Additionally, there is evidence that people with type 2 diabetes and severe hyperglycemia can also be effectively treated with a sulfonylurea, a GLP-1 RA, or dual GIP and GLP-1 RA, though evidence is scarce for individuals with baseline A1C above 10–12% (104,109–111). GLP-1 RAs and tirzepatide have additional benefits over insulin and sulfonylureas, specifically lower risks for hypoglycemia (both) and favorable weight (both), cardiovascular (GLP-1 RAs), kidney (GLP-1 RAs), and liver (both) end points.

Combination Therapy

Because type 2 diabetes is a progressive disease, maintenance of glycemic goals often requires combination therapy. Traditional recommendations have called for the use of stepwise addition of medications to metformin to maintain A1C goals. The advantage of this is to provide a clear assessment of the positive and negative effects of new drugs and reduce potential side effects and expense (112). However, some data support initial combination therapy for more rapid attainment of glycemic goals (113,114) and later combination therapy for longer durability of glycemic effect (115). Initial combination therapy should be considered in people presenting

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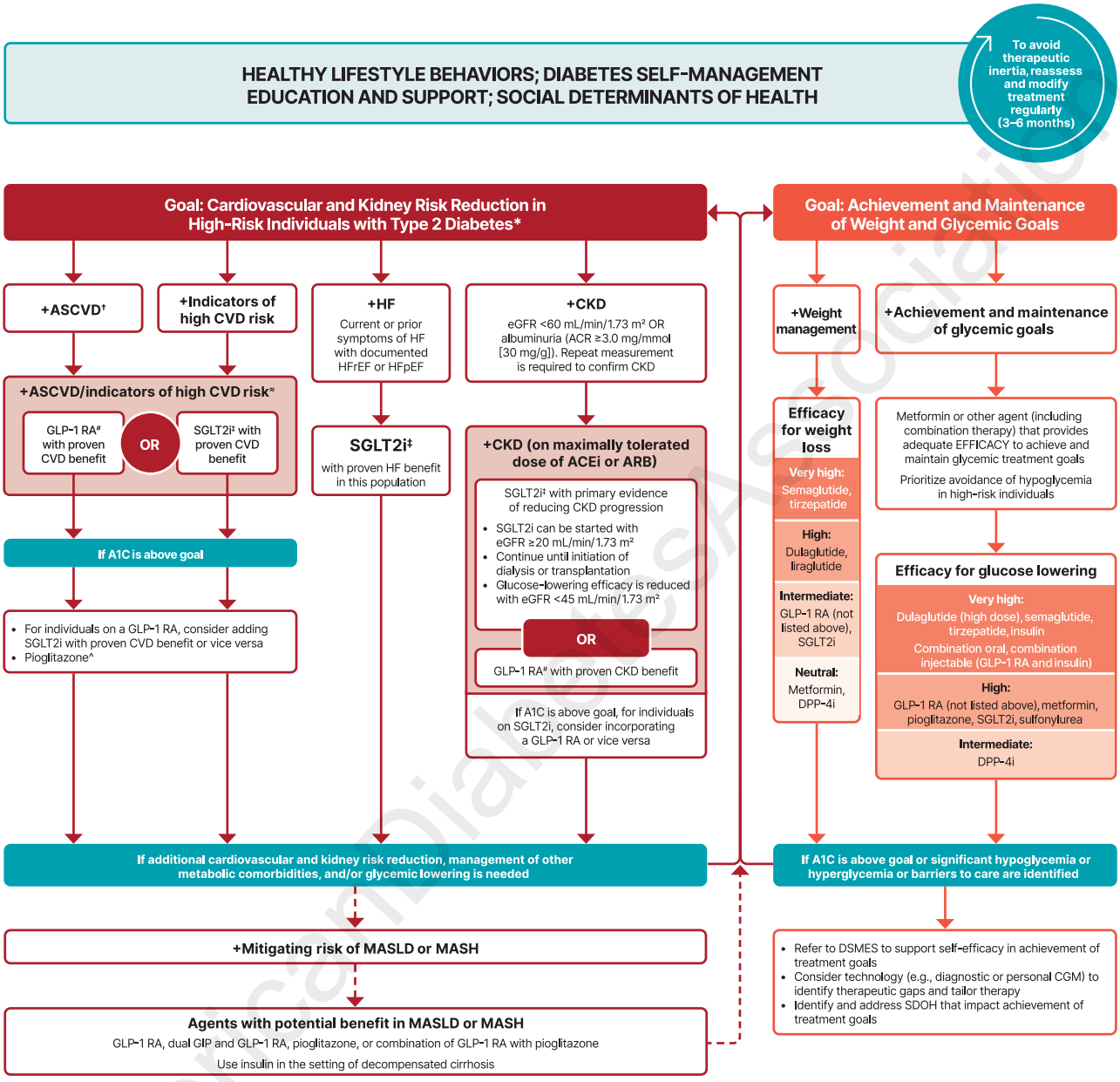
Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of background use of metformin or A1C.

† ASCVD: Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, and arterial revascularization procedure) and variably included conditions such as transient ischemic attack, unstable angina, amputation, and symptomatic or asymptomatic coronary artery disease. Indicators of high risk: While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

≈ A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high-risk CVD. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.

For GLP-1 RAs, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and kidney end points in individuals with T2D with established or high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1 RA in individuals with CKD and T2D.

‡ For SGLT2is, CV and kidney outcomes trials demonstrate their efficacy in reducing the risks of composite MACE, CV death, all-cause mortality, MI, HHF, and kidney outcomes in individuals with T2D and established or high risk of CVD.

^ Low-dose pioglitazone may be better tolerated and similarly effective as higher doses.

Figure 9.3—Use of glucose-lowering medications in the management of type 2 diabetes. The left side of the algorithm prioritizes mitigation of diabetes-related complications and end-organ effects, while the right side addresses weight and glucose management goals. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; DSMES, diabetes self-management education and support; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2D, type 2 diabetes. Adapted from Davies et al. (89).

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Table 9.2—Features of medications for lowering glucose in type 2 diabetes

Medication (route of administration)	Glucose-lowering efficacy[1]	Hypoglycemia risk	Weight effects[2]	CV effects		Kidney effects		MASH effects	Clinical considerations and adverse effects
				Effect on MACE	Effect on HF	Progression of CKD	Dosing/use considerations*		
Metformin (oral)	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min/1.73 m^2	Neutral	• GI side effects: mitigate with slow dose titration, extended-release formulations, and administration with food. • Potential for vitamin B12 deficiency: monitor and replete as appropriate.
SGLT2 inhibitors (oral)	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels of individual agents for dosage considerations for kidney function • Glucose-lowering effect is minimal at eGFR <45 mL/min/1.73 m^2 and lower; continue for cardiovascular and kidney benefit until dialysis or transplantation	Unknown	• DKA risk in individuals with insulin deficiency (rare in T2D): discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentations (including euglycemic DKA); mitigate risk with sick-day planning; discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting. • Genital mycotic infections: mitigate risk with genital hygiene and avoid use in high-risk individuals. • Necrotizing fasciitis of the perineum (Fournier gangrene): rare; prompt treatment if suspected. • Intravascular volume depletion: attention to volume status and blood pressure, particularly when ill or fasting; adjust other volume-contracting agents as applicable; monitor kidney function upon initiation.
GLP-1 RAs (SQ; semaglutide also available in oral formulation)	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal end points in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ) Demonstrated benefit for progression of CKD for semaglutide (SQ)	• See labels of individual agents for dosage considerations for kidney function • No dose adjustment for dulaglutide, liraglutide, or semaglutide • Monitor kidney function when initiating or escalating doses in individuals with kidney impairment reporting severe adverse GI reactions	Potential benefit	• Thyroid C-cell tumors identified in rodents; human relevance not determined. • Ileus: risk level is not well established; provide guidance on discontinuation prior to surgical procedures. • Pancreatitis: acute pancreatitis has been reported, but causality has not been established. Do not initiate if at high risk for pancreatitis, and discontinue if pancreatitis is suspected. • Biliary disease: evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected; avoid use in at-risk individuals. • Diabetic retinopathy: close monitoring of retinopathy in those at high risk (older individuals and those with longer duration of T2D [≥10 years]). • Impact on drug absorption: orally administered drug absorption may be impaired during dose titration (including of oral contraceptives). • GI side effects: counsel on potential for GI side effects; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g. stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for those experiencing GI challenges. Not recommended for individuals with gastroparesis.
Dual GIP and GLP-1 RA (SQ)	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See labels of individual agents for dosage considerations for kidney function • No dose adjustment • Monitor kidney function when initiating or escalating doses in individuals with kidney impairment reporting severe adverse GI reactions	Potential benefit	
DPP-4 inhibitors (oral)	Intermediate	No	Neutral	Neutral	Neutral (potential risk: saxagliptin)	Neutral	• Dose adjustment required based on kidney function (sitagliptin, saxagliptin, alogliptin) • No dose adjustment required for linagliptin	Unknown	• Pancreatitis has been reported, but causality has not been established. Discontinue if pancreatitis is suspected. • Postmarketing concerns about joint pain (consider discontinuing if debilitating and other treatment options are feasible) and bullous pemphigoid (discontinue if suspected).
Pioglitazone (oral)	High	No	Gain	Potential benefit	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in kidney impairment due to potential for fluid retention	Potential benefit	• Increased risk of HF and fluid retention. Do not use in the setting of HF. • Risk of bone fractures. • Bladder cancer: do not use in individuals with active bladder cancer, and use caution in those with prior history of bladder cancer.
Sulfonylureas (2nd generation) (oral)	High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in CKD • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	Unknown	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text). • Use with caution in individuals at risk for hypoglycemia, particularly if in combination with insulin.
Insulin (human) (SQ; regular insulin also available as inhaled formulation) **Insulin (analogs)** (SQ)	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	Unknown	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs • Risk of hypoglycemia and duration of activity increases with the severity of impaired kidney function. • Refer to device-specific instructions for insulins compatible with different delivery systems (i.e., pumps, connected insulin pens, insulin patches).

CKD, chronic kidney disease; CV, cardiovascular; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; MACE, major adverse cardiovascular events; MASH, metabolic dysfunction-associated steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2D, type 2 diabetes. *For agent-specific dosing recommendations, please refer to manufacturers' prescribing information. [1]Tsapas et al. (106). [2]Tsapas et al. (241). Adapted from Davies et al. (89).

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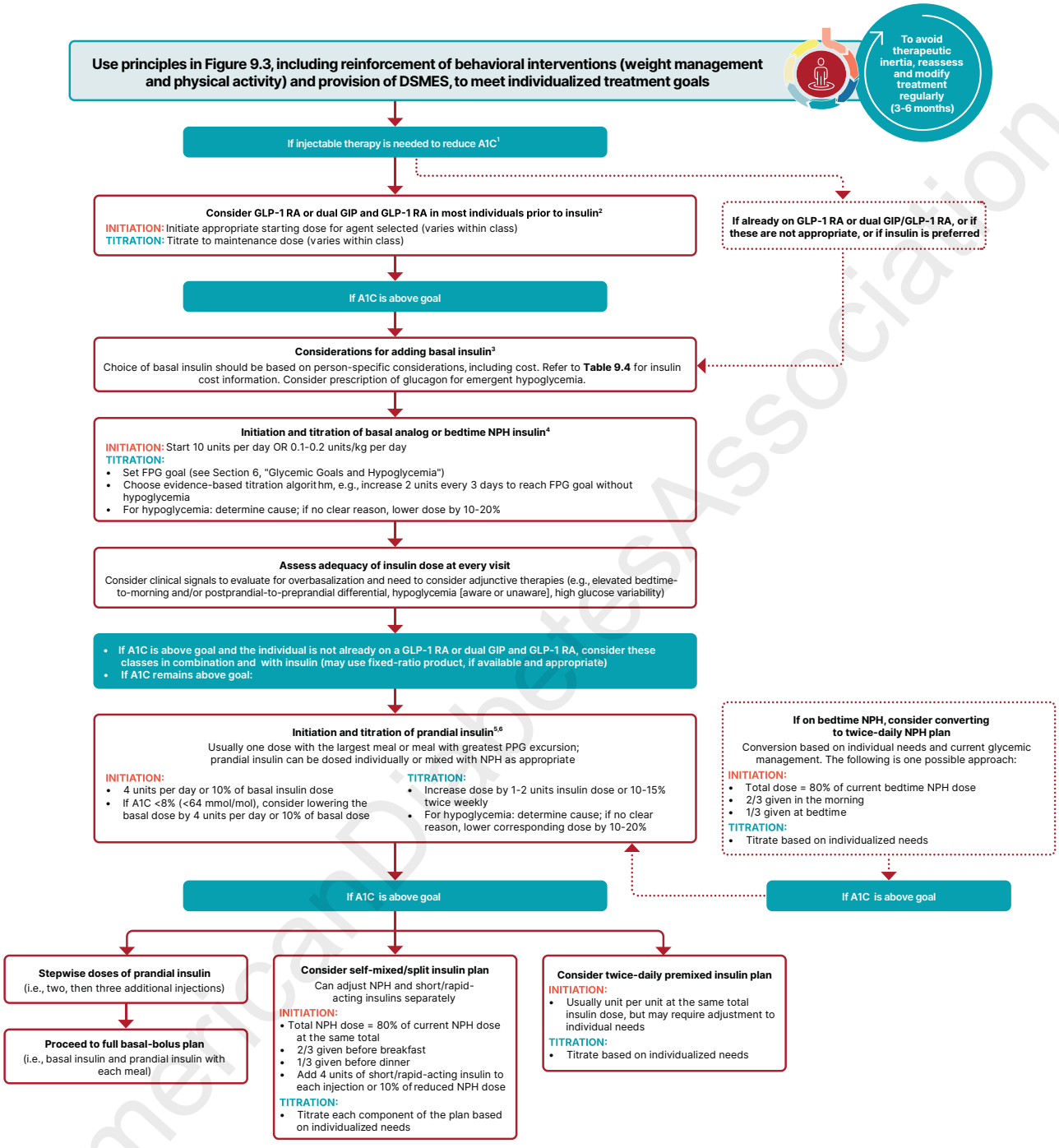

1. Consider insulin as the first injectable if symptoms of hyperglycemia are present, when A1C or blood glucose levels are very high (i.e., A1C >10% [>86 mmol/mol] or blood glucose ≥300 mg/dL [≥16.7 mmol/L]), or when a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RAs, consider individual preference, A1C lowering, weight-lowering effect, and frequency of injection. If CVD is present, consider GLP-1 RA with proven CVD benefit; oral or injectable GLP-1 RAs are appropriate.
3. For people on GLP-1 RA and basal Insulin combination, consider use of a fixed-ratio combination product (IDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the individual develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with a morning dose of a long-acting basal Insulin. Consider dosing NPH in the morning for steroid-induced hyperglycemia.
5. Prandial insulin options include injectable rapid- and ultra-rapid-acting analog insulins, injectable short-acting human insulin, or inhaled human insulin.
6. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin plan to decrease the number of injections required.

Figure 9.4—Intensifying to injectable therapies in type 2 diabetes. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide 1 receptor agonist; GIP, glucose-dependent insulinotropic polypeptide; PPG, postprandial glucose. Adapted from Davies et al. (242).

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with A1C levels 1.5–2.0% above their individualized goal. Finally, incorporation of high-glycemic-efficacy therapies or therapies for cardiovascular and kidney disease risk reduction (e.g., GLP-1 RAs, dual GIP and GLP-1 RA, and SGLT2 inhibitors) may reduce the need for agents that increase the risks of hypoglycemia and weight gain or are less well tolerated. Thus, treatment intensification requires purposeful selection of medications in alignment with multiple individualized person-centered treatment goals simultaneously (**Fig. 9.3**).

Treatment intensification, deintensification, or modification, as appropriate, for people not meeting individualized treatment goals should not be delayed (therapeutic inertia) (116). Results from comparative effectiveness meta-analyses suggest that each new class of oral noninsulin agents when added to metformin generally lowers A1C by approximately 0.7–1.0% (8–11 mmol/mol). Addition of GLP-1 RAs or the dual GIP and GLP-1 RA to metformin usually results in 1 to ≥2% lowering of A1C (104,117,118) (**Fig. 9.3** and **Table 9.2**). We do not recommend using GLP-1 RAs (or the dual GIP and GLP-1 RA) together with a DPP-4 inhibitor as there is no added glucose-lowering benefit beyond that of the GLP-1 RA alone (119–121).

When even greater potency of glucose reduction is needed, basal insulin, either human NPH or a long-acting insulin analog, should be initiated. However, if the individual is not already receiving GLP-1 RA or dual GIP and GLP-1 RA therapy, an agent from these classes should be started first, as it may be sufficient for achieving individualized A1C goals but with lower risk of hypoglycemia and with favorable weight, cardiovascular, kidney, and liver profiles. While most GLP-1 RAs are injectable medications, an oral formulation of semaglutide is commercially available (122). In trials analyzing the addition of an injectable GLP-1 RA, dual GIP and GLP-1 RA, or insulin in people needing further glucose lowering, glycemic efficacies of GLP-1 RAs and the dual GIP and GLP-1 RA were similar to or greater than that of basal insulin (123–130). GLP-1 RAs and dual GIP and GLP-1 RA in these trials also had a lower risk of hypoglycemia and beneficial effects on body weight compared with insulin, albeit with greater gastrointestinal side effects. Thus, trial results support high-potency GLP-1 RAs and dual GIP and GLP-1 RA as the preferred options for individuals requiring more intensive glucose management (**Fig. 9.4**).

In individuals who are intensified to insulin therapy, combination therapy with a GLP-1 RA or a dual GIP and GLP-1 RA has been shown to have greater efficacy and durability of glycemic treatment effects, as well as weight and hypoglycemia benefits, than treatment intensification with insulin alone (89,131). However, cost, accessibility, and tolerability are important considerations for GLP-1 RA and dual GIP and GLP-1 RA use.

In all cases, treatment plans need to be continuously reviewed for efficacy, side effects (including hypoglycemia), and treatment burden (**Table 9.2**). In some instances, the individual will require medication reduction or discontinuation. Common reasons for this include ineffectiveness, hypoglycemia, intolerable side effects, new contraindications, expense, or a change in glycemic goals (e.g., in response to development of comorbidities). See below for cost considerations of glucose-lowering therapies (MEDICATION COSTS AND AFFORDABILITY). Section 13, "Older Adults," has a full discussion of treatment considerations in older adults. Treatment deintensification may also be needed in the setting of weight loss and/or optimization of lifestyle behaviors, when fewer pharmacologic agents are needed to maintain A1C goals. In this case, we recommend preferential deescalation of therapies that are most likely to cause side effects, hypoglycemia, and/or treatment burden and do not have cardiovascular, kidney, or metabolic benefits for continued use.

Glucose-Lowering Therapy for People With Cardiovascular Disease or Risk Factors for Cardiovascular Disease

For people with type 2 diabetes and established ASCVD or indicators of high ASCVD risk, HF, or CKD, an SGLT2 inhibitor and/or GLP-1 RA with demonstrated cardiovascular benefit (**Table 9.2**) is recommended independent of A1C, with or without metformin use, and in consideration of person-specific factors (**Fig. 9.3**). Individuals with these comorbidities already achieving their individualized glycemic goals with other medications may benefit from switching to these preferred medications to reduce risk of ASCVD, HF, and/or CKD in addition to achieving glycemic goals (see Section 10, "Cardiovascular Disease and Risk Management," and Section 11, "Chronic Kidney Disease and Risk Management"). This is particularly important because SGLT2 inhibitors and GLP-1 RAs are associated with lower risk of hypoglycemia and individuals with ASCVD, HF, and CKD have higher hypoglycemia risk than individuals without these conditions (132).

Individuals at lower risk for ASCVD may still benefit from GLP-1 RA therapy to reduce their risk of future cardiovascular events. The GRADE trial, which was designed to examine the comparative effectiveness of insulin glargine U-100, glimepiride, liraglutide, and sitagliptin in individuals with relatively short duration of diabetes (and, due to study eligibility criteria, low ASCVD risk) with respect to achieving and maintaining A1C below 7%, found that individuals treated with liraglutide had a slightly lower risk of cardiovascular disease than individuals receiving the other three treatments (hazard ratio 0.7 [95% CI 0.6–0.9]), although no significant differences were found for major adverse cardiovascular events, hospitalization for HF, or cardiovascular death (133). Individuals with type 2 diabetes and moderate levels of CVD risk appear to derive cardiovascular and mortality benefits with preferential use of GLP-1 RA and SGLT2 inhibitors compared with sulfonylurea or DPP-4 inhibitors (134). Similarly, while greater reductions in HF hospitalization risk are observed with SGLT2 inhibitor therapy in individuals with higher baseline HF risk, some benefit is observed across the full range of HF risk (135).

Glucose-Lowering Therapy for People With Chronic Kidney Disease

For individuals with type 2 diabetes and CKD, considerations for selection of glucose-lowering medications include their effectiveness and safety when eGFR is reduced as well as the potential to impact CKD progression, CVD risk, and hypoglycemia (136). Preferred medications for glucose management in individuals with CKD are GLP-1 RAs and SGLT2 inhibitors (can be initiated if eGFR is above 20 mL/min/1.73 m^2). GLP-1 RAs are effective in lowering glucose levels, regardless of kidney function, with a low risk for hypoglycemia, and a recent clinical trial suggests that the GLP-1 RA semaglutide has a beneficial effect on CVD, mortality, and kidney outcomes among people with CKD,

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leading to the recommendation that semaglutide can be used as another first-line agent for people with CKD (137,138). Other GLP-1 RAs (liraglutide and dulaglutide) may also have CKD benefits, but no other dedicated kidney trials have been published. Similarly, no dedicated kidney outcomes studies for the dual GIP and GLP-1 RA (tirzepatide) have been published. Dedicated kidney outcomes trials in people with CKD and type 2 diabetes have shown that the SGLT2 inhibitors empagliflozin, canagliflozin, and dapagliflozin have beneficial effects on slowing progression of CKD and CV outcomes in this population (139–141). However, their ability to lower glucose levels declines when the eGFR falls below 45 mL/min/1.73 m^2 (142–144). Metformin is also a preferred agent for those with CKD due to its well-documented efficacy and safety profile for all people with type 2 diabetes. However, there is no documented direct kidney benefit. Importantly, metformin should not be started in those whose eGFR is $<$45 mL/min/1.73 m^2. For those already treated with metformin, the dose of metformin should be reduced once eGFR is $<$45 mL/min/1.73 m^2 and should be stopped once eGFR is $<$30 mL/min/1.73 m^2 (98). A secondary analysis of the GRADE trial found that insulin glargine, liraglutide, sitagliptin, and glimepiride did not prevent the development of CKD when added to metformin monotherapy in individuals without underlying CKD (145). Importantly, an SGLT2 inhibitor was not included in the GRADE trial.

Individuals with CKD, particularly advanced CKD and kidney failure, are at high risk for hypoglycemia (132). If treated with insulin and/or sulfonylureas, treatment needs to be closely monitored and adjusted as eGFR declines and individuals need to be educated about and closely monitored for hypoglycemia occurrence (136). See Section 11, "Chronic Kidney Disease and Risk Management," for more details about prevention and treatment of CKD in individuals with diabetes.

Glucose-Lowering Therapy for People With Metabolic Comorbidities

Many adults with diabetes, either type 2 diabetes or type 1 diabetes, with obesity are at high risk of developing MASLD or MASH as well as MASH cirrhosis. Hence, the presence of MASLD or MASH should be a consideration when choosing glucose-lowering therapies. Accruing randomized clinical trial data suggest that pioglitazone, GLP-1 RA, and a dual GIP and GLP-1 RA have potential benefits in terms of decreasing hepatic steatosis and in the resolution of MASH without worsening of fibrosis in individuals with biopsy-proven MASH or those at higher risk of clinically significant liver fibrosis identified with noninvasive tests (146–153). Combination therapy with pioglitazone plus GLP-1 RA should also be considered for treatment of hyperglycemia in adults with type 2 diabetes with biopsy-proven MASH or those at higher risk of clinically significant liver fibrosis identified with noninvasive tests, as such therapy is safe and effective and has been shown to reduce hepatic steatosis (154–156). It is important to note that these studies are based on phase 2 clinical trials and await further phase 3 confirmation of evidence. However, these plans are preferred as they offer potential benefit compared with lack of histological benefit (or clinical trial data) from other glucose-lowering therapies in MASLD. Further details regarding liver health in diabetes can be found in Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities."

Obesity is present in over 90% of people with type 2 diabetes, and in these individuals weight management is a key treatment goal, along with glucose lowering. In the setting of obesity, the choice of glucose-lowering medications should take into consideration their effects on weight. Insulins, sulfonylureas, and thiazolidinediones can promote weight gain and should be used judiciously and at the lowest possible dose. Glucose-lowering medications that promote weight loss should be prioritized. Of the currently available agents, tirzepatide and semaglutide have the highest efficacy in terms of glucose lowering as well as weight loss, followed by dulaglutide, liraglutide, and extended-release exenatide (157–161). Other glucose-lowering medications (metformin, SGLT2 inhibitors, DPP-4 inhibitors, dopamine agonists, bile acid sequestrants, and α-glucosidase inhibitors) are weight neutral or have a modest beneficial effect on weight. These medications can be used as add-on therapies in people with type 2 diabetes and obesity who require additional glucose lowering or if the more effective medications are not tolerated, are contraindicated, or are unavailable. Metabolic surgery, especially Roux-en-Y gastric bypass and sleeve gastrectomy, are very effective interventions to achieve both weight and glycemic goals and have additional health benefits beyond improving metabolism (162). Further details regarding treatment of obesity can be found in Section 8 ("Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes").

Insulin Therapy

Many adults with type 2 diabetes eventually require and benefit from insulin therapy (**Fig. 9.4**). See INSULIN ADMINISTRATION TECHNIQUE, above, for guidance on how to administer insulin safely and effectively. The progressive nature of type 2 diabetes should be regularly and objectively explained to individuals with diabetes, and clinicians should avoid using insulin as a threat or describing it as a sign of personal failure. The utility and importance of insulin to achieve and maintain glycemic goals once progression of the disease overcomes the effect of other agents as well as for temporary use for acute situations (such as hospitalization, acute illness, or high-dose glucocorticoid therapy) should be emphasized. Educating and involving people with diabetes in insulin management is beneficial. For example, instruction of individuals with type 2 diabetes initiating insulin on self-titration of insulin doses based on glucose monitoring improves glycemic management (163). Comprehensive education regarding glucose monitoring, nutrition, physical activity, contingency planning (for illness, fasting, or medication unavailability), and the prevention and appropriate treatment of hypoglycemia are critically important for all individuals using insulin. Assessment and education tailored to improve health literacy and numeracy may be necessary for individuals to effectively use various insulin dosing strategies and tools (64,65). See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for guidance on diabetes self-management education.

Basal Insulin

Basal insulin alone is the most convenient initial insulin treatment and can be added to noninsulin glucose-lowering medications. For individuals with type 2 diabetes, starting doses can be estimated based on body weight (0.1–0.2 units/kg/day) and the degree of hyperglycemia, with individualized titration over days to weeks as

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needed to achieve and maintain glycemic goals. The principal action of basal insulin is to restrain hepatic glucose production and limit hyperglycemia overnight and between meals (164,165). Attainment of fasting glucose goals can be achieved with human NPH insulin or a long-acting insulin analog. In clinical trials, long-acting basal analogs (U-100 glargine and detemir) have been demonstrated to reduce the risk of level 2 hypoglycemia and nocturnal hypoglycemia compared with NPH insulin (166). Longer-acting basal analogs (U-300 glargine or degludec) convey a lower nocturnal hypoglycemia risk than U-100 glargine (167,168). It is important to understand how to convert individuals from one basal insulin to another, as switching insulins may be required due to the availability of more clinically appropriate insulin alternatives, removal of a product from the market (i.e., insulin detemir), or changes to insurance coverage. Often doses can be converted unit for unit and subsequently adjusted based on glucose monitoring; however, an initial dose reduction of 10–20% can be used for individuals in very tight management or at high risk for hypoglycemia and is typically needed when switching from insulin detemir or U-300 glargine to another insulin (169). Clinicians should also be aware of the potential for overbasalization with insulin therapy (i.e., use of higher than clinically necessary and appropriate dose of basal insulin, typically masking insufficient mealtime insulin). Clinical signals that should prompt evaluation for overbasalization include high bedtime-to-morning or preprandial-to-postprandial glucose differential (e.g., bedtime-to-morning glucose differential ≥50 mg/dL [≥2.8 mmol/L]), hypoglycemia (aware or unaware), and high glucose variability. Evidence of overbasalization should prompt reevaluation of the glucose-lowering treatment plan to better address postprandial hyperglycemia (170).

Combination Injectable Therapy and Prandial Insulin

If basal insulin has been titrated to an acceptable fasting blood glucose level and A1C remains above goal, if there is evidence of significant postprandial hyperglycemia, or if signs of overbasalization are present, advancement to combination injectable therapy is necessary (**Fig. 9.4**). This approach can use a GLP-1 RA or dual GIP and GLP-1 RA added to basal insulin or multiple doses of prandial insulin (131,171). If an individual is not already being treated with a GLP-1 RA or dual GIP and GLP-1 RA, a GLP-1 RA (either as an individual product or in a fixed-ratio combination with a basal insulin product) or dual GIP and GLP-1 RA should be considered prior to starting prandial insulin to address prandial management and to lower the risks of hypoglycemia and weight gain associated with insulin therapy (131,172).

Further intensification of insulin therapy entails adding doses of prandial insulin to basal insulin. Starting with a single prandial dose with the largest meal of the day is simple and effective, and it can be advanced to a plan with multiple prandial doses if necessary (173). We suggest starting with a prandial insulin dose of 4 units or 10% of the amount of basal insulin at the largest meal or the meal with the greatest postprandial excursion. The prandial insulin plan can then be intensified based on individual needs (**Fig. 9.4**). Alternatively, for an individual treated with basal insulin in whom additional prandial coverage is desired but administering insulin prior to one or more meals is not feasible, the medication plan can be converted to two doses of a premixed insulin. Each approach has advantages and disadvantages. For example, basal-prandial plans offer greater flexibility for individuals who eat on irregular schedules, have variable meal content, or otherwise benefit from greater individualization and flexibility in insulin administration. On the other hand, two doses of premixed insulin is a simple, convenient means of spreading insulin across the day. Moreover, human insulins, separately, self-mixed, or as premixed NPH/regular (for example, 70/30) formulations, are often less costly alternatives to insulin analogs.

Individuals with type 2 diabetes are generally more insulin resistant than those with type 1 diabetes, require higher daily doses (~1 unit/kg), and have lower rates of hypoglycemia (174). Meta-analyses of trials comparing rapid-acting insulin analogs with human regular insulin in type 2 diabetes have not reported meaningful differences in A1C or hypoglycemia (175,176). Titration of prandial insulin can be based on home self-monitored blood glucose or CGM. When significant additions to the prandial insulin dose are made, particularly with the evening meal, consideration should be given to decreasing basal insulin to reduce risk of hypoglycemia. When initiating intensification of insulin therapy, metformin, SGLT2 inhibitors, and GLP-1 RAs (or a dual GIP and GLP-1 RA) should be maintained, unless adverse effects (including significant treatment burden) or contraindications are present. Use of sulfonylureas, meglitinides, and DPP-4 inhibitors should be limited or discontinued, as these medications do not have additional beneficial effects on cardiovascular, kidney, weight, or liver outcomes and (for sulfonylureas and meglitinides) increase risk of hypoglycemia and weight gain. Adjunctive use of pioglitazone may help to improve glycemia and reduce the amount of insulin needed, although potential side effects should be considered.

Once a basal-bolus insulin plan is initiated, dose titration is important, with adjustments made in both prandial and basal insulins based on blood glucose levels and an understanding of the pharmacodynamic profile of each formulation (also known as pattern control or pattern management). In some people with type 2 diabetes with significant clinical complexity, multimorbidity, and/or treatment burden, it may become necessary to simplify or deintensify complex insulin plans to decrease risk of hypoglycemia and improve quality of life (see Section 13, "Older Adults").

Concentrated Insulins

Concentrated preparations may be more convenient (fewer injections to achieve goal dose) and comfortable (less volume to inject the desired dose and/or less injection effort) for individuals and may improve treatment plan engagement in those with insulin resistance who require large doses of insulin. Several concentrated insulin preparations are currently available. U-500 regular insulin is, by definition, five times more concentrated than U-100 regular insulin. U-500 regular insulin has distinct pharmacokinetics with similar onset but a delayed, blunted, and prolonged peak effect and longer duration of action compared with U-100 regular insulin; thus, it has characteristics more like a premixed intermediate-acting (NPH) and regular insulin product and can be used as two or three daily injections (177,178). U-300 glargine and U-200 degludec are three and two times, respectively, as concentrated as their U-100 formulations and allow higher doses of basal insulin administration per volume used. U-300 glargine has a longer duration of action

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than U-100 glargine but modestly lower efficacy per unit administered (179–181). The U-200 formulations of insulin degludec, insulin lispro, and insulin lispro-aabc have pharmacokinetics similar to those of their U-100 counterparts (182–184). While U-500 regular insulin is available in both prefilled pens and vials, other concentrated insulins are available only in prefilled pens to minimize the risk of dosing errors. If U-500 regular insulin vials are prescribed, the prescription should be accompanied by a prescription for U-500 syringes to minimize the risk of dosing errors.

Alternative Insulin Routes

Insulin is primarily administered via subcutaneous injection or infusion. Administration devices provide some additional variation in the subcutaneous delivery beyond vial and syringe versus insulin pen. Those devices include continuous insulin pumps (programmable or automated basal and bolus settings and fixed basal and bolus settings) and bolus-only insulin patch pump. In addition, prandial or correction insulin doses may be administered using inhaled human insulin. Inhaled insulin is available as monomers of regular human insulin; studies in individuals with type 1 diabetes suggest that inhaled insulin has pharmacokinetics similar to those of RAA (185). Studies comparing inhaled insulin with injectable insulin have demonstrated its faster onset and shorter duration compared with the RAA insulin lispro as well as clinically meaningful A1C reductions and weight reductions compared with the RAA insulin aspart over 24 weeks (186–188). Use of inhaled insulin may result in a decline in lung function (reduced forced expiratory volume in 1 s [FEV_1]). Inhaled insulin is contraindicated in individuals with chronic lung disease, such as asthma and chronic obstructive pulmonary disease, and is not recommended in individuals who smoke or who recently stopped smoking. All individuals require spirometry (FEV_1) testing to identify potential lung disease prior to and after starting inhaled insulin therapy.

ADDITIONAL RECOMMENDATIONS FOR ALL INDIVIDUALS WITH DIABETES

Recommendations

9.27 Monitor for signs of overbasalization during insulin therapy, such as significant bedtime-to-morning or postprandial-to-preprandial glucose differential, occurrences of hypoglycemia (aware or unaware), and high glycemic variability. When overbasalization is suspected, a thorough reevaluation should occur promptly to further tailor therapy to the individual's needs. **E**

9.28 Glucagon should be prescribed for all individuals requiring intensive insulin therapy or at high risk for hypoglycemia. Family, caregivers, school personnel, and others providing support to these individuals should know its location and be educated on how to administer it. Glucagon preparations that do not require reconstitution are preferred. **B**

9.29 Routinely assess all people with diabetes for financial obstacles that could impede their diabetes management. Clinicians, members of the diabetes care team, and social services professionals should work collaboratively, as appropriate and feasible, to support these individuals by implementing strategies to reduce costs, thereby improving their access to evidence-based care. **E**

9.30 In adults with diabetes and cost-related barriers, consider use of lower-cost medications for glycemic management (i.e., metformin, sulfonylureas, thiazolidinediones, and human insulin) within the context of their risks for hypoglycemia, weight gain, cardiovascular and kidney events, and other adverse effects. **E**

Several key aspects of insulin management that are relevant to all people with diabetes requiring insulin therapy, including available formulations, insulin plans and delivery systems, administration technique, and overbasalization, were discussed earlier in this section. Additional considerations for glucose-lowering therapy that may be relevant to people with all types of diabetes include glucagon coprescription and affordability of diabetes therapies.

Glucagon

Due to the risk of hypoglycemia with insulin treatment, all individuals treated with insulin or who are at high risk for hypoglycemia should be prescribed glucagon. Individuals with diabetes who are prescribed glucagon and those in close contact with them should be educated on the use and administration of the individual's prescribed glucagon product. The glucagon product available to individuals may differ based on coverage and cost; however, products that do not require reconstitution are preferred for ease of administration (189,190). Clinicians should routinely review the individual's access to glucagon, as appropriate glucagon prescribing is low (191–193). See Section 6, "Glycemic Goals and Hypoglycemia," for additional information on hypoglycemia and glucagon in individuals with diabetes.

Medication Costs and Affordability

Costs for noninsulin and insulin diabetes medications have increased dramatically over the past two decades, and an increasing proportion of cost is now passed on to people with diabetes and their families (194). **Table 9.3** provides cost information for currently approved noninsulin therapies, while **Table 9.4** provides these data for insulin. Of note, prices listed are average wholesale prices (AWP) (195) and National Average Drug Acquisition Costs (NADAC) (196); these estimates allow for a comparison of drug prices but do not represent the actual costs to people with diabetes because they do not account for various discounts, rebates, and other price adjustments often involved in prescription sales that affect the actual cost incurred by the individual. Medication costs can be a major source of stress for people with diabetes and contribute to worse medication-taking behavior (197); cost-reducing strategies may improve medication-taking behavior in some cases (198).

Although caps on out-of-pocket costs for insulin have been implemented for individuals with Medicare and for individuals on some commercial health plans, and three major insulin manufacturers have capped costs at $35 per month per insulin (199–202) (see Section 1, "Improving Care and Promoting Health in Populations"), individuals with high-deductible health plans and those without insurance coverage can incur very high out-of-pocket expenses for glucose-lowering therapies. Moreover, no such caps exist for diabetes durable medical equipment (i.e., equipment for glucose monitoring and insulin administration) or for

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noninsulin medications. It is therefore essential to screen all people with diabetes for financial concerns and cost-related barriers to care and to engage members of the health care team, including pharmacists, certified diabetes care and education specialists, social workers, community health workers, community paramedics, and others, to identify cost-saving opportunities for medications, diabetes durable medical equipment, and glucagon (203).

SPECIAL CIRCUMSTANCES AND POPULATIONS

Recommendations

9.31a Use of compounded products that are not approved by the FDA is not recommended due to uncertainty about their content and resulting concerns about safety, quality, and effectiveness. **E**

9.31b If a glucose-lowering medication is unavailable (e.g., in shortage), it is recommended to switch to a different FDA-approved medication with similar efficacy, as clinically appropriate. **E**

9.31c Upon resolution of the unavailability (e.g., shortage), reassess the appropriateness of resuming the original FDA-approved medication. **E**

9.32a Individuals with diabetes of childbearing potential should be counseled on contraception options **A** and the impact of some glucose-lowering medications on contraception efficacy. **C**

9.32b A person-centered shared decision-making approach to preconception planning is essential for all individuals with diabetes and of childbearing potential. **A** Preconception planning should address attainment of glycemic goals, **A** the time frame for discontinuing noninsulin glucose-lowering medications, **E** and optimal glycemic management in preparation for pregnancy. **A**

9.33 Educate individuals with diabetes who are at risk for developing diabetic ketoacidosis and/or follow a ketogenic eating pattern and who are treated with SGLT inhibitors on the risks and signs of ketoacidosis and methods of risk mitigation management, and provide them with appropriate tools for accurate ketone measurement (i.e., serum β-hydroxybutyrate). **E**

Therapeutic Strategies With Medication Unavailability

Health care professionals and people with diabetes struggle when medication supplies are insufficient to meet the demand. Recent examples of such circumstances include recalls involving a number of metformin products and the marked increase in demand for agents from the GLP-1 RA and dual GIP and GLP-1 RA classes. The latter circumstance led to such a low level of availability that products were determined by the FDA to be in shortage (204). To assist with supply of medications during the time they are in shortage (as signaled by their inclusion on the FDA Drug Shortages Database), compounding pharmacies and outsourcing compounding facilities are allowed to make copies, or products that are essentially duplicates of the marketed FDA-approved product (205). A significant number of concerning reports regarding safety and efficacy of compounded incretin products have emerged, however, including using salt forms of the FDA-approved product's active ingredient that are not proven safe or effective for use in humans, incorporation of additional ingredients not clinically tested when mixed with incretin products (e.g., vitamin B12 and vitamin B6), products provided in nonstandard concentrations and doses and/or multidose vials and prefilled syringes not accompanied by education or labeling to mitigate administration errors, and the emergence of counterfeit products that pose significant risk to individuals taking these products (206–209). Due to safety, quality, and effectiveness concerns, use of non–FDA-approved compounded products is not recommended (210). Instead, consider switching to a different FDA-approved medication as clinically appropriate (211). Once the desired FDA-approved product becomes available, individuals should be reassessed to determine the appropriateness of resuming the product based on their current care needs, preferences, and priorities.

Care Considerations for Individuals of Childbearing Potential

The impact of glycemia during pregnancy is well understood; however, evidence for the safe use of noninsulin glucose-lowering medications is limited (see Section 15, "Management of Diabetes in Pregnancy"). Studies on the efficacy and safety of glucose-lowering medications exclude individuals who are pregnant and require individuals of childbearing potential to use one or two forms of contraception. It is recommended that individuals of childbearing potential use a form of contraception when also taking glucose-lowering medications with unknown risks, limited evidence on safety, or known risks during pregnancy, regardless of the individual's intention to become pregnant, as many pregnancies are unplanned. The options for contraception should be discussed with all individuals of childbearing potential with diabetes and should include information regarding the potential impact of glucose-lowering medications on the effectiveness of contraception. Medications that impact gastrointestinal emptying time (e.g., GLP-1 RAs or dual GIP and GLP-1 RA) may affect the absorption of orally administered medications, including oral contraception. The impact on gastric emptying with GLP-1 RAs and the dual GIP and GLP-1 RA is highest at initiation and with dosage increases and then diminishes with continued administration (212). Tirzepatide, the dual GIP and GLP-1 RA, was shown to impact the levels of oral contraception during the time of its highest impact on gastric emptying; the GLP-1 RAs may impact the levels of oral contraception as well but to a lesser extent than tirzepatide (213,214). Thus, individuals starting or increasing doses of tirzepatide who also take oral contraception should use a second form of contraception until the maintenance dose of tirzepatide is achieved and used for at least 4 weeks (215).

Preconception counseling should be part of the routine care of individuals with diabetes who have childbearing potential. Counseling should include the known benefits and risks of glucose-lowering medications as well as other medications (e.g., lipid-lowering and antihypertensive therapies) during pregnancy and recommendations for when changes in medications should occur prior to pregnancy (see Section 15, "Management of Diabetes in Pregnancy," for more information on preconception counseling and glucose-lowering treatment during pregnancy).

Therapeutic Strategies for Individuals Receiving Cancer Treatment

Hyperglycemia due to chemotherapy may either be transient (improving upon treatment cessation) or represent permanent

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Table 9.3—Median monthly (30-day) AWP and NADAC of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

Class	Compound	Dosage strength/ product (if applicable)	Maximum approved daily dose†	Median AWP (min, max)*	Median NADAC (min, max)*
Biguanides	• Metformin	500 mg (ER)	2,000 mg	$89 ($5, $6,719)	$3 ($3, $79)
		850 mg (IR)	2,550 mg	$108 ($4, $189)	$2
		1,000 mg (IR)	2,000 mg	$87 ($3, $146)	$1
		1,000 mg (ER)	2,000 mg	$1,884 ($242, $7,214)	$26 ($21, $31)
		500 mg (Sol)	2,000 mg	$1,144 ($810, $1478)	$427
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	8 mg	$73 ($71, $198)	$2
	• Glipizide	10 mg (IR)	40 mg	$72 ($67, $91)	$5
		10 mg (XL/ER)	20 mg	$48 ($46, $48)	$8
	• Glyburide	6 mg (micronized)	12 mg	$54 ($48, $71)	$13
		5 mg	20 mg	$82 ($63, $432)	$7
Thiazolidinedione	• Pioglitazone	45 mg	45 mg	$348 ($7, $349)	$3
α-Glucosidase inhibitors	• Acarbose	100 mg	300 mg	$106 ($104, $378)	$20
	• Miglitol	100 mg	300 mg	$294 ($241, $346)	$320
Meglitinides	• Nateglinide	120 mg	360 mg	$155	$23
	• Repaglinide	2 mg	16 mg	$878 ($799, $897)	$26
DPP-4 inhibitors	• Alogliptin	25 mg	25 mg	$234	$145
	• Linagliptin	5 mg	5 mg	$630	$503
	• Saxagliptin	5 mg	5 mg	$524 ($523, $524)	$165
	• Sitagliptin	100 mg	100 mg	$588	$550
SGLT2 inhibitors	• Bexagliflozin	20 mg	20 mg	$47	NA
	• Canagliflozin	300 mg	300 mg	$718	$574
	• Dapagliflozin	10 mg	10 mg	$664	$352
	• Empagliflozin	25 mg	25 mg	$733	$586
	• Ertugliflozin	15 mg	15 mg	$428	$343
GLP-1 RAs	• Dulaglutide	4.5 mg pen	4.5 mg‡	$1,173	$941
	• Exenatide	10 mg pen	20 mg	$1,020	$818
	• Exenatide (ER)	2 mg pen	2 mg‡	$993	$1,101
	• Liraglutide	18 mg/3 mL pen	1.8 mg	$929	$1,077
	• Semaglutide	2 mg pen	2 mg‡	$1,162	$933
		14 mg (tablet)	14 mg	$1,162	$933
Dual GIP and GLP-1 RA	• Tirzepatide	15 mg pen	15 mg‡	$1,283	$1,030
Bile acid sequestrant	• Colesevelam	625 mg tabs	3.75 g	$692 ($674, $712)	$47
		3.75 g suspension	3.75 g	$674 ($673, $675)	$115
Dopamine-2 agonist	• Bromocriptine	0.8 mg	4.8 mg	$1,220	$981
Amylin mimetic	• Pramlintide	120 μg pen	120 μg§	$2,952	NA

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; max, maximum; min, minimum; NA, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium–glucose cotransporter 2. AWP (195) and NADAC (196) prices are as of 1 July 2024. *Calculated for 30-day supply (AWP or NADAC unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price. †Used to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. ‡Administered once weekly. §AWP and NADAC calculated based on 120 μg three times daily.

diabetes. Immune checkpoint inhibitors (ICIs) (agents that block programmed cell death protein 1 [PD-1] and programmed cell death protein ligand 1 [PD-L1]) suppress physiologic blocks on immune responses, which can result in autoimmune toxicities, including autoimmune diabetes (incidence approximately ≤1%). ICI-diabetes is an insulin-deficient phenotype that presents as acute severe hyperglycemia or DKA and appears to occur more abruptly than type 1 diabetes (216–218).

Alpelisib, a phosphatidylinositol-3-kinase (PI3K) inhibitor, frequently results in hyperglycemia by inhibiting PI3Kα, which systemically blocks the intracellular action of insulin, resulting in a transient state of insulin resistance and hyperglycemia (219). Hyperglycemia occurs early during therapy (median time of onset of about 2 weeks from initiation of alpelisib) with an incidence of ∼60% overall and typically resolves upon treatment cessation (220–222). Metformin is the first-line oral agent to treat alpelsib-induced hyperglycemia, and prophylactic initiation of metformin has been recommended for people with prediabetes receiving alpelsib (223). SGLT2 inhibitors and pioglitazone are appropriate second- or third-line agents, depending on side effect and clinical profiles, and may be used in combination with or without metformin. Insulin and sulfonylureas should be considered last-line agents, as insulin can reactivate the PI3K pathway, negating the effects of alpelisib (223,224).

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Table 9.4—Median cost of insulin products in the U.S. calculated as AWP and NADAC per 1,000 units of specified dosage form or product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC (min, max)*
Rapid-acting	• Aspart	U-100 vial	$87†	$70†
		U-100 cartridge	$107†	$86†
		U-100 prefilled pen	$112†	$90†
	• Aspart ("faster acting product")	U-100 vial	$347	$278
		U-100 cartridge	$430	$344
		U-100 prefilled pen	$447	$357
	• Glulisine	U-100 vial	$102	$82
		U-100 prefilled pen	$132	$105
	• Inhaled insulin	Inhalation cartridges	$1,503	$1,298
	• Lispro	U-100 vial	$30†	$24†
		U-100 cartridge	$123	$98
		U-100 prefilled pen	$127†	$102†
		U-200 prefilled pen	$424	$339
	• Lispro-aabc	U-100 vial	$330	$263
		U-100 prefilled pen	$424	$339
		U-200 prefilled pen	$424	$339
	• Lispro follow-on product	U-100 vial	$118	$94
		U-100 prefilled pen	$151	$121
Short-acting	• Human regular	U-100 vial	$58 ($54, $58)‡	$46 ($43, $58)‡
		U-100 prefilled pen	$73 ($54, $178)	$58
Intermediate-acting	• Human NPH	U-100 vial	$58 ($54, $58)‡	$45 ($43, $46)‡
		U-100 prefilled pen	$93 ($73, $113)	$74 ($58, $91)
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$142
		U-500 prefilled pen	$230	$184
Long-acting	• Degludec	U-100 vial	$142†	$114†
		U-100 prefilled pen	$142†	$114†
		U-200 prefilled pen	$85†	$114†
	• Glargine	U-100 vial	$77	$109†
		U-100 prefilled pen	$77	$109†
		U-300 prefilled pen	$152†	$122†
	• Glargine biosimilar/follow-on products	U-100 vial	$118 ($76,† $323)	$61†
		U-100 prefilled pen	$118 ($74,† $323)	$59 ($59,† $209)
Premixed insulin products	• Aspart 70/30	U-100 vial	$87†‡	$69†‡
		U-100 prefilled pen	$112†‡	$90†‡
	• Lispro 50/50	U-100 vial	$102	NA
		U-100 prefilled pen	$127	$102
	• Lispro 75/25	U-100 vial	$102	$82
		U-100 prefilled pen	$127†	$102†
	• NPH/regular 70/30	U-100 vial	$58 ($54, $58)	$45 ($43, $46)
		U-100 prefilled pen	$73 ($73, $113)‡	$74 ($58, $90)‡
Premixed insulin/GLP-1 RA products	• Degludec/liraglutide	100/3.6 mg prefilled pen	$1,037	$791
	• Glargine/lixisenatide	100/33 mg prefilled pen	$713	$570

AWP, average wholesale price; GLP-1 RA, glucagon-like peptide 1 receptor agonist; NA, data not available; NADAC, National Average Drug Acquisition Cost. AWP (195) and NADAC (196) prices as of 1 July 2024. *AWP or NADAC calculated as in **Table 9.3**. †Unbranded product prices used when available. ‡AWP and NADAC data presented do not include human insulins (approximately $25/vial or $43/box of 5 pens) or select analog insulins (approximately $73/vial or $86/box of 5 pens) available at Walmart; median listed alone when only one product and/or price.

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mTOR kinase inhibitors, including everilomus, cause hyperglycemia by interfering with insulin signaling, leading to impaired insulin secretion and increased insulin resistance. Metformin is the first-line treatment of hyperglycemia secondary to mTOR inhibitor treatment, with insulin and other noninsulin treatments added in a stepwise fashion dependent on glucose level (225).

Therapeutic Strategies for Individuals With Other Types of Diabetes

Individuals with pancreatogenic diabetes may require early insulin initiation to achieve and maintain glycemic goals. In

individuals with a history of pancreatitis, use of incretin medications (i.e., GLP-1 RAs, GIP and GLP-1 RA, and DPP-4 inhibitors) should be avoided (see Section 2, "Diagnosis and Classification of Diabetes"). Individuals with cystic fibrosis–related diabetes should be treated with insulin therapy; insulin pump therapy, including automated insulin delivery systems, should be considered when appropriate (226).

There are limited data to inform the optimal pharmacologic management of posttransplant diabetes (227) (see Section 2, "Diagnosis and Classification of Diabetes"). While immediately posttransplant many individuals require insulin therapy, noninsulin therapies can be used for long-term management. Studies of metformin, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 RAs, and pioglitazone in individuals who have undergone kidney, heart, or liver transplantation have demonstrated effectiveness and safety but are limited by small sample sizes, short follow-up, and risk of bias due to retrospective or single-arm prospective designs (228). Metformin should be used with caution; it should not be initiated if eGFR is $<$45 mL/min/1.73 m^2, it should be stopped with eGFR $\geq$30 mL/min/1.73 m^2, and it should not be used in the setting of clinical instability due to concerns for acute kidney injury and lactic acidosis. Metformin use may be associated with lower risks of cardiac allograph vasculopathy after heart transplantation (229) and all-cause, malignancy-related, and infection-related mortality after kidney transplantation (230). GLP-1 RA therapy may be preferred for many individuals due to the demonstrated benefit of GLP-1 RAs on cardiovascular, kidney, weight, and liver outcomes. Studies have not found evidence of drug interaction with immunosuppression, including finding no changes in dosing or toxicity (231–233). SGLT2 inhibitors may be similarly preferred for individuals with ASCVD, HF, and CKD and appear to be safe and effective in posttransplantation diabetes. However, there is increased risk of genitourinary tract infection, which is a concern in individuals receiving immunosuppression and in those who have undergone kidney transplantation.

Individuals with maturity-onset diabetes of the young due to *HNF1A* and *HNF4A* mutations can be treated with low-dose sulfonylurea therapy but may ultimately require insulin therapy (234) (see Section 2, "Diagnosis and Classification of Diabetes") (**Table 2.7**). For those with *HNF1A* mutations, addition of a DPP-4 inhibitor to the sulfonylurea may help improve glycemic variability and attainment of glycemic goals (235). Individuals with neonatal diabetes due to *KCNJ22* and *ABCC8* mutations can be treated with high-dose sulfonylureas, while those with *INS*, *GATA6*, *EIF2AK3*, and *FOXP3* mutations require insulin therapy (234).

SGLT Inhibition and Risk of Ketosis

Individuals with type 1 diabetes (84,236) and insulin-deficient type 2 diabetes are at increased risk for DKA with SGLT inhibitor therapy. SGLT inhibitor–associated DKA occurs in approximately 4% of people with type 1 diabetes; the risk can be 5–17 times higher than that in people with T1D not treated with SGLT inhibitors (237). It is important to note that SGLT2 inhibitors are not approved for use in people with type 1 diabetes. In contrast, DKA is uncommon in people with type 2 diabetes treated with SGLT inhibitors, with an estimated incidence of 0.6–4.9 events per 1,000 person-years (238). Risk factors for DKA in individuals with either type 1 or type 2 diabetes treated with SGLT inhibitors include very-low-carbohydrate diets, prolonged fasting, dehydration, excessive alcohol intake, and other common precipitating factors (84,236). Up to a third of people treated with SGLT2 inhibitors who developed DKA present with glucose levels $<$200 mg/dL (11.1 mmol/L) (239), and in one study 71% presented with glucose levels $\leq$250 mg/dL (13.9 mmol/L) (240); therefore, it is important to educate at-risk individuals about the signs and symptoms of DKA and DKA mitigation and management and to prescribe accurate tools for ketone measurement. Individuals who have experienced DKA should not be treated with SGLT inhibition. Additional guidance on DKA risk mitigation is available in Section 6, "Glycemic Goals and Hypoglycemia."

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10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, "Children and Adolescents."

Atherosclerotic cardiovascular disease (ASCVD) broadly refers to a history of acute coronary syndrome, myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease (PAD) including aortic aneurysm and is the leading cause of morbidity and mortality in people with diabetes (1). Diabetes itself confers independent ASCVD risk, and among people with diabetes, all major cardiovascular risk factors, including hypertension, hyperlipidemia, and obesity, are clustered and common (2). Numerous studies have shown the efficacy of managing individual cardiovascular risk factors in preventing or slowing ASCVD in people with diabetes. Furthermore, large benefits are seen when multiple cardiovascular risk factors (glycemic, blood pressure, and lipid management) are addressed simultaneously, with evidence for long-lasting benefits (3–5). Notably, most of the evidence supporting interventions to reduce cardiovascular risk in diabetes comes from trials of people with type 2 diabetes. No randomized trials have been specifically designed to assess the impact of cardiovascular risk reduction strategies in people with type 1 diabetes. Therefore, the recommendations for cardiovascular risk factor modification for people with type 1 diabetes are extrapolated from data obtained in people with type 2 diabetes and are similar to those for people with type 2 diabetes.

Under the current paradigm of comprehensive risk factor modification, cardiovascular morbidity and mortality have notably decreased in people with both type 1 and type 2 diabetes (1). In addition to the evidence from prospective intervention studies to support comprehensive ASCVD risk factor reduction, a large cohort study confirmed no or only marginally increased mortality, MI, and stroke risk compared with the general population when all major cardiovascular risk factors are managed to goal levels in people with type 2 diabetes (6). Despite these encouraging opportunities to reduce morbidity and mortality, cardiovascular risk factors are predicted to

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.*

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increase and only a minority of people with type 2 diabetes achieve recommended risk factor goals and are treated with guideline-recommended therapy (7–9). Therefore, continued focus on delivering high-quality comprehensive cardiovascular care and on addressing barriers to risk factor management are required to implement the treatment recommendations (1,10) outlined in this section.

Diabetes is also an important risk factor for incident heart failure, which is at least twofold more prevalent in people with diabetes compared with those without diabetes and is a major cause of morbidity and mortality (11). People with diabetes may present with a wide spectrum of heart failure, including heart failure with preserved ejection fraction (HFpEF), heart failure with mildly reduced ejection fraction (HFmEF), or heart failure with reduced ejection fraction (HFrEF) (12). Comorbid conditions including excess body weight and hypertension often precede the development of HFpEF and have been implicated in the pathophysiology of HFpEF (13). Coronary artery disease and prior MI are major risk factors and a cause of myocardial injury in ischemic heart disease leading to HFrEF. In addition, people with diabetes are at risk for developing structural heart disease and HFrEF in the absence of obstructive coronary artery disease (14). The pathophysiology of heart failure in people with diabetes and further details of screening, diagnosis, and treatment of people with heart failure and diabetes are also outlined in a previous consensus statement by the American Diabetes Association (ADA) (15).

There is an increasing appreciation of the common pathophysiology and interrelationship of cardiometabolic risk factors leading to both adverse cardiovascular and adverse kidney outcomes in people with diabetes, including ASCVD, heart failure, and chronic kidney disease (CKD) (16). These three comorbidities are frequently caused by metabolic risk, which is frequently driven by obesity and its associated risk factors, and the incidence of all three conditions rises with increasing A1C levels (17). Collectively, this combination of comorbidities has been termed cardiorenal metabolic disease or cardiovascular-kidney-metabolic health (18,19). Reasons to concurrently consider cardiovascular and kidney comorbidities in the management of people with diabetes include not only the common metabolic risk but also the major benefit observed across the spectrum of cardiovascular disease, heart failure, and renal outcomes in people with type 2 diabetes treated with sodium–glucose cotransporter 2 (SGLT2) inhibitors or glucagon-like peptide 1 receptor agonists (GLP-1 RAs). Therefore, in addition to the management of hyperglycemia, hypertension, and hyperlipidemia, treatment with SGLT2 inhibitors and/or GLP-1 RAs that have demonstrated benefit is considered a fundamental element of risk reduction and the pharmacological strategy to improve cardiovascular and kidney outcomes in people with type 2 diabetes (**Fig. 10.1**). In addition to the standards of care for the prevention and treatment of cardiovascular disease outlined below, the reader is referred to Section 9, "Pharmacologic Approaches to

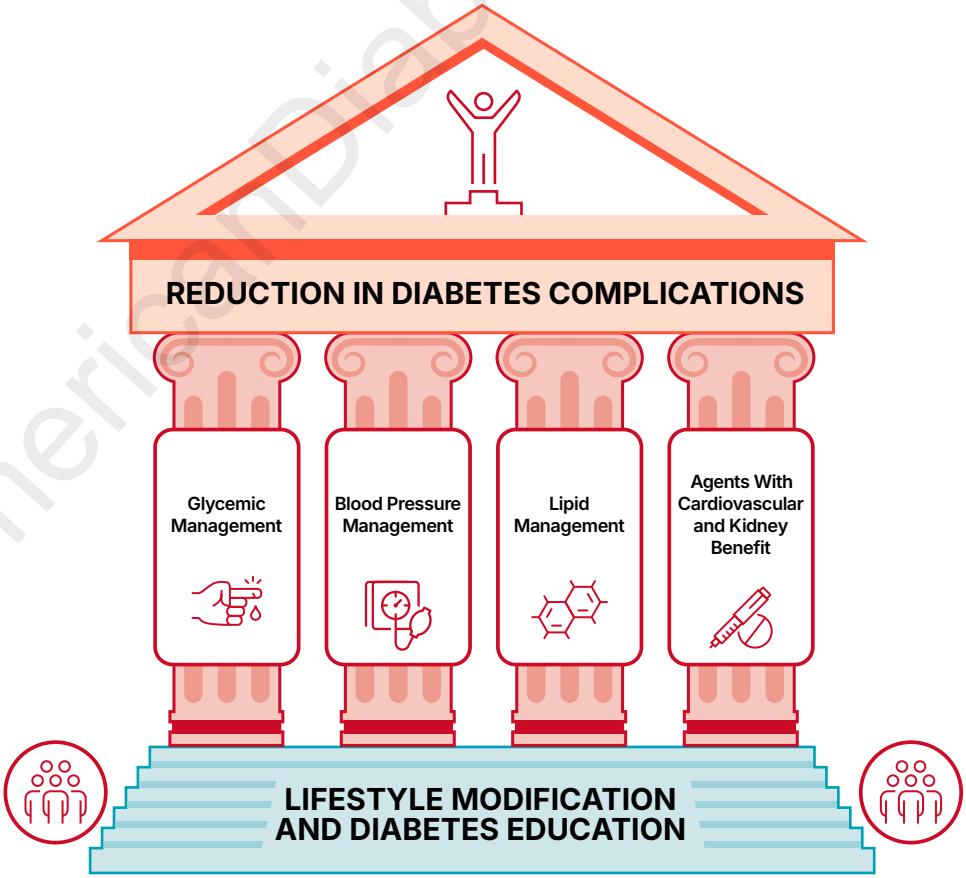

Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications.

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Glycemic Treatment," and Section 11, "Chronic Kidney Disease and Risk Management," for a comprehensive review of pharmacological management of hyperglycemia and kidney benefit from SGLT2 inhibitors and GLP-1 RAs.

HYPERTENSION AND BLOOD PRESSURE MANAGEMENT

An elevated blood pressure is defined as a systolic blood pressure 120–129 mmHg and a diastolic blood pressure <80 mmHg (20). Hypertension is defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥80 mmHg (20). This is in agreement with the definition of hypertension by the American College of Cardiology and American Heart Association (20). Hypertension is common among people with either type 1 or type 2 diabetes. Hypertension is a major risk factor for ASCVD, heart failure, and microvascular complications. Moreover, numerous studies have shown that antihypertensive therapy reduces ASCVD events, heart failure, and microvascular complications. Please refer to the ADA position statement "Diabetes and Hypertension" for a detailed review of the epidemiology, diagnosis, and treatment of hypertension (21) and hypertension guideline recommendations (22–25).

Screening and Diagnosis

Recommendations

10.1 Blood pressure should be measured at every routine clinical visit, or at least every 6 months. Individuals found to have elevated blood pressure without a diagnosis of hypertension (systolic blood pressure 120–129 mmHg and diastolic blood pressure <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. **A** Hypertension is defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥80 mmHg based on an average of two or more measurements obtained on two or more occasions. **A** Individuals with blood pressure ≥180/110 mmHg and cardiovascular disease could be diagnosed with hypertension at a single visit. **E**

10.2 Counsel all people with hypertension and diabetes to monitor their blood pressure at home after appropriate education. **A**

Blood pressure should be measured at every routine clinical visit by a trained individual who should follow the guidelines established for the general population: measurement in the seated position, with feet on the floor and arm supported at heart level, after 5 min of rest. Cuff size should be appropriate for the upper-arm circumference (26). Individuals identified to have elevated blood pressure or hypertension should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. However, in individuals with cardiovascular disease and blood pressure ≥180/110 mmHg, it is reasonable to diagnose hypertension at a single visit (22). Postural changes in blood pressure and pulse may be evidence of autonomic neuropathy and therefore require adjustment of blood pressure goals. Orthostatic blood pressure measurements should be checked on initial visit and as indicated.

Home blood pressure self-monitoring and 24-h ambulatory blood pressure monitoring may provide evidence of white coat hypertension, masked hypertension, or other discrepancies between office and true blood pressure (27,28). In addition to confirming or refuting a diagnosis of hypertension, home blood pressure assessment may be useful to monitor antihypertensive treatment. A systematic review and meta-analysis of prospective studies concluded that blood pressure measurements from either 24-h ambulatory or home blood pressure measurements can predict cardiovascular risk (27–29). Moreover, home blood pressure monitoring may improve medication-taking behavior and thus help reduce cardiovascular risk (30).

Treatment Goals

Recommendations

10.3 For people with diabetes and hypertension, blood pressure goals should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and individual preferences. **B**

10.4 The on-treatment blood pressure goal is <130/80 mmHg, if it can be safely attained. **A**

10.5 In pregnant individuals with diabetes and chronic hypertension, a blood pressure threshold of 140/90 mmHg for initiation or titration of therapy is associated with better pregnancy outcomes than reserving treatment for severe hypertension, with no increase in risk of small-for-gestational-age birth weight. **A** There are limited data on the optimal lower limit, but therapy should be deintensified for blood pressure <90/60 mmHg. **E** A blood pressure goal of 110–135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension. **A**

Randomized clinical trials have demonstrated unequivocally that treatment of hypertension reduces cardiovascular events as well as microvascular complications (31–37). There has been controversy on the recommendation of a specific blood pressure goal in people with diabetes. The committee recognizes that there has been no randomized controlled trial to specifically demonstrate a decreased incidence of cardiovascular events in people with diabetes by achieving a blood pressure <130/80 mmHg. The recommendation to support a blood pressure goal of <130/80 mmHg in people with diabetes is consistent with guidelines from the American College of Cardiology and American Heart Association (21), the International Society of Hypertension, and Europe European Society of Cardiology/European Society of Hypertension Blood Pressure/Hypertension Guidelines (24). The committee's recommendation for the blood pressure goal of <130/80 mmHg derives primarily from the collective evidence of the following randomized controlled trials. The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that treatment to a goal systolic blood pressure of <120 mmHg decreases cardiovascular event rates by 25% in high-risk individuals, although people with diabetes were excluded from this trial (38). The Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial included nearly 20% of people with diabetes and noted decreased cardiovascular events with treatment of hypertension to a systolic blood pressure goal of <130 mmHg (39). While the ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial

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(ACCORD BP) did not confirm that aiming for a systolic blood pressure <120 mmHg in people with diabetes results in decreased cardiovascular event rates, the prespecified secondary outcome of stroke was reduced by 41% with intensive treatment (40). The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial revealed that treatment with perindopril and indapamide to an achieved systolic blood pressure of ~135 mmHg significantly decreased cardiovascular event rates compared with a placebo treatment with an achieved blood pressure of 140 mmHg (41). Therefore, it is recommended that people with diabetes who have hypertension should be treated to blood pressure goals of <130/80 mmHg. Notably, there is an absence of high-quality data available to guide blood pressure goals in people with type 1 diabetes, but a similar blood pressure goal of <130/80 mmHg is recommended in people with type 1 diabetes. As discussed below, treatment should be individualized, and treatment goals should not be set to achieve <120/80 mmHg, as a mean achieved blood pressure <120/80 mmHg is associated with adverse events. For more information on individualized blood pressure goals in older individuals, please see Section 13, "Older Adults."

Randomized Controlled Trials of Intensive Versus Standard Blood Pressure Management

SPRINT provides the strongest evidence to support lower blood pressure goals in individuals at increased cardiovascular risk, although this trial excluded people with diabetes (38). The trial enrolled 9,361 individuals with a systolic blood pressure of ≥130 mmHg and increased cardiovascular risk and treated to a systolic blood pressure goal of <120 mmHg (intensive treatment) versus a goal of <140 mmHg (standard treatment). The primary composite outcome of MI, coronary syndromes, stroke, heart failure, or death from cardiovascular causes was reduced by 25% in the intensive treatment group. The achieved systolic blood pressures in the trial were 121 mmHg and 136 mmHg in the intensive versus standard treatment group, respectively. Adverse outcomes, including hypotension, syncope, electrolyte abnormality, and acute kidney injury (AKI), were more common in the intensive treatment arm; risk of adverse outcomes needs to be weighed against the cardiovascular benefit of more intensive blood pressure lowering.

ACCORD BP provides the strongest direct assessment of the benefits and risks of intensive blood pressure management in people with type 2 diabetes (40). In the study, a total of 4,733 individuals with type 2 diabetes were assigned to intensive therapy (aiming for a systolic blood pressure <120 mmHg) or standard therapy (aiming for a systolic blood pressure <140 mmHg). The mean achieved systolic blood pressures were 119 mmHg and 133 mmHg in the intensive and standard groups, respectively. The primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes was not significantly reduced in the intensive treatment group. The prespecified secondary outcome of stroke was significantly reduced by 41% in the intensive treatment group. Adverse events attributed to blood pressure treatment, including hypotension, syncope, bradycardia, hyperkalemia, and elevations in serum creatinine, occurred more frequently in the intensive treatment arm than in the standard therapy arm.

Of note, the ACCORD BP and SPRINT trials aimed for a similar systolic blood pressure <120 mmHg, but in contrast to SPRINT, the primary composite cardiovascular end point was nonsignificantly reduced in ACCORD BP. The results have been interpreted to be generally consistent between the two trials, but ACCORD BP was viewed as underpowered due to the composite primary end point being less sensitive to blood pressure regulation (38,40).

The more recent STEP trial assigned 8,511 individuals aged 60–80 years with hypertension to a systolic blood pressure goal of 110 to <130 mmHg (intensive treatment) or a goal of 130 to <150 mmHg (37). In this trial, the primary composite outcome of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes occurred in 3.5% of individuals in the intensive treatment group versus 4.6% in the standard treatment group (hazard ratio [HR] 0.74 [95% CI 0.60–0.92]; $P = 0.007$). In this trial, 18.9% of individuals in the intensive treatment arm and 19.4% in the standard treatment arm had a diagnosis of type 2 diabetes. Hypotension occurred more frequently in the intensive treatment group (3.4%) compared with the standard treatment group (2.6%) without significant differences in other adverse events, including dizziness, syncope, or fractures. For more information on hypotensive events in older adults, please see Section 13, "Older Adults."

In ADVANCE, 11,140 people with type 2 diabetes were randomized to receive either treatment with a fixed combination of perindopril and indapamide or matching placebo (41). The primary end point, a composite of cardiovascular death, nonfatal stroke or MI, or new or worsening renal or eye disease, was reduced by 9% in the combination treatment. The achieved systolic blood pressure was ~135 mmHg in the treatment group and 140 mmHg in the placebo group.

The Hypertension Optimal Treatment (HOT) trial enrolled 18,790 individuals and aimed for a diastolic blood pressure <90 mmHg, <85 mmHg, or <80 mmHg (42). The cardiovascular event rates, defined as fatal or nonfatal MI, fatal and nonfatal strokes, and all other cardiovascular events, were not significantly different between diastolic blood pressure goals (≤90 mmHg, ≤85 mmHg, and ≤80 mmHg), although the lowest incidence of cardiovascular events occurred with an achieved diastolic blood pressure of 82 mmHg. However, in people with diabetes, there was a significant 51% reduction in the treatment group with a goal diastolic blood pressure of <80 mmHg compared with a goal diastolic blood pressure of <90 mmHg.

Meta-analyses of Trials

To clarify optimal blood pressure goals in people with diabetes, multiple meta-analyses have been performed. One of the largest meta-analyses included 73,913 people with diabetes. Compared with a less intensive blood pressure management, allocation to a tighter blood pressure management significantly reduced the risk of stroke by 31% but did not reduce the risk of MI (43). Another meta-analysis of 19 trials that included 44,989 individuals showed that a mean blood pressure of 133/76 mmHg is associated with a 14% risk reduction for major cardiovascular events compared with a mean blood pressure of 140/81 mmHg (37). This benefit was greatest in people with diabetes. An analysis of trials including people with type 2 diabetes and

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impaired glucose tolerance with achieved systolic blood pressures of <135 mmHg in the intensive blood pressure treatment group and <140 mmHg in the standard treatment group revealed a 10% reduction in all-cause mortality and a 17% reduction in stroke (35). More intensive reduction to <130 mmHg was associated with a further reduction in stroke but not other cardiovascular events.

Several meta-analyses stratified clinical trials by mean baseline blood pressure or mean blood pressure attained in the intervention (or intensive treatment) arm. Based on these analyses, antihypertensive treatment appears to be most beneficial when mean baseline blood pressure is ≥140/90 mmHg (20,31,32,34–36). Among trials with lower baseline or attained blood pressure, antihypertensive treatment reduced the risk of stroke, retinopathy, and albuminuria, but effects on other ASCVD outcomes and heart failure were not evident. A recent systematic review and meta-analysis of nine trials enrolling 11,005 participants with type 2 diabetes reported that intensive blood pressure lowering resulted in a reduction in risk of stroke (risk ratio 0.64 [95% CI 0.52–0.79]) and macroalbuminuria (0.77 [0.63–0.93) with a posttreatment blood pressure of 125/73 mmHg, suggesting that blood pressure goals could be lowered from the current recommendations of 130/80 mmHg if tolerated (44).

Individualization of Treatment Goals

People with diabetes and clinicians should engage in a shared decision-making process to determine individual blood pressure goals (20). This approach acknowledges that the benefits and risks of intensive blood pressure goals are uncertain and may vary across individuals and is consistent with a person-focused approach to care that values individual priorities and health care professional judgment (45). Secondary analyses of ACCORD BP and SPRINT suggest that clinical factors can help identify individuals more likely to benefit from and less likely to be harmed by intensive blood pressure management (46,47).

Absolute benefit from blood pressure reduction correlated with absolute baseline cardiovascular risk in SPRINT and in earlier clinical trials conducted at higher baseline blood pressure levels (47,48). Extrapolation of these studies suggests that people with diabetes may also be more likely to benefit from intensive blood pressure management when they have high absolute cardiovascular risk. This approach is consistent with guidelines from the American College of Cardiology and American Heart Association, which also advocate a blood pressure goal of <130/80 mmHg for all people, with or without diabetes (21).

Potential adverse effects of antihypertensive therapy (e.g., hypotension, syncope, falls, AKI, and electrolyte abnormalities) should also be taken into account (38,40,49,50). Older individuals and those with CKD and frailty have been shown to be at higher risk of adverse effects of intensive blood pressure management (49). In addition, individuals with orthostatic hypotension, substantial comorbidity, functional limitations, or polypharmacy may be at high risk of adverse effects, and some individuals may prefer higher blood pressure goals to enhance quality of life. However, ACCORD BP demonstrated that intensive blood pressure lowering decreased the risk of cardiovascular events irrespective of baseline diastolic blood pressure in individuals who also received standard glycemic management (51). Therefore, the presence of low diastolic blood pressure is not necessarily a contraindication to more intensive blood pressure management in the context of otherwise standard care.

Pregnancy and Antihypertensive Medications

There are few randomized controlled trials of antihypertensive therapy in pregnant individuals with diabetes. A 2018 Cochrane systematic review of antihypertensive therapy for mild to moderate chronic hypertension included 63 trials and over 5,909 women and suggested that antihypertensive therapy probably reduces the risk of developing severe hypertension but may not affect the risk of fetal or neonatal death, small-for-gestational-age babies, or preterm birth (52). The Control of Hypertension in Pregnancy Study (CHIPS) (53) enrolled mostly women with chronic hypertension. In CHIPS, aiming for a diastolic blood pressure of 85 mmHg during pregnancy was associated with reduced likelihood of developing accelerated maternal hypertension and no demonstrable adverse outcome for infants compared with aiming for a higher diastolic blood pressure. The mean systolic blood pressure achieved in the more intensively treated group was 133.1 ± 0.5 mmHg, and the mean diastolic blood pressure achieved in that group was 85.3 ± 0.3 mmHg. A similar approach is supported by the International Society for the Study of Hypertension in Pregnancy, which specifically recommends use of antihypertensive therapy to maintain systolic blood pressure between 110 and 140 mmHg and diastolic blood pressure between 80 and 85 mmHg (54).

The more recent Chronic Hypertension and Pregnancy (CHAP) trial assigned pregnant individuals with mild chronic hypertension to antihypertensive medications to achieve a blood pressure goal of <140/90 mmHg (active treatment group) or to control treatment, in which antihypertensive therapy was withheld unless severe hypertension (systolic pressure ≥160 mmHg or diastolic pressure ≥105 mmHg) developed (control group) (55). The primary outcome, a composite of preeclampsia with severe features, medically indicated preterm birth at <35 weeks of gestation, placental abruption, or fetal or neonatal death, occurred in 30.2% of female participants in the active treatment group versus 37.0% in the control group ($P < 0.001$). The mean systolic blood pressure between randomization and delivery was 129.5 mmHg in the active treatment group and 132.6 mmHg in the control group. There are subtle difference in recommendations by different guidelines; however, internationally, the majority of hypertension societies endorse a more aggressive approach, recommending therapy when blood pressure is ≥140/90 mmHg and attaining a therapeutic goal of 130/80 mmHg (56).

Current evidence supports managing blood pressure to 110–135/85 mmHg to reduce the risk of accelerated maternal hypertension and to minimize impairment of fetal growth. During pregnancy, treatment with ACE inhibitors, angiotensin receptor blockers (ARBs), direct renin inhibitors, mineralocorticoid receptor antagonists (MRAs), and neprilysin inhibitors are contraindicated, as they may cause fetal damage. Special consideration should be taken for individuals of childbearing potential, and people intending to become pregnant should switch from an ACE inhibitor or ARB, renin inhibitor, MRA, or neprilysin inhibitor to an alternative antihypertensive medication approved during pregnancy. Antihypertensive drugs known

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to be effective and safe in pregnancy include methyldopa, labetalol, and long-acting nifedipine, while hydralazine may be considered in the acute management of hypertension in pregnancy or severe preeclampsia (56). Diuretics are not recommended for blood pressure management in pregnancy but may be used during late-stage pregnancy if needed for volume management (56). The American College of Obstetricians and Gynecologists also recommends that, postpartum, individuals with gestational hypertension, preeclampsia, and superimposed preeclampsia have their blood pressures observed for 72 h in the hospital and 7–10 days postpartum. Long-term follow-up is recommended for these individuals, as they have increased lifetime cardiovascular risk (57). See Section 15, "Management of Diabetes in Pregnancy," for additional information.

Treatment Strategies

Lifestyle Intervention

Recommendation

10.6 For people with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)–style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, smoking cessation, and increased physical activity. **A**

Lifestyle management is an important component of hypertension treatment because it lowers blood pressure, enhances the effectiveness of some antihypertensive medications, promotes other aspects of metabolic and vascular health, and generally leads to few adverse effects. Lifestyle therapy consists of reducing excess body weight through caloric restriction (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes"), at least 150 min of moderate-intensity aerobic activity per week (see Section 3, "Prevention or Delay of Diabetes and Associated Comorbidities"), restricting sodium intake (<2,300 mg/day), increasing consumption of fruits and vegetables (8–10 servings per day) and low-fat dairy products (2–3 servings per day), avoiding excessive alcohol consumption (no more than 2 servings per day in men and no more than 1 serving per day in women) (58), and increasing activity levels (59) (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes"). A systematic review of 10 randomized controlled trials reported that compared with control diet, the modified Dietary Approaches to Stop Hypertension (DASH) eating pattern could reduce mean systolic (−3.26 mmHg [95% CI −5.58 to −0.94 mmHg]; P = 0.006) and diastolic (−2.07 mmHg [95% CI −3.68 to −0.46 mmHg]; P = 0.01) blood pressure (60).

These lifestyle interventions are reasonable for individuals with diabetes and mildly elevated blood pressure (systolic >120 mmHg or diastolic >80 mmHg) and should be initiated along with pharmacologic therapy when hypertension is diagnosed (**Fig. 10.2**) (59). A lifestyle therapy plan should be developed in collaboration with the person with diabetes and discussed as part of diabetes management. Use of internet or mobile-based digital platforms to reinforce healthy behaviors may be considered as a component of care, as these interventions have been found to enhance the efficacy of medical therapy for hypertension (61,62).

Pharmacologic Interventions

Recommendations

10.7 In individuals with confirmed office-based blood pressure ≥130/80 mmHg, pharmacologic therapy should be initiated and titrated to achieve the recommended blood pressure goal of <130/80 mmHg. **A**

10.8 Individuals with confirmed office-based blood pressure ≥150/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in people with diabetes. **A**

10.9 Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in people with diabetes. **A** ACE inhibitors or angiotensin receptor blockers (ARBs) are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. **A**

10.10 Multiple-drug therapy is generally required to achieve blood pressure goals. Avoid combinations of ACE inhibitors and ARBs and combinations of ACE inhibitors or ARBs (including ARBs and neprilysin inhibitors) with direct renin inhibitors. **A**

10.11 An ACE inhibitor or ARB, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in people with diabetes and urinary albumin-to-creatinine ratio ≥300 mg/g creatinine **A** or 30–299 mg/g creatinine. **B** If one class is not tolerated, the other should be substituted. **B**

10.12 Monitor for increased serum creatinine and for increased serum potassium levels when ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists (MRAs) are used, for hypokalemia when diuretics are used at routine visits, and 7–14 days after initiation or after a dose change. **B**

10.13 ACE inhibitors, angiotensin receptor blockers, MRAs, direct renin inhibitors, and neprilysin inhibitors should be avoided in sexually active individuals of childbearing potential who are not using reliable contraception and are contraindicated in pregnancy. **A**

Initial Number of Antihypertensive Medications. Initial treatment for people with diabetes depends on the severity of hypertension (**Fig. 10.2**). Those with blood pressure between 130/80 mmHg and 150/90 mmHg may begin with a single drug. For individuals with blood pressure ≥150/90 mmHg, initial pharmacologic treatment with two antihypertensive medications is recommended to more effectively achieve blood pressure goals (63–65). Single-pill antihypertensive combinations may improve medication taking in some individuals (66).

Classes of Antihypertensive Medications. Initial treatment for hypertension should include any of the drug classes demonstrated to reduce cardiovascular events in people with diabetes (25): ACE inhibitors (67,68), ARBs (67,68), thiazide-like diuretics (69), or dihydropyridine calcium channel blockers (70). In people with diabetes and established coronary artery disease, ACE inhibitors or ARBs are recommended first-line therapy for hypertension (71–73). For individuals with albuminuria (urine albumin-to-creatinine ratio [UACR] ≥30 mg/g), initial treatment should include an ACE inhibitor or ARB to reduce the risk of progressive kidney disease (21) (**Fig. 10.2**). In individuals

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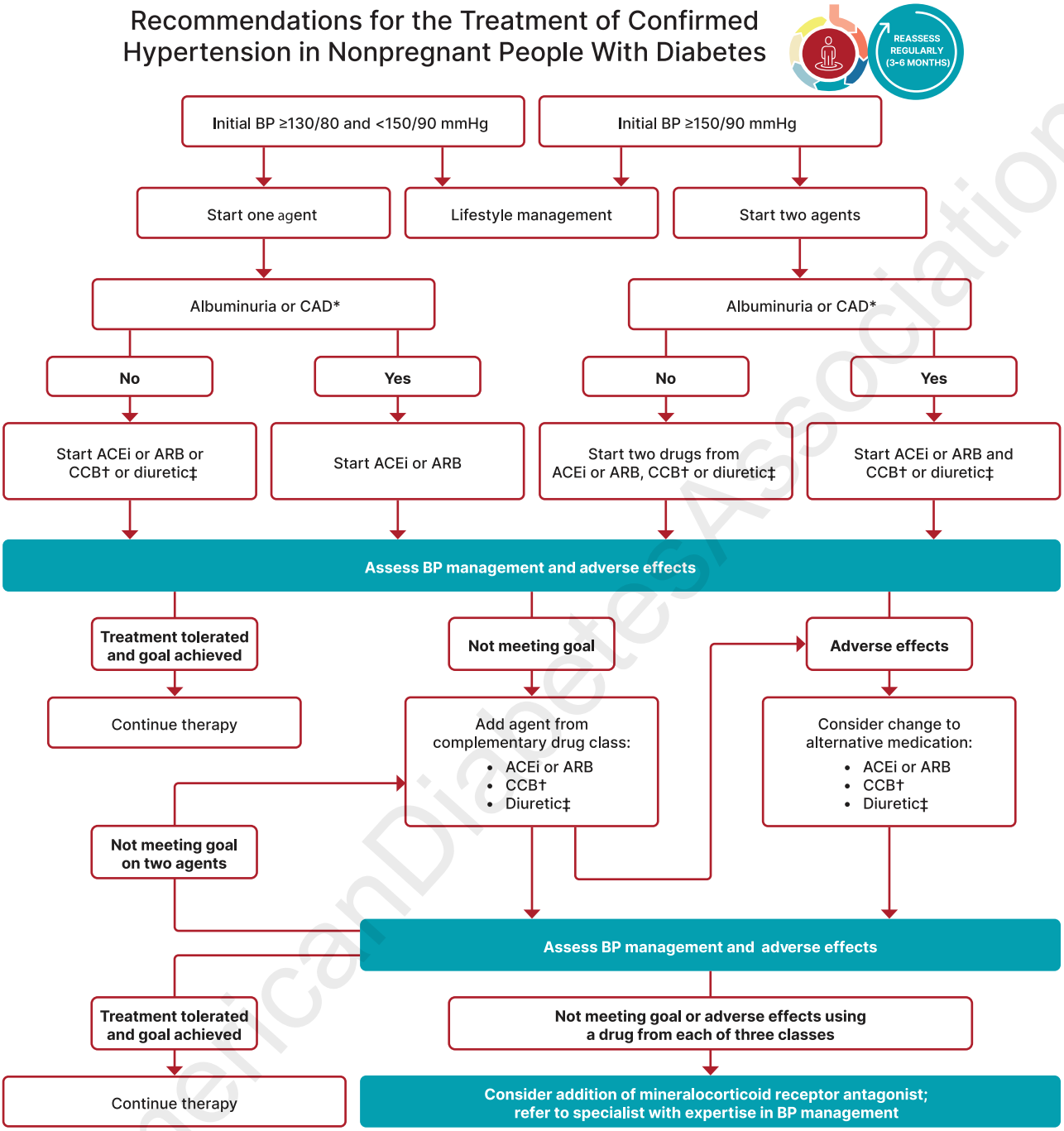

Figure 10.2—Recommendations for the treatment of confirmed hypertension in nonpregnant people with diabetes. *An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested for the treatment of hypertension in people with coronary artery disease (CAD) or urine albumin-to-creatinine ratio 30–299 mg/g creatinine and is strongly recommended for individuals with urine albumin-to-creatinine ratio ≥300 mg/g creatinine. †Dihydropyridine calcium channel blocker (CCB). ‡Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. BP, blood pressure. Adapted from de Boer et al. (21).

receiving ACE inhibitor or ARB therapy, continuation of those medications as kidney function declines to estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 may provide cardiovascular benefit without significantly increasing the risk of end-stage kidney disease (74). In the absence of albuminuria, risk of progressive kidney disease is low, and ACE inhibitors and ARBs have not been found to afford superior cardioprotection compared with thiazide-like diuretics or dihydropyridine calcium channel blockers (75). β-Blockers are indicated in the setting of prior MI, active angina, or HFrEF but have not been shown to reduce mortality as blood pressure–lowering agents in the absence of these conditions (33,76,77).

Multiple-Drug Therapy. Multiple-drug therapy is often required to achieve blood pressure goals (**Fig. 10.2**), particularly in the setting of CKD in people with diabetes. However, the use of both ACE

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inhibitors and ARBs in combination, or the combination of an ACE inhibitor or ARB and a direct renin inhibitor, is contraindicated given the lack of added ASCVD benefit and increased rate of adverse events—namely, hyperkalemia, syncope, and AKI (78–80). Titration of and/or addition of further blood pressure medications should be made in a timely fashion to overcome therapeutic inertia in achieving blood pressure goals.

Bedtime Dosing. Although prior analyses of randomized clinical trials found a benefit to evening versus morning dosing of antihypertensive medications (81,82), these results have not been reproduced in subsequent trials. Therefore, preferential use of antihypertensives at bedtime is not recommended (83).

Hyperkalemia and Acute Kidney Injury. Treatment with ACE inhibitors and ARBs or MRAs can cause AKI and hyperkalemia, while diuretics can cause AKI and either hypokalemia or hyperkalemia (depending on mechanism of action) (84,85). Detection and management of these abnormalities is important because AKI and hyperkalemia each increase the risks of cardiovascular events and death (86). Therefore, serum creatinine and potassium should be monitored after initiation of treatment with an ACE inhibitor or ARB, MRA, or diuretic and monitored during treatment and following uptitration of these medications, particularly among individuals with reduced glomerular filtration who are at increased risk of hyperkalemia and AKI (84,85,87).

Resistant Hypertension

Recommendation

10.14 Individuals with hypertension who are not meeting blood pressure goals on three classes of antihypertensive medications (including a diuretic) should be considered for MRA therapy. **A**

Resistant hypertension is defined as blood pressure ≥140/90 mmHg despite a therapeutic strategy that includes appropriate lifestyle management plus a diuretic and two other antihypertensive drugs with complementary mechanisms of action at adequate doses. Prior to diagnosing resistant hypertension, a number of other conditions should be excluded, including missed doses of antihypertensive medications, white coat hypertension, and primary and secondary hypertension. Difficulty following the care plan may also be a reason for resistant hypertension. International Society of Hypertension guidelines put a strong emphasis on screening for care plan difficulties in management of hypertension and recommend using objective measures such as review of pharmacy records, pill counting, and the chemical analysis of blood or urine rather than subjective methods of detecting inconsistencies in care plan engagement in routine clinical practice. However, this may not be feasible in all practice settings (22).

People with diabetes and confirmed resistant hypertension should be evaluated for secondary causes of hypertension, including primary hyperaldosteronism, renal artery stenosis, CKD, and obstructive sleep apnea. In general, barriers to medication taking (such as cost and side effects) should be identified and addressed (**Fig. 10.2**). MRAs, including spironolactone and eplerenone, are effective for management of resistant hypertension in people with type 2 diabetes when added to existing treatment with an ACE inhibitor or ARB, thiazide-like diuretic, or dihydropyridine calcium channel blocker (88). In addition, MRAs reduce albuminuria in people with diabetic nephropathy (89–91). However, adding an MRA to a treatment plan that includes an ACE inhibitor or ARB may increase the risk for hyperkalemia, emphasizing the importance of regular monitoring for serum creatinine and potassium in these individuals, and long-term outcome studies are needed to better evaluate the role of MRAs in blood pressure management.

LIPID MANAGEMENT

Lifestyle Intervention

Recommendations

10.15 Lifestyle modification focusing on weight loss (if indicated); application of a Mediterranean or DASH eating pattern; reduction of saturated fat and *trans* fat; increase of dietary n-3 fatty acids, viscous fiber, and plant stanol and sterol intake; and increased physical activity should be recommended to improve the lipid profile and reduce the risk of developing atherosclerotic cardiovascular disease (ASCVD) in people with diabetes. **A**

10.16 Intensify lifestyle therapy and optimize glycemic management for people with diabetes with elevated triglyceride levels (≥150 mg/dL [≥1.7 mmol/L]) and/or low HDL cholesterol (<40 mg/dL [<1.0 mmol/L] for men and <50 mg/dL [<1.3 mmol/L] for women). **C**

Lifestyle intervention, including weight loss in people with overweight or obesity (when appropriate) (19,92), increased physical activity, and medical nutrition therapy, allows some individuals to reduce ASCVD risk factors. Nutrition intervention should be tailored according to each person's age, pharmacologic treatment, lipid levels, and medical conditions.

Recommendations should focus on application of a Mediterranean (93) or DASH eating pattern, reducing saturated and *trans* fat intake, and increasing plant stanol and sterol, n-3 fatty acid, and viscous fiber (such as in oats, legumes, and citrus) intake (19,92). Glycemic management may also beneficially modify plasma lipid levels, particularly in people with very high triglycerides and poor glycemic management. See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for additional nutrition information.

Ongoing Therapy and Monitoring With Lipid Panel

Recommendations

10.17 In adults with prediabetes or diabetes not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diagnosis, at an initial medical evaluation, annually thereafter, or more frequently if indicated. **E**

10.18 Obtain a lipid profile at initiation of statins or other lipid-lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter, as it facilitates monitoring the response to therapy and informs medication-taking behavior. **A**

In adults with diabetes, it is reasonable to obtain a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) at the time of diagnosis, at the initial medical evaluation, and at least every 5 years thereafter in individuals <40 years of age. In younger

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people with longer duration of disease (such as those with youth-onset type 1 diabetes), more frequent lipid profiles may be reasonable. A lipid panel should also be obtained immediately before initiating statin therapy. Once an individual is taking a statin, LDL cholesterol levels should be assessed 4–12 weeks after initiation of statin therapy, after any change in dose, and annually (e.g., to monitor for medication taking and efficacy). Monitoring lipid profiles after initiation of statin therapy and during therapy increases the likelihood of dose titration and following the statin treatment plan (94–96). If LDL cholesterol levels are not responding despite medication taking, clinical judgment is recommended to determine the need for and timing of lipid panels. In individuals, the highly variable LDL cholesterol-lowering response seen with statins is poorly understood (97). Clinicians should attempt to find a dose or alternative statin that is tolerable if side effects occur. There is evidence for benefit from even extremely low, less-than-daily statin doses (98).

STATIN TREATMENT

Primary Prevention

Recommendations

10.19 For people with diabetes aged 40–75 years without ASCVD, use moderate-intensity statin therapy in addition to lifestyle therapy. **A**

10.20 For people with diabetes aged 20–39 years with additional ASCVD risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy. **C**

10.21 For people with diabetes aged 40–75 years at higher cardiovascular risk, including those with one or more additional ASCVD risk factors, high-intensity statin therapy is recommended to reduce LDL cholesterol by ≥50% of baseline and to obtain an LDL cholesterol goal of <70 mg/dL (<1.8 mmol/L). **A**

10.22 For people with diabetes aged 40–75 years at higher cardiovascular risk, especially those with multiple additional ASCVD risk factors and an LDL cholesterol ≥70 mg/dL (≥1.8 mmol/L), it may be reasonable to add ezetimibe or a PCSK9 inhibitor to maximum tolerated statin therapy. **B**

10.23 In adults with diabetes aged >75 years already on statin therapy, it is reasonable to continue statin treatment. **B**

10.24 In adults with diabetes aged >75 years, it may be reasonable to initiate moderate-intensity statin therapy after discussion of potential benefits and risks. **C**

10.25 In people with diabetes intolerant to statin therapy, treatment with bempedoic acid is recommended to reduce cardiovascular event rates as an alternative cholesterol-lowering plan. **A**

10.26 In most circumstances, lipid-lowering agents should be stopped prior to conception and avoided in sexually active individuals of childbearing potential who are not using reliable contraception. **B** In some circumstances (e.g., for individuals with familial hypercholesterolemia or prior ASCVD event), statin therapy may be continued when the benefits outweigh risks. **E**

Secondary Prevention

Recommendations

10.27 For people of all ages with diabetes and ASCVD, high-intensity statin therapy should be added to lifestyle therapy. **A**

10.28 For people with diabetes and ASCVD, treatment with high-intensity statin therapy is recommended to obtain an LDL cholesterol reduction of ≥50% from baseline and an LDL cholesterol goal of <55 mg/dL (<1.4 mmol/L). Addition of ezetimibe or a PCSK9 inhibitor with proven benefit in this population is recommended if this goal is not achieved on maximum tolerated statin therapy. **B**

10.29a For individuals who do not tolerate the intended statin intensity, the maximum tolerated statin dose should be used. **E**

10.29b For people with diabetes and ASCVD intolerant to statin therapy, PCSK9 inhibitor therapy with monoclonal antibody treatment, **A** bempedoic acid therapy, **A** or PCSK9 inhibitor therapy with inclisiran siRNA **E** should be considered as an alternative cholesterol-lowering therapy.

Initiating Statin Therapy

People with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of ASCVD. Multiple clinical trials have demonstrated the beneficial effects of statin therapy on ASCVD outcomes in subjects with and without coronary heart disease (CHD) (99,100). Subgroup analyses of people with diabetes in larger trials (101–105) and trials in people with diabetes (106,107) showed significant primary and secondary prevention of ASCVD events and CHD death in people with diabetes. Meta-analyses including data from >18,000 people with diabetes from 14 randomized trials of statin therapy (mean follow-up 4.3 years) demonstrated a 9% proportional reduction in all-cause mortality and 13% reduction in vascular mortality for each 1 mmol/L (39 mg/dL) reduction in LDL cholesterol (108). The cardiovascular benefit in this large meta-analysis did not depend on baseline LDL cholesterol levels and was linearly related to the LDL cholesterol reduction without a low threshold beyond which there was no benefit observed (108). It is important to note that the effects of statin therapy do not differ based on sex (109).

Accordingly, statins are the drugs of choice for LDL cholesterol lowering and cardioprotection. **Table 10.1** shows the two statin dosing intensities that are

Table 10.1—High-intensity and moderate-intensity statin therapy

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 1–4 mg

Once-daily dosing. XL, extended release.

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recommended for use in clinical practice. High-intensity statin therapy will achieve an approximately ≥50% reduction in LDL cholesterol, and moderate-intensity statin plans achieve 30–49% reductions in LDL cholesterol. Low-dose statin therapy is generally not recommended in people with diabetes but is sometimes the only dose of statin that an individual can tolerate. For individuals who do not tolerate the intended intensity of statin, the maximum tolerated statin dose should be used.

As in those without diabetes, absolute reductions in ASCVD outcomes (CHD death and nonfatal MI) are greatest in people with high baseline ASCVD risk (known ASCVD and/or very high LDL cholesterol levels), but the overall benefits of statin therapy in people with diabetes at moderate or even low risk for ASCVD are convincing (110,111). The relative benefit of lipid-lowering therapy has been uniform across most subgroups tested (100,108), including subgroups that varied with respect to age and other risk factors.

Primary Prevention (People Without ASCVD)

For primary prevention, moderate-dose statin therapy is recommended for those aged ≥40 years (19,112,113), although high-intensity therapy should be considered in the context of additional ASCVD risk factors (**Fig. 10.3**). The evidence is strong for people with diabetes aged 40–75 years, an age-group well represented in statin trials showing benefit. Since cardiovascular risk is enhanced in people with diabetes, as noted above, individuals who also have multiple other coronary risk factors have increased risk, equivalent to that of those with ASCVD. Therefore, current guidelines recommend that in people with diabetes who are at higher cardiovascular risk, especially those with one or more ASCVD risk factors, high-intensity statin therapy should be prescribed to reduce LDL cholesterol by ≥50% from baseline and to obtain an LDL cholesterol of <70 mg/dL (<1.8 mmol/L) (114–116). Since, in clinical practice, it is frequently difficult to ascertain the baseline LDL cholesterol level prior to statin therapy initiation, in those individuals, a focus on an LDL cholesterol goal of <70 mg/dL (<1.8 mmol/L) rather than percent reduction in LDL cholesterol is recommended. In those individuals, it may also be reasonable to add ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy to maximum tolerated statin therapy if needed to reduce LDL cholesterol levels by ≥50% and to achieve the recommended LDL cholesterol goal of <70 mg/dL (<1.8 mmol/L) (117). While there are no randomized controlled trials specifically assessing cardiovascular outcomes of adding ezetimibe or PCSK9 inhibitors to statin therapy in primary prevention, a portion of the participants without established cardiovascular disease were included in some studies, which also included participants with established cardiovascular disease. A meta-analysis suggests that there is a cardiovascular benefit of adding ezetimibe or PCSK9 inhibitors to treatment for people at high risk (118). There is less evidence for individuals aged >75 years; relatively few older people with diabetes have been enrolled in primary prevention trials. However, heterogeneity by age has not been seen in the relative benefit of lipid-lowering therapy in trials that included older participants (100,107,108), and because older age confers higher risk, the absolute benefits are actually greater (100,119). Moderate-intensity statin therapy is recommended in people with diabetes who are ≥75 years of age. However, the risk-benefit profile should be routinely evaluated in this population, with downward titration of dose performed as needed. See Section 13, "Older Adults," for more details on clinical considerations for this population.

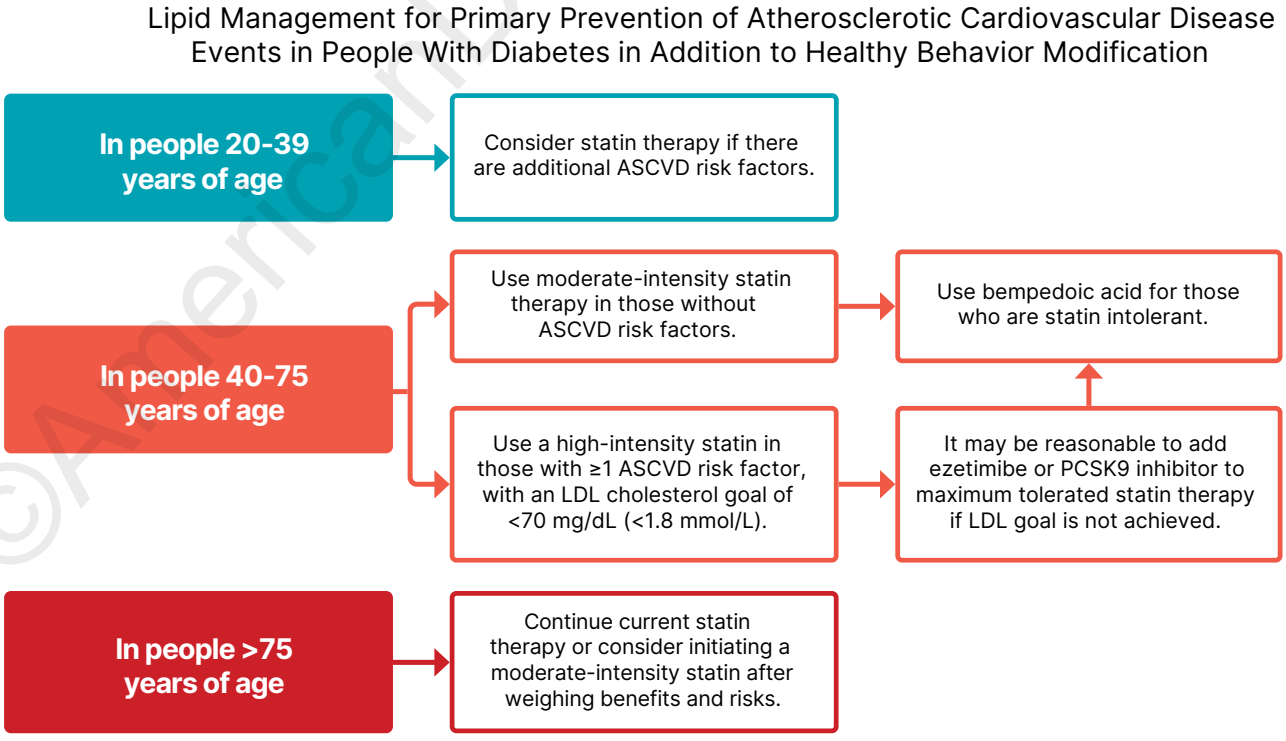

Figure 10.3—Recommendations for primary prevention of atherosclerotic cardiovascular disease (ASCVD) in people with diabetes using cholesterol-lowering therapy. Adapted from *"Standards of Care in Diabetes—2024* Abridged for Primary Care Professionals" (325).

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Age <40 Years and/or Type 1 Diabetes. Very little clinical trial evidence exists for people with type 2 diabetes under the age of 40 years or for people with type 1 diabetes of any age. For pediatric recommendations, see Section 14, "Children and Adolescents." In the Heart Protection Study (lower age limit 40 years), the subgroup of ~600 people with type 1 diabetes had a reduction in risk proportionately similar, although not statistically significant, to that in people with type 2 diabetes (102). Even though the data are not definitive, similar statin treatment approaches should be considered for people with type 1 or type 2 diabetes, particularly in the presence of other cardiovascular risk factors. Individuals <40 years of age have lower risk of developing a cardiovascular event over a 10-year horizon; however, their lifetime risk of developing cardiovascular disease and experiencing an MI, stroke, or cardiovascular death is high. For people who are <40 years of age and/or have type 1 diabetes with other ASCVD risk factors, it is recommended that the individual and health care professional discuss the relative benefits and risks and consider the use of moderate-intensity statin therapy. Please refer to "Type 1 Diabetes Mellitus and Cardiovascular Disease: A Scientific Statement From the American Heart Association and American Diabetes Association" (120) for additional discussion.

Secondary Prevention (People With ASCVD)

Intensive therapy is indicated because cardiovascular event rates are increased in people with diabetes and established ASCVD, and it has been shown to be of benefit in multiple large meta-analyses and randomized cardiovascular outcomes trials (99,100,108,119,121). High-intensity statin therapy is recommended for all people with diabetes and ASCVD to obtain an LDL cholesterol reduction of ≥50% from baseline and an LDL cholesterol goal of <55 mg/dL (<1.4 mmol/L) (**Fig. 10.4**). The addition of ezetimibe or a PCSK9 inhibitor is recommended if this goal is not achieved on maximum tolerated statin therapy. These recommendations are based on the observation that high-intensity versus moderate-intensity statin therapy reduces cardiovascular event rates in high-risk individuals with established cardiovascular disease in randomized trials (99). The Cholesterol Treatment Trialists' Collaboration, involving 26 statin trials, of which 5 compared high-intensity versus moderate-intensity statins, showed a 21% reduction in major cardiovascular events in people with diabetes for every 39 mg/dL (1 mmol/L) of LDL cholesterol lowering, irrespective of baseline LDL cholesterol or individual characteristics (108). The evidence to support lower LDL cholesterol goals in people with diabetes and established cardiovascular disease derives from multiple large, randomized trials investigating the benefits of adding nonstatin agents to statin therapy, including combination treatment with statins and ezetimibe (119,122) or PCSK9 inhibitors (121,123–125). Each trial found a large benefit in reducing ASCVD events that was directly related to the degree of further LDL cholesterol lowering. A large number of participants with diabetes were included in these trials, and prespecified analyses were completed to evaluate cardiovascular outcomes in people with and without diabetes (122,124,125). The decision to add a nonstatin agent should be made following a discussion between a clinician and a person with diabetes about the net benefit, safety, and cost of combination therapy.

Combination Therapy for LDL Cholesterol Lowering

Statins and Ezetimibe

The best evidence for combination therapy of statins and ezetimibe comes from the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). The trial showed the addition of ezetimibe to a moderate-intensity statin led to a 6.4% relative benefit and a 2% absolute reduction in major adverse cardiovascular events (atherosclerotic cardiovascular events), with the degree of benefit being directly proportional to the change in LDL cholesterol (119). A subanalysis of participants with diabetes (27% of the 18,144 participants) showed a significant reduction of major adverse cardiovascular events with the combination treatment over moderate-intensity statin alone (122).

Statins and PCSK9 Inhibitors

The addition of the PCSK9 inhibitors evolocumab and alirocumab to maximum tolerated doses of statin therapy in participants who were at high risk for ASCVD demonstrated an average reduction in LDL cholesterol ranging from 36% to 59% (126,127). No cardiovascular outcome trials have been performed to assess whether PCSK9 inhibitor therapy reduces ASCVD event rates in individuals at low or moderate risk for ASCVD (primary prevention). The evidence on the effect of PSCK9 inhibition on ASCVD outcomes is from studies of treatment with the monoclonal antibodies alirocumab and evolocumab. When added to a maximally tolerated statin, these agents reduced LDL cholesterol by ~60% (121) and significantly reduced the risk of major adverse cardiovascular events by 15–20% in the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) (evolocumab) and ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trials (121,123,128). In the subanalyses of the participants with diabetes (40% in FOURIER and 28.8% in ODYSSEY OUTCOMES), similar benefits were seen compared with those for individuals without diabetes in FOURIER (125), whereas a greater absolute

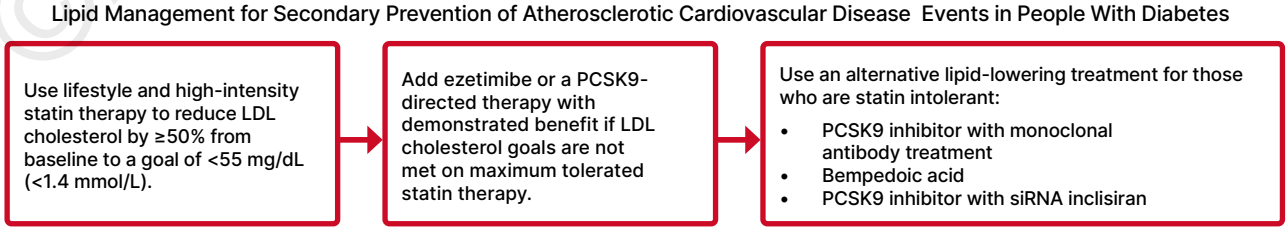

Figure 10.4—Recommendations for secondary prevention of atherosclerotic cardiovascular disease (ASCVD) in people with diabetes using cholesterol-lowering therapy. Adapted from *"Standards of Care in Diabetes—2024* Abridged for Primary Care Professionals" (325).

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reduction was seen for participants with diabetes (2.3% [95% CI 0.4–4.2]) than for those with prediabetes (1.2% [0.0–2.4]) or normoglycemia (1.2% [−0.3 to 2.7]) in the ODYSSEY OUTCOMES trial (124).

In addition to the monoclonal antibodies, an siRNA, inclisiran, which also targets PSCK9, has demonstrated the ability to reduce LDL cholesterol by 49–52% in trials evaluating individuals with established cardiovascular disease or ASCVD risk equivalent (129). Inclisiran allows less frequent administration compared with monoclonal antibodies and was administered on day 1, on day 90, and every 6 months in these trials. In an exploratory analysis, the prespecified cardiovascular end point of nonadjudicated cardiovascular events, including cardiac death, signs or symptoms of cardiac arrest, nonfatal MI, or stroke, occurred less frequently with inclisiran than placebo (7.4% vs. 10.2% in one trial and 7.8% vs. 10.3% in another trial). Cardiovascular outcome trials using inclisiran in people with established cardiovascular disease (130,131) and for primary prevention in those at high risk for cardiovascular disease (132) are currently ongoing.

Intolerance to Statin Therapy

Statin therapy is a hallmark approach to cardiovascular prevention and treatment; however, a subset of individuals experience partial (inability to tolerate sufficient dosage necessary to achieve therapeutic objectives due to adverse effects) or complete (inability to tolerate any dose) intolerance to statin therapy (133). Although the definition of statin intolerance differs between organizations and across clinical study methods, these individuals will require an alternative treatment approach. Initial steps in people intolerant to statins may include switching to a different high-intensity statin if a high-intensity statin is indicated, switching to moderate-intensity or low-intensity statin, lowering the statin dose, or using nondaily dosing with statins. While considering these alternative treatment plans, the addition of nonstatin treatment plans to maximum tolerated statin therapy should be considered, as these are frequently associated with improved medication-taking behavior and achievement of LDL cholesterol goals (133).

PCSK9-Directed Therapies

The PCSK9 monoclonal antibodies alirocumab and evolocumab both have been shown to be effective for LDL cholesterol reduction and fewer skeletal muscle–related adverse effects when studied in populations considered statin intolerant. The Study of Alirocumab in Patients With Primary Hypercholesterolemia and Moderate, High, or Very High Cardiovascular Risk, Who Are Intolerant to Statins (ODYSSEY ALTERNATIVE) trial studied the reduction in LDL cholesterol with alirocumab compared with ezetimibe or 20 mg atorvastatin in individuals at moderate to very high cardiovascular risk for 24 weeks. The proportion of the study population with type 2 diabetes was ∼24%. After the 24 weeks, alirocumab lowered LDL cholesterol levels by 54.8% versus 20.1% with ezetimibe. There were similar rates of any adverse event for all treatments; however, fewer events that led to treatment discontinuation and few skeletal muscle–related adverse events occurred with alirocumab (134).

The Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 1, 2, and 3 (GAUSS 1, 2, and 3) trials, as well as the Open-Label Study of Long-term Evaluation Against LDL Cholesterol (OSLER) open-label extension of the GAUSS 1 and 2 trials, evaluated the safety and LDL cholesterol reduction of evolocumab plus ezetimibe compared with ezetimibe alone in individuals with statin intolerance.

Reductions in LDL cholesterol ranged from 55% and 56% for evolocumab biweekly and monthly plus daily oral placebo, respectively, to 19% and 16% for ezetimibe daily plus biweekly or monthly subcutaneous placebo, respectively. Fewer musculoskeletal adverse effects occurred in those treated with evolocumab or ezetimibe than in those treated with ezetimibe plus placebo, although rates of discontinuation due to these effects were similar. Use of low-dose statins was allowed in these studies and was associated with an increase in the incidence of musculoskeletal adverse effects (135,136). Similar LDL cholesterol reductions were demonstrated in the GAUSS 3 trial after 24 weeks (54.5% with evolocumab compared with 16.7% with ezetimibe), with slightly higher rates of musculoskeletal adverse events (20.7% with evolocumab and 28.8% with ezetimibe). The higher rates of these adverse events may be due in part to the first phase of this trial, which randomized individuals to a statin rechallenge with either atorvastatin or placebo (137).

Inclisiran has also been proposed as an option for individuals with statin intolerance. Although most of the individuals in studies of inclisarin were on statin therapy, one short-term study (Trial to Evaluate the Effect of ALN-PCSSC Treatment on Low-density Lipoprotein Cholesterol [ORION-1]) included individuals with documented statin intolerance (138) and could continue into an open-label extension trial (Extension Trial of Inclisiran in Participants With Cardiovascular Disease and High Cholesterol [ORION-3]), where an LDL cholesterol reduction of ∼45% was maintained through the end of year 4 (139). It is important to note that of the ORION-3 participants, only 23% had diabetes and 33% were not taking statin therapy. Although it may be expected that those with statin intolerance experienced a response similar to the response of those on statin therapy, evaluation of response based on background lipid-lowering therapy was not described.

Bempedoic Acid

Bempedoic acid, a novel LDL cholesterol–lowering agent acting in the same pathway as statin but without activity in skeletal muscle, which limits the muscle-related adverse effects, lowers LDL cholesterol levels by 15% for those on statins and 24% for those not taking statins (140). Use of this agent with ezetimibe results in an additional 19% reduction in LDL cholesterol (140). The Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid or Placebo (CLEAR Outcomes) trial found a reduction in four-point major adverse cardiovascular events by 13% compared with placebo for individuals with established ASCVD (70% of population) or at high risk for ASCVD (30% of population) and considered to be intolerant to statin therapy. It is important to note that ∼19% of individuals were on very-low-dose statin therapy at baseline (141). Prespecified subanalyses evaluated the impact for individuals with diabetes and showed a 17% reduction in four-point major adverse cardiovascular events when treated with bempedoic acid (142). For individuals requiring primary prevention, the use of bempedoic acid resulted in a 30% reduction in primary composite outcome compared with placebo (143).

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Lipid-Lowering Care Considerations for Individuals of Childbearing Potential

Individuals of childbearing potential are less likely to be treated with statins or achieve their LDL cholesterol goals based on their cardiovascular risk (144–146). This is likely related to concerns and lack of knowledge related to use of lipid-lowering agents during pregnancy. The trials evaluating the efficacy and safety of lipid-lowering medications exclude individuals who are pregnant and require individuals of childbearing potential to use contraception (some requiring two forms). Therefore, for many pregnant individuals, it is recommended that they discontinue lipid-lowering therapies during gestation. However, some individuals are at higher risk for cardiovascular events (e.g., those with familial hypercholesterolemia or preexisting ASCVD), and the risk of discontinuing all lipid-lowering therapy during preconception and pregnancy periods may be associated with an increased risk for cardiovascular events. Consideration of initiating or continuing statin therapy during pregnancy should occur with these high-risk individuals. Although the evidence is limited, statins did not increase teratogenic effects for individuals with familial hypercholesterolemia (147,148), and a meta-analysis of pravastatin in pregnant individuals showed a reduction in preeclampsia, premature birth, and neonatal intensive care unit admissions (149). There is limited information regarding the use of lipid-lowering therapies (other than bile acid sequestrants) during pregnancy. Thus, it is recommended that individuals of childbearing potential use a form of contraception when also using lipid-lowering medications with unknown risks, limited evidence on safety, or known risks during pregnancy regardless of intention to become pregnant, as many pregnancies are unplanned, and preconception counseling should be part of the routine care of individuals with diabetes who have childbearing potential. Counseling should include the known benefits and risks of lipid-lowering medications versus the risks and benefits of not treating the conditions for which they are prescribed, as well as other medications (e.g., noninsulin glucose-lowering therapies and antihypertensive agents), during pregnancy and recommendations for when changes in medications should occur prior to pregnancy (144) (see Section 15, "Management of Diabetes in Pregnancy," for more information on preconception counseling and lipid-lowering treatment during pregnancy).

Treatment of Other Lipoprotein Fractions or Goals

Recommendations

10.30 For individuals with fasting triglyceride levels ≥500 mg/dL (≥5.7 mmol/L), evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. **C**

10.31 In adults with hypertriglyceridemia (fasting triglycerides >150 mg/dL [>1.7 mmol/L] or nonfasting triglycerides >175 mg/dL [>2.0 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, and hypothyroidism), and medications that raise triglycerides. **C**

10.32 In individuals with ASCVD or other cardiovascular risk factors on a statin with managed LDL cholesterol but elevated triglycerides (150–499 mg/dL [1.7–5.6 mmol/L]), the addition of icosapent ethyl can be considered to reduce cardiovascular risk. **B**

Hypertriglyceridemia should be addressed with nutritional and lifestyle changes, including weight loss and abstinence from alcohol (150). Severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.7 mmol/L] and especially >1,000 mg/dL [>11.3 mmol/L]) may warrant pharmacologic therapy (fibric acid derivatives and/or fish oil) and reduction in dietary fat to reduce the risk of acute pancreatitis (151). Moderate- or high-intensity statin therapy should also be used as indicated to reduce risk of cardiovascular events (see STATIN TREATMENT, above) (150,152). In people with hypertriglyceridemia (fasting triglycerides >150 mg/dL [>1.7 mmol/L] or nonfasting triglycerides >175 mg/dL [>2.0 mmol/L]), lifestyle interventions, treatment of secondary factors, and avoidance of medications that might raise triglycerides are recommended.

For individuals with established cardiovascular disease or with risk factors for cardiovascular disease with elevated triglycerides (150–499 mg/dL [1.7–5.6 mmol/L]) after maximizing statin therapy, icosapent ethyl may be added to reduce cardiovascular risk. The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) showed that the addition of icosapent ethyl to statin therapy in this population resulted in a 25% relative risk reduction ($P < 0.001$) for the primary end point composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina compared with placebo. This risk reduction was seen in individuals with or without diabetes at baseline. The composite of cardiovascular death, nonfatal MI, or nonfatal stroke was reduced by 26% ($P < 0.001$). Additional ischemic end points were significantly lower in the icosapent ethyl group than in the placebo group, including cardiovascular death, which was reduced by 20% ($P = 0.03$). The proportions of individuals experiencing adverse events and serious adverse events were similar between the active and placebo treatment groups. It should be noted that data are lacking for other n-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products (153). As an example, the addition of 4 g per day of a carboxylic acid formulation of the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (n-3 carboxylic acid) to statin therapy in individuals with atherogenic dyslipidemia and high cardiovascular risk, 70% of whom had diabetes, did not reduce the risk of major adverse cardiovascular events compared with the inert comparator of corn oil (154).

Low levels of HDL cholesterol, often associated with elevated triglyceride levels, are the most prevalent pattern of dyslipidemia in people with type 2 diabetes. However, the evidence for the use of drugs that target these lipid fractions is substantially less robust than that for statin therapy (155). In a large trial in people with diabetes, fenofibrate improved cardiovascular outcomes in subgroups with both elevated triglycerides (>200 mg/dL [2.3 mmol/L]) and low HDL cholesterol (<40 mg/dL [1.0 mmol/L]) (156); however, another fibrate, pemafibrate, failed to reduce overall cardiovascular outcomes in a similar population (157).

Other Combination Therapy

Recommendations

10.33 Statin plus fibrate combination therapy has not been shown to improve ASCVD outcomes and is generally not recommended. **A**

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10.34 Statin plus niacin combination therapy has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. **A**

Statin and Fibrate Combination Therapy

Combination therapy (statin and fibrate) is associated with an increased risk for abnormal transaminase levels, myositis, and rhabdomyolysis. The risk of rhabdomyolysis is more common with higher doses of statins and renal insufficiency and appears to be higher when statins are combined with gemfibrozil (compared with fenofibrate) (158).

In the ACCORD study, in people with type 2 diabetes who were at high risk for ASCVD, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke compared with simvastatin alone. Prespecified subgroup analyses suggested heterogeneity in treatment effects with possible benefit for men with both a triglyceride level ≥204 mg/dL (≥2.3 mmol/L) and an HDL cholesterol level ≤34 mg/dL (≤0.9 mmol/L) (159).

Statin and Niacin Combination Therapy

Large clinical trials, including the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) and Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trials, failed to demonstrate a benefit of adding niacin to individuals on appropriate statin therapy. In fact, there was a possible increased risk of ischemic stroke in the AIM-HIGH trial (160) and an increased incidence of new-onset diabetes (absolute excess, 1.3 percentage points; $P < 0.001$) and disturbances in diabetes management among those with diabetes in the HPS2-THRIVE trial in those on combination therapy (161). Therefore, combination therapy with a statin and niacin is not recommended, given the lack of efficacy on major ASCVD outcomes and increased side effects.

Diabetes Risk With Statin Use

Several studies have reported a modestly increased risk of incident type 2 diabetes with statin use (162,163), which may be limited to those with diabetes risk factors. An analysis of one of the initial studies suggested that although statin use was associated with diabetes risk, the cardiovascular event rate reduction with statins far outweighed the risk of incident diabetes, even for individuals at highest risk for diabetes (164). The absolute risk increase was small (over 5 years of follow-up, 1.2% of participants on placebo developed diabetes and 1.5% on rosuvastatin developed diabetes) (164). A meta-analysis of 13 randomized statin trials with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of diabetes, so that (on average) treatment of 255 individuals with statins for 4 years resulted in one additional case of diabetes while simultaneously preventing 5.4 vascular events among those 255 individuals (163).

Lipid-Lowering Agents and Cognitive Function

Although concerns regarding a potential adverse impact of lipid-lowering agents on cognitive function have been raised, several lines of evidence argue against this association, as detailed in a 2018 European Atherosclerosis Society Consensus Panel statement (165). First, there are three large, randomized trials of statin versus placebo where specific cognitive tests were performed, and no differences were seen between statin and placebo (166–169). In addition, no change in cognitive function has been reported in studies with the addition of ezetimibe (119) or PCSK9 inhibitors (121,170) to statin therapy, including among individuals treated to very low LDL cholesterol levels. In addition, systematic reviews of randomized controlled trials and prospective cohort studies evaluating cognition in individuals receiving statins found that published data do not reveal an adverse effect of statins on cognition (171,172). Therefore, a concern that statins or other lipid-lowering agents might cause cognitive dysfunction or dementia is not currently supported by evidence and should not deter their use in individuals with diabetes at high risk for ASCVD (173).

ANTIPLATELET AGENTS

Recommendations

10.35 Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of ASCVD. **A**

10.36a For individuals with ASCVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**

10.36b The length of treatment with dual antiplatelet therapy using low-dose aspirin and a P2Y12 inhibitor in individuals with diabetes after an acute coronary syndrome, acute ischemic stroke, or transient ischemic attack should be determined by an interprofessional team approach that includes a cardiovascular or neurological specialist, respectively. **E**

10.37 Combination therapy with aspirin plus low-dose rivaroxaban should be considered for individuals with stable coronary and/or peripheral artery disease (PAD) and low bleeding risk to prevent major adverse limb and cardiovascular events. **A**

10.38 Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk after a comprehensive discussion with the individual on the benefits versus the comparable increased risk of bleeding. **A**

Risk Reduction

Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk individuals with previous MI or stroke (secondary prevention) and is strongly recommended. In primary prevention, however, among individuals with no previous cardiovascular events, its net benefit is more controversial (162,174).

Previous randomized controlled trials of aspirin, specifically in people with diabetes, failed to consistently show a significant reduction in overall ASCVD end points, raising questions about the efficacy of aspirin for primary prevention in people with diabetes, although some sex differences were suggested (175–177).

The Antithrombotic Trialists' Collaboration published an individual participant–level meta-analysis (178) of six large trials of aspirin for primary prevention in the general population. These trials collectively enrolled over 95,000 participants, including almost 4,000 with diabetes. Overall, they found that aspirin reduced the risk of serious vascular events by 12% (relative risk 0.88 [95% CI 0.82–0.94]). The largest reduction was for nonfatal MI, with little effect on CHD death (relative risk 0.95 [95% CI 0.78–1.15]) or total stroke.

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Most recently, the ASCEND (A Study of Cardiovascular Events iN Diabetes) trial randomized 15,480 people with diabetes but no evident cardiovascular disease to aspirin 100 mg daily or placebo (179). The primary efficacy end point was vascular death, MI, stroke, or transient ischemic attack. The primary safety outcome was major bleeding (i.e., intracranial hemorrhage, sight-threatening bleeding in the eye, gastrointestinal bleeding, or other serious bleeding). During a mean follow-up of 7.4 years, there was a significant 12% reduction in the primary efficacy end point (8.5% vs. 9.6%; $P = 0.01$). In contrast, major bleeding was significantly increased from 3.2% to 4.1% in the aspirin group (rate ratio 1.29; $P = 0.003$), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There were no significant differences by sex, weight, or duration of diabetes or other baseline factors, including ASCVD risk score.

Two other large, randomized trials of aspirin for primary prevention, in people without diabetes (ARRIVE [Aspirin to Reduce Risk of Initial Vascular Events]) (180) and in the elderly (ASPREE [Aspirin in Reducing Events in the Elderly]) (181), in which 11% of participants had diabetes, found no benefit of aspirin on the primary efficacy end point and an increased risk of bleeding. In ARRIVE, with 12,546 individuals over a period of 60 months of follow-up, the primary end point occurred in 4.29% vs. 4.48% of individuals in the aspirin versus placebo groups (HR 0.96 [95% CI 0.81–1.13]; $P = 0.60$). Gastrointestinal bleeding events (characterized as mild) occurred in 0.97% of individuals in the aspirin group vs. 0.46% in the placebo group (HR 2.11 [95% CI 1.36–3.28]; $P = 0.0007$). In ASPREE, which included 19,114 individuals, for cardiovascular disease (fatal CHD, MI, stroke, or hospitalization for heart failure) after a median of 4.7 years of follow-up, the rates per 1,000 person-years were 10.7 vs. 11.3 events in aspirin vs. placebo groups (HR 0.95 [95% CI 0.83–1.08]). The rate of major hemorrhage per 1,000 person-years was 8.6 events versus 6.2 events, respectively (HR 1.38 [95% CI 1.18–1.62]; $P < 0.001$).

Thus, aspirin appears to have a modest effect on ischemic vascular events, with the absolute decrease in events depending on the underlying ASCVD risk. The main adverse effect is an increased risk of gastrointestinal bleeding. The excess risk may be as high as 5 per 1,000 per year in real-world settings. However, for adults with ASCVD risk >1% per year, the number of ASCVD events prevented will be similar to the number of episodes of bleeding induced, although these complications do not have equal effects on long-term health (182).

Recommendations for using aspirin as primary prevention include both men and women aged ≥50 years with diabetes and at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or CKD or albuminuria) who are not at increased risk of bleeding (e.g., older age, anemia, or renal disease) (183–186). Noninvasive imaging techniques such as coronary calcium scoring may help further tailor aspirin therapy, particularly in those at low risk (187,188). For people >70 years of age (with or without diabetes), the balance appears to have greater risk than benefit (179,181). Thus, for primary prevention, the use of aspirin needs to be carefully considered and generally may not be recommended. Aspirin may be considered in the context of high cardiovascular risk with low bleeding risk but generally not in older adults. Aspirin therapy for primary prevention may be considered in the context of shared decision-making, which carefully weighs the cardiovascular benefits with the fairly comparable increase in risk of bleeding.

For people with documented ASCVD, use of aspirin for secondary prevention has far greater benefit than risk; for this indication, aspirin is still recommended (174).

Aspirin Use in People <50 Years of Age

Aspirin is not recommended for those at low risk of ASCVD (such as men and women aged <50 years with diabetes with no other major ASCVD risk factors), as the low benefit is likely to be outweighed by the risk of bleeding. Clinical judgment should be used for those at intermediate risk (younger individuals with one or more risk factors or older individuals with no risk factors) until further research is available. Individuals' willingness to undergo long-term aspirin therapy should also be considered in shared decision-making (189). Aspirin use in individuals aged <21 years is generally contraindicated due to the associated risk of Reye syndrome.

Aspirin Dosing

Average daily dosages used in most clinical trials involving people with diabetes ranged from 50 to 650 mg but were mostly in the range of 100–325 mg/day. There is little evidence to support any specific dose, but using the lowest possible dose may help to reduce side effects (190). In the ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness) trial of individuals with established cardiovascular disease, 38% of whom had diabetes, there were no significant differences in cardiovascular events or major bleeding between individuals assigned to 81 mg and those assigned to 325 mg of aspirin daily (191). In the U.S., the most common low-dose tablet is 81 mg. Although platelets from people with diabetes have altered function, it is unclear what, if any, effect that finding has on the required dose of aspirin for cardioprotective effects in people with diabetes. Many alternate pathways for platelet activation exist that are independent of thromboxane A_2 and thus are not sensitive to the effects of aspirin (192). "Aspirin resistance" has been described in people with diabetes when measured by a variety of ex vivo and in vitro methods (platelet aggregometry and measurement of thromboxane B_2) (193), but other studies suggest no impairment in aspirin response among people with diabetes (194). A trial suggested that more frequent dosing of aspirin may reduce platelet reactivity in individuals with diabetes (195); however, these observations alone are insufficient to empirically recommend that higher doses of aspirin be used in this group at this time. Another meta-analysis raised the hypothesis that low-dose aspirin efficacy is reduced in those weighing >70 kg (196); however, the ASCEND trial found benefit of low-dose aspirin in those in this weight range, which would not validate this suggested hypothesis (179). It appears that 75–162 mg/day is optimal.

Indications for P2Y12 Receptor Antagonist Use

Combination dual antiplatelet therapy with aspirin and a P2Y12 receptor antagonist is indicated after acute coronary syndromes and coronary revascularization with stenting (197). In addition, current guidelines recommend short-term dual antiplatelet therapy after high-risk transient ischemic attack and minor stroke (198). The

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indications for dual antiplatelet therapy and length of treatment are rapidly evolving and should be determined by an interprofessional team approach that includes a cardiovascular or neurological specialist, as appropriate. Evidence supports use of either ticagrelor or clopidogrel if no percutaneous coronary intervention was performed and clopidogrel, ticagrelor, or prasugrel if a percutaneous coronary intervention was performed (199). In people with diabetes and prior MI (1–3 years before), adding ticagrelor to aspirin significantly reduces the risk of recurrent ischemic events, including cardiovascular and CHD death (200). Similarly, the addition of ticagrelor to aspirin reduced the risk of ischemic cardiovascular events compared with aspirin alone in people with diabetes and stable coronary artery disease (201,202). However, a higher incidence of major bleeding, including intracranial hemorrhage, was noted with dual antiplatelet therapy. The net clinical benefit (ischemic benefit vs. bleeding risk) was improved with ticagrelor therapy in the large prespecified subgroup of individuals with history of percutaneous coronary intervention, while no net benefit was seen in individuals without prior percutaneous coronary intervention (202). However, early aspirin discontinuation compared with continued dual antiplatelet therapy after coronary stenting may reduce the risk of bleeding without a corresponding increase in the risks of mortality and ischemic events, as shown in a prespecified analysis of people with diabetes enrolled in the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial and a meta-analysis (203,204).

Combination Antiplatelet and Anticoagulation Therapy

Combination therapy with aspirin plus low-dose rivaroxaban may be considered for people with stable coronary and/or PAD to prevent major adverse limb and cardiovascular complications. In the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial of 27,395 individuals with established coronary artery disease and/or PAD, aspirin plus rivaroxaban 2.5 mg twice daily was superior to aspirin plus placebo in the reduction of cardiovascular ischemic events, including major adverse limb events. The absolute benefits of combination therapy appeared larger in people with diabetes, who comprised 10,341 of the trial participants (205,206). A similar treatment strategy was evaluated in the Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease (VOYAGER PAD) trial (207), in which 6,564 individuals with PAD who had undergone revascularization were randomly assigned to receive rivaroxaban 2.5 mg twice daily plus aspirin or placebo plus aspirin. Rivaroxaban treatment in this group of individuals was also associated with a significantly lower incidence of ischemic cardiovascular events, including major adverse limb events. However, an increased risk of major bleeding was noted with rivaroxaban added to aspirin treatment in both COMPASS and VOYAGER PAD.

The risks and benefits of dual antiplatelet or antiplatelet plus anticoagulant treatment strategies should be thoroughly discussed with eligible individuals, and shared decision-making should be used to determine an individually appropriate treatment approach. This field of cardiovascular risk reduction is evolving rapidly, as are the definitions of optimal care for individuals with differing types and circumstances of cardiovascular complications.

CARDIOVASCULAR DISEASE

Screening

Recommendations

10.39a In asymptomatic individuals, routine screening for coronary artery disease is not recommended, as it does not improve outcomes as long as ASCVD risk factors are treated. **A**

10.39b Consider investigations for coronary artery disease in the presence of any of the following: signs or symptoms of cardiac or associated vascular disease, including carotid bruits, transient ischemic attack, stroke, claudication, or PAD; or electrocardiogram abnormalities (e.g., Q waves). **E**

10.40a Adults with diabetes are at increased risk for the development of asymptomatic cardiac structural or functional abnormalities (stage B heart failure) or symptomatic (stage C) heart failure. Consider screening adults with diabetes by measuring a natriuretic peptide (B-type natriuretic peptide [BNP] or N-terminal pro-BNP [NT-proBNP]) to facilitate prevention of stage C heart failure. **B**

10.40b In asymptomatic individuals with diabetes and abnormal natriuretic peptide levels, echocardiography is recommended to identify stage B heart failure. **A**

10.41 In asymptomatic individuals with diabetes and age ≥65 years, microvascular disease in any location, or foot complications or any end-organ damage from diabetes, screening for PAD with ankle-brachial index testing is recommended if a PAD diagnosis would change management. **B** In individuals with diabetes duration ≥10 years and high cardiovascular risk, screening for PAD should be considered. **E**

Treatment

Recommendations

10.42 Among people with type 2 diabetes who have established ASCVD or established kidney disease, a sodium–glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 receptor agonist (GLP-1 RA) with demonstrated cardiovascular disease benefit is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering treatment plans. **A**

10.42a In people with type 2 diabetes and established ASCVD, multiple ASCVD risk factors, or chronic kidney disease (CKD), an SGLT2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. **A**

10.42b In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, a GLP-1 RA with demonstrated car-diovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. **A**

10.42c In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, combined therapy with an SGLT2 inhibitor with demonstrated cardiovascular benefit and a GLP-1 RA with demonstrated cardiovascular benefit may be considered for additive reduction of the risk of adverse cardiovascular and kidney events. **A**

10.43a In people with type 2 diabetes and established heart failure with

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either preserved or reduced ejection fraction, an SGLT2 inhibitor (including SGLT1/2 inhibitor) with proven benefit in this population is recommended to reduce the risk of worsening heart failure and cardiovascular death. **A**

10.43b In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, an SGLT2 inhibitor with proven benefit in this population is recommended to improve symptoms, physical limitations, and quality of life. **A**

10.44 For individuals with type 2 diabetes and CKD with albuminuria treated with maximum tolerated doses of ACE inhibitor or ARB, recommend treatment with a nonsteroidal MRA with demonstrated benefit to improve cardiovascular outcomes and reduce the risk of CKD progression. **A**

10.45 In individuals with diabetes with established ASCVD or aged ≥55 years with additional cardiovascular risk factors, ACE inhibitor or ARB therapy is recommended to reduce the risk of cardiovascular events and mortality. **A**

10.46a In individuals with diabetes and asymptomatic stage B heart failure, an interprofessional approach to optimize guideline-directed medical therapy, which should include a cardiovascular disease specialist, is recommended to reduce the risk for progression to symptomatic (stage C) heart failure. **A**

10.46b In individuals with diabetes and asymptomatic stage B heart failure, ACE inhibitors or ARBs and β-blockers are recommended to reduce the risk for progression to symptomatic (stage C) heart failure. **A**

10.46c In individuals with type 2 diabetes and asymptomatic stage B heart failure or with high risk of or established cardiovascular disease, treatment with an SGLT inhibitor with proven heart failure prevention benefit is recommended to reduce the risk of hospitalization for heart failure. **A**

10.46d In individuals with type 2 diabetes, obesity, and symptomatic heart failure with preserved ejection fraction, therapy with a GLP-1 RA with demonstrated benefit for reduction of heart failure–related symptoms, physical limitations, and exercise function is recommended. **A**

10.46e In individuals with type 2 diabetes and CKD, recommend treatment with a nonsteroidal MRA with demonstrated benefit to reduce the risk of hospitalization for heart failure. **A**

10.46f In individuals with diabetes, guideline-directed medical therapy for myocardial infarction and symptomatic stage C heart failure is recommended with ACE inhibitors or ARBs, MRAs, angiotensin receptor or neprilysin inhibitor, β-blockers, and SGLT2 inhibitors, similar to guideline-directed medical therapy for people without diabetes. **A**

10.47 In people with type 2 diabetes with stable heart failure, metformin may be continued for glucose lowering if estimated glomerular filtration rate remains >30 mL/min/1.73 m^2 but should be avoided in unstable or hospitalized individuals with heart failure. **B**

10.48 Individuals with type 1 diabetes and those with type 2 diabetes who are ketosis prone and/or follow a ketogenic eating pattern who are treated with SGLT inhibition should be educated on the risks and signs of ketoacidosis and methods of risk management and provided with appropriate tools for accurate ketone measurement (i.e., serum β-hydroxybutyrate). **E**

Cardiac Testing

Candidates for advanced or invasive cardiac testing include those with *1*) symptoms or signs of cardiac or vascular disease and *2*) an abnormal resting electrocardiogram (ECG). Exercise ECG testing without or with echocardiography may be used as the initial test. In adults with diabetes ≥40 years of age, measurement of coronary artery calcium is also reasonable for cardiovascular risk assessment. Pharmacologic stress echocardiography or nuclear imaging should be considered in individuals with diabetes in whom resting ECG abnormalities preclude exercise stress testing (e.g., left bundle branch block or ST-T abnormalities). In addition, individuals who require stress testing and are unable to exercise should undergo pharmacologic stress echocardiography or nuclear imaging.

Screening Asymptomatic Individuals for Atherosclerotic Cardiovascular Disease

The screening of asymptomatic individuals with high ASCVD risk is not recommended (**Fig. 10.5**), in part because these high-risk people should already be receiving intensive medical therapy—an approach that provides benefits similar to those of invasive revascularization (208,209). A randomized observational trial demonstrated no clinical benefit of routine screening with adenosine-stress radionuclide myocardial perfusion imaging in asymptomatic people with type 2 diabetes and normal ECGs (210). Another randomized study showed that routine screening with coronary computed tomography angiography did not reduce the composite rate of all-cause mortality, nonfatal MI, or unstable angina in asymptomatic people with type 1 or type 2 diabetes (211). Studies have also found that a risk factor–based approach to the initial diagnostic evaluation and subsequent follow-up for coronary artery disease fails to identify which people with type 2 diabetes will have silent ischemia on screening tests (212,213).

Any benefit of noninvasive coronary artery disease screening methods, such as computed tomography calcium scoring, to identify subgroups for different treatment strategies remains unproven in asymptomatic people with diabetes, though research is ongoing. Coronary calcium scoring in asymptomatic people with diabetes may help in risk stratification (214,215) and provide reasoning for treatment intensification and/or guiding informed individual decision-making and willingness for medication initiation and participation. However, their routine use leads to radiation exposure and may result in unnecessary invasive testing, such as coronary angiography and revascularization procedures. The ultimate balance of benefit, cost, and risk of such an approach in asymptomatic individuals remains controversial, particularly in the modern setting of aggressive ASCVD risk factor management.

Screening for Asymptomatic Heart Failure in People With Diabetes

People with diabetes are at an increased risk for developing heart failure, as shown in multiple longitudinal, observational studies (216,217). This association is not only observed in people with type 2 diabetes but also evident in people with type 1 diabetes (216,217). In a large multinational cohort of 750,000 people with diabetes without established cardiovascular disease, heart failure and CKD were the most frequent first manifestations of cardiovascular or kidney disease (218). For a detailed

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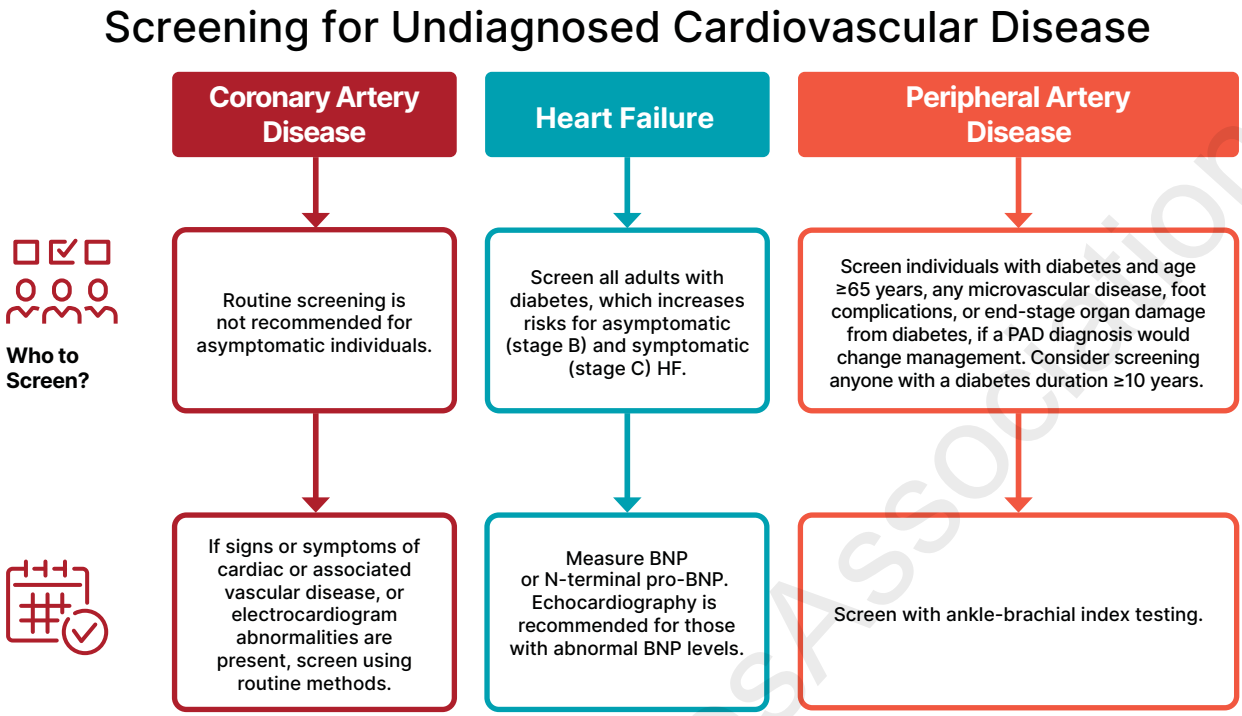

Figure 10.5—Recommendations for screening of asymptomatic and undiagnosed cardiovascular disease. BNP, B-type natriuretic peptide; HF, heart failure; PAD, peripheral artery disease. Adapted from *"Standards of Care in Diabetes—2024* Abridged for Primary Care Professionals" (325).

review of screening, diagnosis, and treatment recommendations of heart failure in people with diabetes, the reader is further referred to the ADA consensus report "Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association" (15).

People with diabetes are at particularly high risk for progression from asymptomatic stage A and B to symptomatic stage C and D heart failure (219,220). Identification, risk stratification, and early treatment of risk factors in people with diabetes and asymptomatic stages of heart failure reduce the risk for progression to symptomatic heart failure (221,222). In people with type 2 diabetes, measurement of natriuretic peptides, including B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP), identifies people at risk for heart failure development, progression of symptoms, and heart failure–related mortality (223–225). A similar association and prognostic values of increased NT-proBNP with increased cardiovascular and all-cause mortality has been reported in people with type 1 diabetes (226). Results from several randomized controlled trials revealed that more intensive treatment of risk factors in people with increased levels of natriuretic peptides reduces the risk for symptomatic heart failure, heart failure hospitalization, and newly diagnosed left ventricular dysfunction (222,227,228).

Based on collective evidence, consider screening asymptomatic adults with diabetes for the development of cardiac structural or functional abnormalities (stage B heart failure) by measurement of natriuretic peptides, including BNP or NT-proBNP levels. The biomarker threshold for abnormal values is BNP level ≥50 pg/mL and NT-proBNP level ≥125 pg/mL. Abnormal levels of natriuretic peptide will need to be evaluated in the context of each person, using clinical judgment, in the absence of any possible competing diagnoses, particularly recognizing conditions that may lead to increased levels of natriuretic peptide, including renal insufficiency, pulmonary disease including pulmonary hypertension and chronic obstructive lung disease, obstructive sleep apnea, ischemic and hemorrhagic stroke, and anemia. Conversely, natriuretic peptide levels may be decreased in the population with obesity, which impairs sensitivity of testing.

In people with diabetes and an abnormal natriuretic peptide level, echocardiography is recommended as the next step to screen for structural heart disease and echocardiographic Doppler indices for evidence of diastolic dysfunction and increased filling pressures (229). At this stage, an interprofessional approach, which should include a cardiovascular disease specialist, is recommended to implement a guideline-directed medical treatment strategy, which may reduce the risk of progression to symptomatic stages of heart failure (221). The recommendations for screening and treatment of heart failure in people with diabetes discussed in this section are consistent with the ADA consensus report on heart failure (15) and with current American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines for the management of heart failure (12).

Screening for Asymptomatic Peripheral Artery Disease in People With Diabetes

The risk for PAD in people with diabetes is higher than that in people without diabetes (230–232). In the PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program, 30% of people aged 50–69 years with a history of cigarette smoking or diabetes, or aged ≥70 years regardless of risk factors, had PAD (233). Similarly, in other screening studies, 26% of people with diabetes have been shown to have PAD (234), and diabetes increased

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the odds of having PAD by 85% (235). Notably, classical symptoms of claudication are uncommon, and almost half of people with newly diagnosed PAD were asymptomatic (233). Conversely, up to two-thirds of people with asymptomatic PAD have been shown to have comorbid diabetes (236). Risk factors associated with an increased risk for PAD in people with diabetes include age, smoking, hypertension, dyslipidemia, worse glycemic management, longer duration of diabetes, neuropathy, and retinopathy as well as a prior history of cardiovascular disease (237,238). In addition, the presence of microvascular disease is associated with adverse outcomes in people with PAD, including an increased risk for future limb amputation (239,240). While a positive screening test for PAD in an asymptomatic population has been associated with increased cardiovascular event rates (241,242), prospective, randomized studies addressing whether screening for PAD in people with diabetes improves long-term limb outcomes and cardiovascular event rates are limited. In the randomized controlled Viborg Vascular (VIVA) trial, 50,156 participants, some with and some without diabetes, were randomized to combined vascular screening for abdominal aortic aneurysm, PAD, and hypertension or to no screening. Vascular screening was associated with increased pharmacologic therapy (antiplatelet, lipid-lowering, and antihypertensive therapy), reduced in-hospital time for PAD and coronary artery disease, and reduced mortality (243). Therefore, the committee recommends screening for asymptomatic PAD using ankle-brachial index in people with diabetes in whom a diagnosis of PAD may help further intensify pharmacologic therapies. These people include those with age ≥65 years, diabetes with duration ≥10 years, microvascular disease, clinical evidence of foot complications, or any end-organ damage from diabetes.

Lifestyle and Pharmacologic Interventions

Intensive lifestyle intervention focusing on weight loss through decreased caloric intake and increased physical activity, as performed in the Look AHEAD (Action for Health in Diabetes) trial, may be considered for improving glucose management, fitness, and some ASCVD risk factors (244). Individuals at increased ASCVD risk should receive statin, ACE inhibitor, or ARB therapy if the individual has hypertension, and possibly aspirin, unless there are contraindications to a particular drug class.

Clear cardiovascular benefit exists for ACE inhibitor or ARB therapy in people with diabetes. The Heart Outcomes Prevention Evaluation (HOPE) study randomized 9,297 individuals aged ≥55 years with a history of vascular disease or diabetes plus one other cardiovascular risk factor to either ramipril or placebo. Ramipril significantly reduced cardiovascular and all-cause mortality, MI, and stroke (245). ACE inhibitors or ARB therapy also have well-established long-term benefit in people with diabetes and CKD or hypertension, and these agents are recommended for hypertension management in people with known ASCVD (particularly coronary artery disease) (72,73,246). People with type 2 diabetes and CKD should be considered for treatment with finerenone to reduce cardiovascular outcomes and the risk of CKD progression (247–250). β-Blockers should be used in individuals with active angina or HFrEF and for 3 years after MI in those with preserved left ventricular function (251,252).

Glucose-Lowering Therapies and Cardiovascular Outcomes

In 2008, the U.S. Food and Drug Administration (FDA) issued guidance for industry to perform cardiovascular outcomes trials for all new medications for the treatment of type 2 diabetes amid concerns of increased cardiovascular risk (253). Previously approved diabetes medications were not subject to the guidance. Recently published cardiovascular outcomes trials have provided additional data on cardiovascular and renal outcomes in people with type 2 diabetes with cardiovascular disease or at high risk for cardiovascular disease.

Cardiovascular outcomes trials of dipeptidyl peptidase 4 (DPP-4) inhibitors have all, so far, not shown cardiovascular benefits relative to placebo. In addition, the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Type 2 Diabetes) study demonstrated noninferiority between a DPP-4 inhibitor, linagliptin, and a sulfonylurea, glimepiride, on cardiovascular outcomes despite lower rates of hypoglycemia in the linagliptin treatment group (254). The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) showed that treatment with empagliflozin reduced the composite outcome of MI, stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group, HR in the empagliflozin group 0.86 [95% CI 0.74–0.99]; $P = 0.04$ for superiority) and cardiovascular death by 38% (absolute rate 3.7% vs. 5.9%, HR 0.62 [95% CI 0.49–0.77]; $P < 0.001$) (255). Similarly, canagliflozin significantly reduced the composite outcome of cardiovascular death, MI, or stroke versus placebo (occurring in 26.9 vs. 31.5 participants per 1,000 person-years; HR 0.86 [95% CI 0.75–0.97]). Of note, there was an increased risk of lower-limb amputation with canagliflozin (6.3 vs. 3.4 participants per 1,000 person-years; HR 1.97 [95% CI 1.41–2.75]) (256). However, no significant increase in lower-limb amputations, fractures, AKI, or hyperkalemia was noted for canagliflozin relative to placebo in other trials of canagliflozin (257).

The Dapagliflozin Effect on Cardiovascular Events-Thrombosis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial met the prespecified criteria for noninferiority to placebo with respect to major adverse cardiovascular events but did not show a lower rate of major adverse cardiovascular events compared with placebo (8.8% in the dapagliflozin group and 9.4% in the placebo group; HR 0.93 [95% CI 0.84–1.03]; $P = 0.17$) (258). A lower rate of cardiovascular death or hospitalization for heart failure was noted (4.9% vs. 5.8%; HR 0.83 [95% CI 0.73–0.95]; $P = 0.005$), which reflected a lower rate of hospitalization for heart failure (HR 0.73 [95% CI 0.61–0.88]). No difference was seen in cardiovascular death between groups. Further studies have shown renoprotective effects of dapagliflozin (259).

The Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) (260) met the prespecified criteria for noninferiority of ertugliflozin to placebo with respect to the primary outcome of major adverse cardiovascular events (11.9% in the pooled ertugliflozin group and 11.9% in the placebo group; HR 0.97 [95% CI 0.85–1.11]; $P < 0.001$). However, ertugliflozin was not superior to placebo for the key secondary outcomes of death from cardiovascular causes or hospitalization for heart failure; death from cardiovascular causes; or the composite of death from renal causes, renal replacement therapy, or doubling of the serum creatinine level. The HR for a secondary outcome of hospitalization for heart failure (ertugliflozin vs.

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placebo) was 0.70 [95% CI 0.54–0.90], consistent with findings from other SGLT2 inhibitor cardiovascular outcomes trials.

GLP-1 Receptor Agonist Trials

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was a randomized, double-blind trial that assessed the effect of liraglutide, a GLP-1 RA, versus placebo on cardiovascular outcomes in 9,340 people with type 2 diabetes at high risk for cardiovascular disease or with cardiovascular disease (261). Study participants had a mean age of 64 years and a mean duration of diabetes of nearly 13 years. Over 80% of study participants had established cardiovascular disease. After a median follow-up of 3.8 years, LEADER showed that the primary composite outcome (MI, stroke, or cardiovascular death) occurred in fewer participants in the treatment group (13.0%) than in the placebo group (14.9%) (HR 0.87 [95% CI 0.78–0.97]; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). Deaths from cardiovascular causes were significantly reduced in the liraglutide group (4.7%) compared with the placebo group (6.0%) (HR 0.78 [95% CI 0.66–0.93]; $P = 0.007$) (261).

Results of trials with semaglutide, albiglutide, and dulaglutide, once-weekly GLP-1 RAs, were consistent with the LEADER trial (262–264). However, lixisenatide and extended-release exenatide were not superior to placebo with respect to the primary end point of cardiovascular outcomes (265). In summary, there are now numerous large randomized controlled trials reporting statistically significant reductions in cardiovascular events for three of the FDA-approved SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin, with lesser benefits seen with ertugliflozin) and four FDA-approved GLP-1 RAs (liraglutide, albiglutide [although that agent was removed from the market for business reasons], semaglutide [lower risk of cardiovascular events in a moderate-sized clinical trial but one not powered as a cardiovascular outcomes trial], and dulaglutide). Meta-analyses of the trials reported to date suggest that GLP-1 RAs and SGLT2 inhibitors reduce risk of atherosclerotic major adverse cardiovascular events to a comparable degree in people with type 2 diabetes and established ASCVD (266,267). SGLT2 inhibitors also reduce risk of heart failure hospitalization and progression of kidney disease in people with established ASCVD, multiple risk factors for ASCVD, or albuminuric kidney disease (268,269). In people with type 2 diabetes and established ASCVD, multiple ASCVD risk factors, or CKD, an SGLT2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, a GLP-1 RA with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. For many individuals, use of either an SGLT2 inhibitor or a GLP-1 RA to reduce cardiovascular risk is appropriate. Emerging data suggest that use of both classes of drugs will provide an additive cardiovascular and kidney outcomes benefit; thus, combination therapy with an SGLT2 inhibitor and a GLP-1 RA may be considered to provide the complementary outcomes benefits associated with these classes of medication (270).

Prevention and Treatment of Heart Failure

Prevention of Symptomatic Heart Failure

ACE Inhibitors or ARBs and β-Blockers. Early primary prevention strategies and treatment of associated risk factors reduce incident, symptomatic heart failure and should include lifestyle intervention with nutrition, physical activity, weight management, and smoking cessation (271–274) (**Fig. 10.6**). The vast majority of incident heart failure is preceded by hypertension; up to 91% of all new heart failure development in the Framingham cohort occurred in people with a previous diagnosis of hypertension (275). Therefore, management of hypertension constitutes a key goal in people with diabetes and stage A or B heart failure. For example, in the UK Prospective Diabetes Study (UKPDS) trial, intensive blood pressure management in people with type 2 diabetes reduced the risk for heart failure by 56% (276). Similarly, in the SPRINT trial, intensive treatment of hypertension decreased the risk for development of incident heart failure by 36% (277). As discussed in the HYPERTENSION AND BLOOD PRESSURE MANAGEMENT section above, use of ACE inhibitors or ARBs is the preferred treatment strategy for management of hypertension in people with diabetes, particularly in the presence of albuminuria or coronary artery disease. People with diabetes and stage B heart failure who remain asymptomatic but have evidence of structural heart disease, including history of MI, acute coronary syndrome, or left ventricular ejection fraction (LVEF) ≤40%, should be treated with ACE inhibitors or ARBs plus β-blockers according to current treatment guidelines (12). In the landmark Studies of Left Ventricular Dysfunction (SOLVD) study, in which 15% of people had diabetes, treatment with enalapril reduced incident heart failure in people with asymptomatic left ventricular dysfunction by 20% (278). In the Survival and Ventricular Enlargement (SAVE) study,

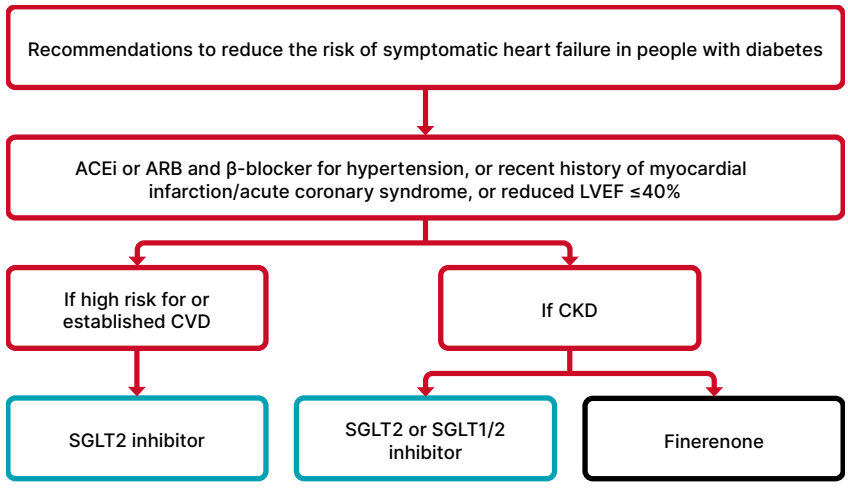

Figure 10.6—Overview of recommendations for the prevention of the development of symptomatic heart failure in people with diabetes. ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; LVEF, left ventricle ejection fraction; SGLT2, sodium–glucose cotransporter 2. Adapted from *"Standards of Care in Diabetes—2024* Abridged for Primary Care Professionals" (325).

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which enrolled asymptomatic people with reduced LVEF after MI, including 23% people with diabetes, treatment with captopril reduced the development of heart failure by 37% (279). Subsequent retrospective analyses from both trials revealed that concomitant use of β-blockers was associated with decreased risk of progression to symptomatic heart failure (280,281). The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) study randomized people with a history of MI and reduced LVEF to treatment with carvedilol (282). Approximately half of the study participants were asymptomatic, and 23% of study participants had a history of diabetes. Treatment with carvedilol reduced mortality by 23%, and there was a 14% risk reduction for heart failure hospitalization. Finally, in the Reversal of Ventricular Remodeling With Toprol-XL (REVERT) trial, in which 45% of the people enrolled had diabetes, metoprolol improved adverse cardiac remodeling in asymptomatic individuals with an LVEF <40% and mild left ventricular dilatation (283).

SGLT Inhibitors. SGLT2 inhibitors constitute a key treatment approach to reduce cardiovascular disease and heart failure outcomes in people with diabetes. People with type 2 diabetes and increased cardiovascular risk or established cardiovascular disease should be treated with an SGLT2 inhibitor to prevent the development of incident heart failure. This includes people with type 2 diabetes and asymptomatic stage B heart failure. In the EMPA-REG OUTCOME trial, only 10% of study participants had a prior history of heart failure, and treatment with empagliflozin reduced the relative risk for hospitalization from heart failure by 35% (255). In the CANVAS Program, hospitalization from heart failure was reduced by 33% in people allocated to canagliflozin, and only 14% of individuals enrolled had a prior history of heart failure (256). In the DECLARE-TIMI 58 study, only 10% of study participants had a prior history of heart failure, and dapagliflozin reduced cardiovascular mortality and hospitalization for heart failure by 17%, which was consistent across multiple study subgroups regardless of a prior history of heart failure (258). Finally, in the Effect of Sotagliflozin on Cardiovascular and Renal Events in Participants With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial, randomization to the SGLT1/2 inhibitor sotagliflozin reduced the primary outcome of death from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure in people with type 2 diabetes, CKD, and risk for cardiovascular disease (284). Therefore, SGLT inhibitor treatment is recommended in asymptomatic people with type 2 diabetes at risk or with established cardiovascular disease to prevent incident heart failure and hospitalization from heart failure.

Finerenone. Finerenone is a nonsteroidal MRA and has recently been studied in people with diabetes and CKD, including the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and the Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease (FIGARO-DKD) studies. In FIDELIO-DKD, finerenone was compared with placebo for the primary outcome of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes in people with type 2 diabetes and CKD (285). A prespecified secondary outcome was death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for heart failure, which was reduced by 13% in the finerenone group. The incidence of heart failure hospitalization occurred less in the finerenone-treated group, and only 7.7% of study participants had a prior history of heart failure. In the FIGARO-DKD trial, finerenone reduced the primary outcome of death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for heart failure (HR 0.87 [95% CI 0.76–0.98]; P = 0.03) in people with type 2 diabetes and CKD (248). Only 7.8% of all participants had a prior history of heart failure, and the incidence of hospitalization for heart failure was reduced in the finerenone-allocated treatment arm (HR 0.71 [95% CI 0.56–0.90]). Owing to these observations, treatment with finerenone is recommended in people with type 2 diabetes and CKD to reduce the risk of progression from stage A heart failure to symptomatic incident heart failure.

Treatment of Symptomatic Heart Failure

In general, current guideline-directed medical therapy for a history of MI and symptomatic stage C and D heart failure in people with diabetes is similar to that for people without diabetes. At these advanced stages of heart failure, a collaborative approach with a cardiovascular specialist is recommended. The treatment recommendations are detailed in current 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines for the management of heart failure (12).

Glucose-Lowering Medications and Heart Failure: Discussion of Heart Failure Outcomes

Data on the effects of glucose-lowering agents on heart failure outcomes have demonstrated that thiazolidinediones have a strong and consistent relationship with increased risk of heart failure (286–288). Therefore, thiazolidinedione use should be avoided in people with symptomatic heart failure. Restrictions to use of metformin in people with medically treated heart failure were removed by the FDA in 2006 (289). Observational studies of people with type 2 diabetes and heart failure suggest that metformin users have better outcomes than individuals treated with other antihyperglycemic agents (290); however, no randomized trial of metformin therapy has been conducted in people with heart failure. Metformin may be used for the management of hyperglycemia in people with stable heart failure as long as kidney function remains within the recommended range for use (291).

Studies examining the relationship between DPP-4 inhibitors and heart failure have had mixed results. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) study showed that individuals treated with the DPP-4 inhibitor saxagliptin were more likely to be hospitalized for heart failure than those given placebo (3.5% vs. 2.8%, respectively) (292). However, three other cardiovascular outcomes trials—Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) (293), Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (294), and the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) (295)—did not find a significant increase in risk of heart failure hospitalization with DPP-4 inhibitor use compared with placebo. No increased risk of heart failure

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hospitalization has been identified in the cardiovascular outcomes trials of the GLP-1 RAs lixisenatide, liraglutide, semaglutide, exenatide once weekly, albiglutide, or dulaglutide compared with placebo (261,264, 265,296,297).

SGLT2 inhibitors reduce the incidence of heart failure and improve heart failure–related outcomes, including hospitalization for heart failure and heart failure–related symptoms, in people with diabetes with preserved or reduced ejection fraction (250,255–257,298–306). The results of these clinical trials have been extensively outlined in the 2024 American Diabetes Association "Standards of Care in Diabetes" (307). Briefly, in the EMPA-REG OUTCOME trial, the addition of empagliflozin to standard care led to a significant 35% reduction in hospitalization for heart failure compared with placebo (255). Similarly, in CANVAS and DECLARE-TIMI 58, there were 33% and 27% reductions, respectively, in hospitalization for heart failure with SGLT2 inhibitor use versus placebo (256,258). Additional data from the CREDENCE trial with canagliflozin showed a 39% reduction in hospitalization for heart failure and a 31% reduction in the composite of cardiovascular death or hospitalization for heart failure, in a population with CKD and albuminuria (UACR >300–5,000 mg/g) (257).

The DAPA-HF trial specifically evaluated the effects of dapagliflozin on the primary outcome of a composite of worsening heart failure or cardiovascular death in individuals with New York Heart Association (NYHA) class II, III, or IV heart failure and an ejection fraction of 40% or less (299,307). Dapagliflozin treatment had a lower risk of the primary outcome (HR 0.74 [95% CI 0.65–0.85]), lower risk of first worsening heart failure event (HR 0.70 [95% CI 0.59–0.83]), and lower risk of cardiovascular death (HR 0.82 [95% CI 0.69–0.98]) compared with placebo. The effect of dapagliflozin on the primary outcome was consistent regardless of the presence or absence of type 2 diabetes (299). Similar results were obtained in clinical trials with empagliflozin (303). In Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved), the primary outcome of cardiovascular death or hospitalization for heart failure was reduced in adults with NYHA functional class I–IV and chronic HFpEF (LVEF >40%), extending the previously seen benefit in people with heart failure to those with preserved ejection fraction irrespective of the presence of type 2 diabetes (250). A similar benefit for heart failure outcomes was seen in the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial for dapagliflozin in people with mildly reduced or preserved ejection fraction (302). In addition, a large meta-analysis (308) including the EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, DELIVER, and the Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trials included 21,947 individuals and demonstrated reduced risk for the composite of cardiovascular death or hospitalization for heart failure, cardiovascular death, first hospitalization for heart failure, and all-cause mortality. The findings on the studied end points were consistent in both trials of heart failure with mildly reduced or preserved ejection fraction and in all five trials combined. In addition to the hospitalization and mortality benefit in people with heart failure, SGLT2 inhibitors improve clinical stability and functional status in individuals with heart failure (301,304–306). Collectively, these studies indicate that SGLT2 inhibitors reduce the risk for heart failure hospitalization and cardiovascular death in a wide range of people with heart failure. Therefore, in people with type 2 diabetes and established HFpEF or HFrEF, an SGLT2 inhibitor with proven benefit in this population is recommended to reduce the risk of worsening heart failure and cardiovascular death. In addition, an SGLT2 inhibitor is recommended in this population to improve symptoms, physical limitations, and quality of life.

Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, was recently approved by the FDA to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure in people with heart failure or type 2 diabetes, CKD, and other cardiovascular risk factors. This drug is distinct from other SGLT inhibitors, as it lowers glucose via delayed glucose absorption in the gut via inhibition of the cotransporter SGLT1 in addition to increasing urinary glucose excretion; however, it is not currently approved by the FDA for glycemic management of type 1 or type 2 diabetes. Sotagliflozin was evaluated in the SCORED trial (284), which was ended early due to lack of funding, and examined the safety and efficacy of sotagliflozin in people with type 2 diabetes and CKD and risks for cardiovascular disease. Changes to the prespecified primary end points were made prior to unblinding to accommodate a lower-than-anticipated number of end point events. The primary end point of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure was reduced with sotagliflozin. In the SOLOIST trial, sotagliflozin initiated during or shortly after hospitalization in people with diabetes also reduced the risk for the primary end point of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure (309). The trial was originally also intended to evaluate the effects of SGLT inhibition in people with HFpEF, and ultimately no evidence of heterogeneity of treatment effect by ejection fraction was noted. However, the relatively small percentage of such individuals enrolled (only 21% of participants had ejection fraction >50%) and the early termination of the trial limited the ability to determine the effects of sotagliflozin in HFpEF specifically (309).

One concern with expanded use of SGLT inhibition is the infrequent but serious risk of diabetic ketoacidosis, including the atypical presentation of euglycemic ketoacidosis. There are multiple proposed pathways through which SGLT inhibition results in ketosis (increased β-hydroxybutyrate and acetoacetate), such as increased production due to reduction in insulin doses, increases in glucagon levels leading to increased lipolysis and ketone production, and decreased renal clearance of ketones (310,311). Thus, the use of SGLT inhibitors (whether for glycemic management or another indication) increases the susceptibility to diabetic ketoacidosis, particularly when other risk factors or situations occur (including, but not limited to, insulin pump malfunctions, significant reduction in insulin doses, and nutritional intake plans with prolonged periods of fasting or carbohydrate restriction). Although there were low rates of ketoacidosis in the cardiovascular and heart failure outcomes trials evaluating SGLT inhibition, these studies excluded individuals with type 1 diabetes and/or recent history of diabetic ketoacidosis (309,312). To decrease the risk of ketoacidosis when using SGLT inhibition in people with type 1 diabetes, it is recommended

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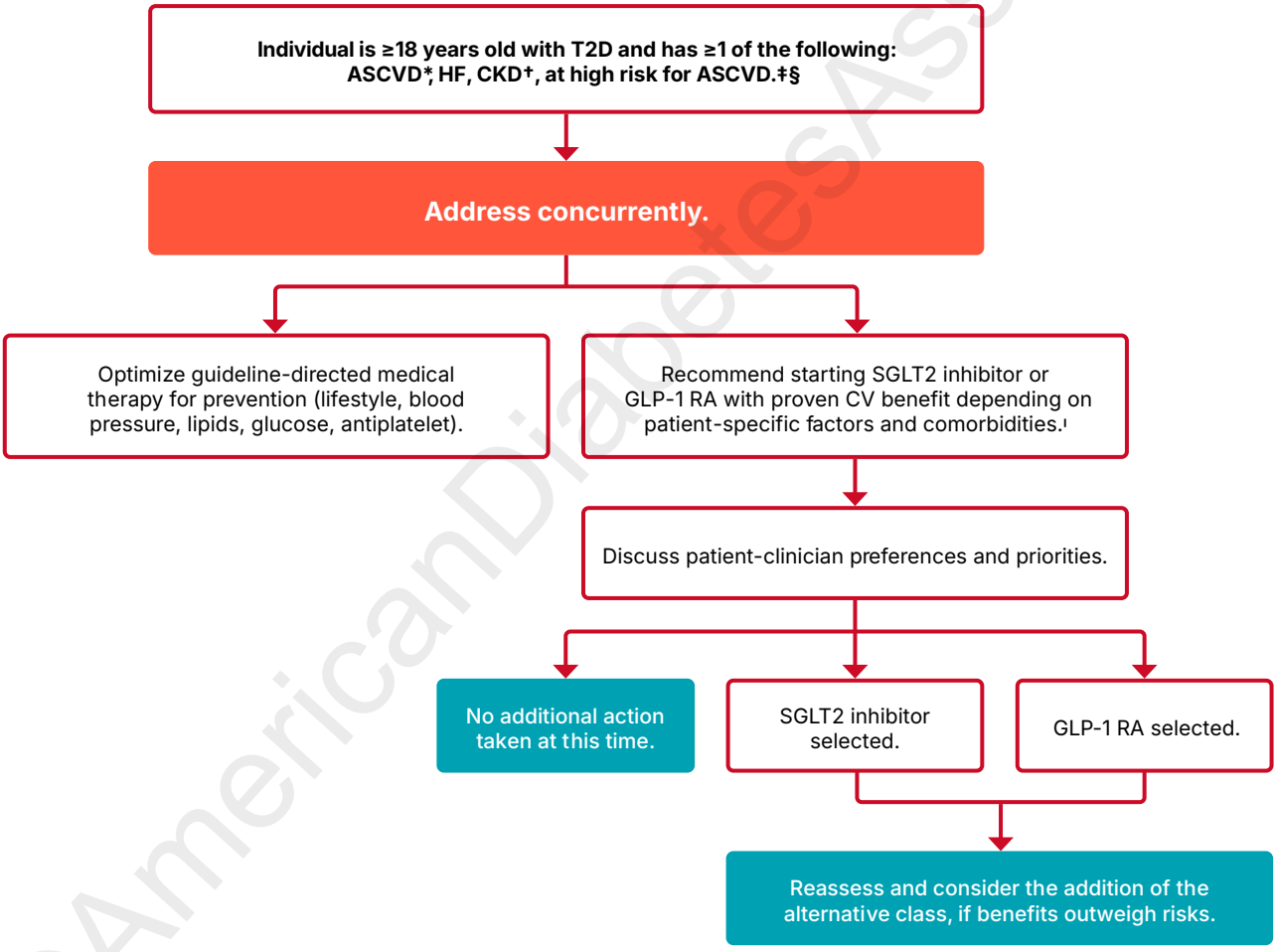
that clinicians assess the underlying susceptibility; provide education regarding the risks, symptoms, and prevention strategies; and prescribe home monitoring supplies for β-hydroxybutyrate (311,313). Use of these processes may have contributed to the lower rates of ketoacidosis seen in some of the studies of these agents for adjunctive glycemic management in people with type 1 diabetes (314–316) compared with those that did not include preventative strategies (310,317). Reassessment of susceptibility, education, and provision of monitoring supplies should reoccur throughout the duration of SGLT inhibitor treatment, particularly as preventative strategies and monitoring can minimize, but not eliminate, the risk of ketoacidosis in those who are susceptible (318,319).

The selective nonsteroidal MRA finerenone has been shown in the FIGARO-DKD trial, which included people with type 2 diabetes and CKD, to reduce the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure (248). A prespecified subgroup analysis from FIGARO-DKD further revealed that in individuals without symptomatic HFrEF, finerenone reduces the risk for new-onset heart failure and improves heart failure outcomes in people with type 2 diabetes and CKD (247). Furthermore, the incidence of heart failure hospitalization was reduced in finerenone-treated people with type 2 diabetes. Finally, in a pooled analysis from both FIDELIO-DKD and FIGARO-DKD, treatment with finerenone reduced the composite of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure was reduced (249). These collective studies indicate that finerenone improves cardiovascular and renal outcomes in people with type 2 diabetes. Therefore, in people



* ASCVD is defined as a history of an acute coronary syndrome or myocardial infarction, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

† CKD is a clinical diagnosis marked by reduced eGFR, the presence of albuminuria, or both.

‡ Consider an SGLT2 inhibitor when the individual has established ASCVD, HF, or CKD or is at high risk for ASCVD. Consider a GLP-1 RA when the individual has established ASCVD or is at high risk for ASCVD.

§ Individuals at high risk for ASCVD include those with end-organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, and obesity).

ˡ Most individuals enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

Figure 10.7—Approach to risk reduction with sodium–glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 receptor agonist (GLP-1 RA) therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; T2D, type 2 diabetes. Adapted with permission from Das et al. (324).

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with type 2 diabetes and CKD with albuminuria treated with maximum tolerated doses of ACE inhibitor or ARB, addition of finerenone should be considered to improve cardiovascular outcomes, including the risk for heart failure hospitalization, and to reduce the risk of CKD progression.

Approximately 45% of people admitted for HFpEF have diabetes, and most people with HFpEF have obesity (320,321). Conversely, weight loss improves symptoms of HFpEF (322). Therefore, the Semaglutide Treatment Effect in People with Obesity and HFpEF (STEP-HFpEF) trial evaluated whether the GLP-1 RA semaglutide improves symptoms related to heart failure (323). In the study, 616 people with type 2 diabetes and a BMI of 30 or greater with HFpEF were assigned to receive once-weekly semaglutide at a dose of 2.4 mg or placebo. The primary end point was the change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (range from 0 to 100) and the change in weight. After 1 year of treatment, the mean change in the score was 13.7 points with semaglutide and 6.4 points with placebo, and the mean body weight was reduced by 9.8% in the group assigned to semaglutide compared with 3.4% with placebo. In addition, in the confirmatory secondary end point, semaglutide treatment improved 6-min walk distance. In a hierarchical analysis, semaglutide favored the composite end point of death, heart failure events, change in the Kansas City Cardiomyopathy Questionnaire clinical summary score, and C-reactive protein levels. Therefore, the committee recommends treatment with a GLP-1 RA with demonstrated benefit in individuals with type 2 diabetes, obesity, and symptomatic HFpEF for the reduction of HF-related symptoms, physical limitations, and exercise function in this population.

Clinical Approach

As has been carefully outlined in **Fig. 9.3** in Section 9, "Pharmacologic Approaches to Glycemic Treatment," people with type 2 diabetes with or at high risk for ASCVD, heart failure, or CKD should be treated with a cardioprotective SGLT2 inhibitor and/or GLP-1 RA as part of the comprehensive approach to cardiovascular and kidney risk reduction. Importantly, these agents should be included in the plan of care irrespective of the need for additional glucose lowering and irrespective of metformin use. Such an approach has also been described in the ADA-endorsed American College of Cardiology "2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes" (324). **Figure 10.7**, reproduced from that decision pathway, outlines the approach to risk reduction with SGLT2 inhibitor or GLP-1 RA therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy.

Adoption of these agents should be reasonably straightforward in people with type 2 diabetes and established cardiovascular or kidney disease. Incorporation of SGLT2 inhibitor or GLP-1 RA therapy in the care of individuals with diabetes may need to replace some or all of their existing medications to minimize risks of hypoglycemia and adverse side effects and potentially to minimize medication costs. Close collaboration between primary and specialty care professionals can help facilitate these transitions in clinical care and, in turn, improve outcomes for people with type 2 diabetes who are at high risk for ASCVD, heart failure, or CKD.

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11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2025

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, "Children and Adolescents."

CHRONIC KIDNEY DISEASE

Screening

Recommendations

11.1a Assess kidney function (i.e., spot urine albumin-to-creatinine ratio [UACR]) and estimated glomerular filtration rate [eGFR] in people with type 1 diabetes with duration of ≥5 years and in all people with type 2 diabetes regardless of treatment. **B**

11.1b In people with established chronic kidney disease (CKD), monitor urinary albumin (e.g., spot UACR) and eGFR 1–4 times per year depending on the stage of the kidney disease (**Fig. 11.1**). **B**

Treatment

Recommendations

11.2 Optimize glucose management to reduce the risk or slow the progression of CKD (**Fig. 9.3**). **A**

11.3 Optimize blood pressure management (aim for <130/80 mmHg [**Fig. 10.2**]) and reduce blood pressure variability to reduce the risk or slow the progression of CKD and reduce cardiovascular risk. **A**

11.4a In nonpregnant people with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker (ARB) is recommended for those with moderately increased albuminuria (UACR 30–299 mg/g creatinine) **B** and is strongly recommended for those with severely increased albuminuria (UACR

*A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.

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CKD is classified based on: • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 2
	G2	Mildly decreased	60-89	Screen 1	Treat 1	Treat and refer 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15-29	Treat and refer 3	Treat and refer 3	**Treat and refer 4+**
	G5	Kidney failure	<15	**Treat and refer 4+**	**Treat and refer 4+**	**Treat and refer 4+**

Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

Figure 11.1—Risk of CKD progression, cardiovascular disease risk, and mortality; frequency of visits; and referral to nephrology according to GFR and albuminuria. The numbers in the boxes are a guide to the frequency of screening or monitoring (number of times per year). Green reflects no evidence of CKD by estimated GFR or albuminuria, with screening indicated once per year. For monitoring of prevalent CKD, suggested monitoring varies from once per year (yellow) to four times or more per year (i.e., every 1–3 months [deep red]) according to risks of CKD progression and CKD complications (e.g., cardiovascular disease, anemia, and hyperparathyroidism). These are general parameters based only on expert opinion and underlying comorbid conditions, and disease state must be taken into account, as should the likelihood of impacting a change in management for any individual. CKD, chronic kidney disease; GFR, glomerular filtration rate. Adapted from de Boer et al. (1).

≥300 mg/g creatinine) and/or eGFR <60 mL/min/1.73 m^2 to maximally tolerated dose to prevent the progression of kidney disease and reduce cardiovascular events. **A**

11.4b Monitor for increased serum creatinine and for increased serum potassium levels when ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists (MRAs) are used, or for hypokalemia when diuretics are used at routine visits and 7–14 days after initiation or after a dose change. **B**

11.4c An ACE inhibitor or an ARB is not recommended for the primary prevention of CKD in people with diabetes who have normal blood pressure, normal UACR (<30 mg/g creatinine), and normal eGFR. **A**

11.4d Continue renin-angiotensin system blockade for mild to moderate increases in serum creatinine (≤30%) in individuals who have no signs of extracellular fluid volume depletion. **A**

11.5a For people with type 2 diabetes and CKD, use of a sodium–glucose cotransporter 2 (SGLT2) inhibitor with demonstrated benefit is recommended to reduce CKD progression and cardiovascular events in individuals with eGFR ≥20 mL/min/1.73 m^2. **A**

11.5b To reduce cardiovascular risk and kidney disease progression in people with type 2 diabetes and CKD, a glucagon-like peptide 1 agonist with demonstrated benefit in this population is recommended. **A**

11.5c To reduce cardiovascular events and CKD progression in people with CKD and albuminuria, a nonsteroidal MRA that has been shown to be effective in clinical trials is recommended (if eGFR is ≥25 mL/min/1.73 m^2). Potassium levels should be monitored. **A**

11.6 Potentially harmful antihypertensive medications in pregnancy should be avoided in sexually active individuals of childbearing potential who are not using reliable contraception and, if used, should be switched prior to conception to antihypertensive medications considered safer during pregnancy. **B**

11.7 Aim to reduce urinary albumin by ≥30% in people with CKD and albuminuria ≥300 mg/g to slow CKD progression. **B**

11.8 For people with non–dialysis-dependent stage G3 or higher CKD, protein intake should be 0.8 g/kg body weight per day, as for the general population. **A** For individuals on dialysis, protein intake of 1.0–1.2 g/kg/day should be considered since protein energy wasting is a major problem for some individuals on dialysis. **B**

11.9 Individuals should be referred for evaluation by a nephrologist if they have continuously increasing urinary albumin levels and/or continuously decreasing eGFR and/or if the eGFR is <30 mL/min/1.73 m^2. **A**

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11.10 Refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease. **B**

EPIDEMIOLOGY OF DIABETES AND CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is diagnosed by the persistent elevation of urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage (1). In this section, the focus is on CKD attributed to diabetes in adults, which occurs in 20–40% of people with diabetes (1–4). CKD in people with diabetes typically develops after a duration of 10 years in type 1 diabetes (the most common presentation is 5–15 years after the diagnosis of type 1 diabetes) but may be present at diagnosis of type 2 diabetes. CKD can progress to kidney failure requiring dialysis or kidney transplantation and is the leading cause of end-stage kidney disease (ESKD) in the U.S. (5). In addition, among people with type 1 or type 2 diabetes, the presence of CKD markedly increases cardiovascular risk and health care costs (6). For details on the management of CKD in children with diabetes, please see Section 14, "Children and Adolescents."

ASSESSMENT OF ALBUMINURIA AND ESTIMATED GLOMERULAR FILTRATION RATE

Screening for albuminuria can be most easily performed by urine albumin-to-creatinine ratio (UACR) in a random spot urine collection (1). Timed or 24-h collections are more burdensome and add little to prediction or accuracy. Measurement of a spot urine sample for albumin alone (whether by immunoassay or by using a sensitive dipstick test specific for albuminuria) without simultaneously measuring urine creatinine is less expensive but susceptible to false-negative and false-positive determinations as a result of variation in urine concentration due to hydration (7). Thus, semiquantitative or qualitative (dipstick) screening will need to be confirmed by UACR values in an accredited laboratory (8,9). Hence, it is better to simply collect a spot urine sample for albumin-to-creatinine ratio because it will ultimately need to be done.

Normal level of urine albumin excretion is defined as $<$30 mg/g creatinine, moderately elevated albuminuria is defined as $\geq$30–300 mg/g creatinine, and severely elevated albuminuria is defined as $\geq$300 mg/g creatinine. However, UACR is a continuous measurement, and differences within the normal and abnormal ranges are associated with kidney and cardiovascular outcomes (6,10,11). Furthermore, because of high biological variability of $>$20% between measurements in urinary albumin excretion, two of three specimens of UACR collected within a 3-to 6-month period should be abnormal before considering an individual to have moderately or severely elevated albuminuria (1,12,13). Exercise within 24 h, infection, fever, heart failure, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage (14). Moreover, a recent analysis showed variability in the measurement of UACR when measured weekly over a 1-month period. Thus, repeated measurements and tracking of trending over time are needed to properly follow changes in UACR (12).

Traditionally, eGFR is calculated from serum creatinine using a validated formula (15). eGFR is routinely reported by laboratories along with serum creatinine, and eGFR calculators are available online at nkdep.nih.gov. An eGFR persistently $<$60 mL/min/1.73 m^2 and/or an urinary albumin value of $>$30 mg/g creatinine is considered abnormal, though optimal thresholds for clinical diagnosis are debated in older adults over age 70 years (1,16). Historically, a correction factor for muscle mass was included in a modified equation for African American people; however, race is a social and not a biologic construct, making it problematic to apply race to clinical algorithms. Hence, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation was refit without the race variable and should be used for everyone (17,18). Additionally, increased use of cystatin C (another marker of eGFR) is suggested in combination with serum creatinine because combining filtration markers (creatinine and cystatin C) is more accurate and would support better clinical decisions than either marker alone.

DIAGNOSIS OF CHRONIC KIDNEY DISEASE IN PEOPLE WITH DIABETES

CKD in people with diabetes is usually a clinical diagnosis made based on the presence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage. The typical presentation of CKD in people with diabetes is considered to include long-standing duration of diabetes, retinopathy, albuminuria without gross hematuria, and gradually progressive loss of eGFR. However, signs of CKD may be present at diagnosis or without retinopathy in type 2 diabetes. Reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 diabetes and is becoming more common over time as the prevalence of diabetes increases in the U.S. (2,3,16,19–21). An active urinary sediment (containing red or white blood cells or cellular casts), rapidly increasing albuminuria or total proteinuria, the presence of nephrotic syndrome, rapidly decreasing eGFR, or the absence of retinopathy (in type 1 diabetes) suggests alternative or additional causes of kidney disease. For individuals with these features, referral to a nephrologist for further diagnosis, including the possibility of kidney biopsy, should be considered. It is rare for people with type 1 diabetes to develop kidney disease without retinopathy. In type 2 diabetes, retinopathy is only moderately sensitive and specific for CKD caused by diabetes, as confirmed by kidney biopsy (22). It cannot be definitively stated that a person with diabetes and CKD has CKD related to diabetes unless the person has a kidney biopsy, as there may be another cause or multiple causes. Hence, without a biopsy, it is recommended to state that the individual has CKD in a person with diabetes. In most people, there is no need for a kidney biopsy, as the other possible diagnoses would not change treatment. Referral to a nephrologist should be done if there are any reasons to consider another cause of CKD in a person with diabetes (**Table 11.1**).

STAGING OF CHRONIC KIDNEY DISEASE

Stage G1 and stage G2 CKD are defined by evidence of high albuminuria with eGFR $\geq$60 mL/min/1.73 m^2, and stages G3-G5 CKD are defined by progressively lower ranges of eGFR (23) (**Fig. 11.1**). At any eGFR, the degree of albuminuria is

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Table 11.1—Reasons to consider nondiabetic kidney diseases in a person with chronic kidney disease and diabetes

- Type 1 diabetes duration <5 years
- Active urine sediment (e.g., containing red blood cells or cellular casts)
- Chronically well-managed blood glucose
- Rapidly declining eGFR
- Rapidly increasing or very high UACR or urine protein/creatinine level
- No retinopathy in a person with type 1 diabetes

Information adapted from Liang et al. (129). eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

associated with risk of cardiovascular disease (CVD), CKD progression, and mortality (6). Therefore, there is an additional subclassification by level of urine albumin (**Fig. 11.1**). Furthermore, Kidney Disease: Improving Global Outcomes (KDIGO) recommends a more comprehensive CKD staging that incorporates albuminuria at all stages of eGFR; this system is more closely associated with risk but is also more complex (1). Thus, based on the current classification system, both eGFR and albuminuria must be quantified to guide treatment decisions. Quantification of eGFR levels is essential for modifications of medication dosages or restrictions of use (**Fig. 11.1**) (23,24), and the degree of albuminuria should influence the choice of antihypertensive medications (see Section 10, "Cardiovascular Disease and Risk Management") or glucose-lowering medications (see below). Observed history of eGFR loss (which is also associated with risk of CKD progression and other adverse health outcomes) and cause of kidney damage (including possible causes other than diabetes) may also affect these decisions (25).

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is diagnosed by a sustained increase in serum creatinine over a short period of time, which is also reflected as a rapid decrease in eGFR (26,27). People with diabetes are at higher risk of AKI than those without diabetes (28). Other risk factors for AKI include preexisting CKD, the use of medications that cause kidney injury (e.g., nonsteroidal anti-inflammatory drugs), certain intravenous dyes (e.g., iodinated radiocontrast agents) and the use of medications that alter renal blood flow and intrarenal hemodynamics. In particular, many antihypertensive medications (e.g., diuretics, ACE inhibitors, and angiotensin receptor blockers [ARBs]) can reduce intravascular volume, renal blood flow, and/or glomerular filtration. There was concern that sodium–glucose cotransporter 2 (SGLT2) inhibitors may promote AKI through volume depletion, particularly when combined with diuretics or other medications that reduce glomerular filtration; however, this has not been found to be true in randomized controlled trials of advanced kidney disease (29) or high CVD risk with normal kidney function (30–32). It is also noteworthy that the nonsteroidal mineralocorticoid receptor antagonists (MRAs) do not increase the risk of AKI when used to slow kidney disease progression (33). Timely identification and treatment of AKI is important because AKI is associated with increased risks of progressive CKD and other poor health outcomes (34).

Elevations in serum creatinine (up to 30% from baseline) with renin-angiotensin system (RAS) blockers (such as ACE inhibitors and ARBs) must not be confused with AKI (35). An analysis of the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial demonstrated that participants randomized to intensive blood pressure lowering with up to a 30% increase in serum creatinine did not have any increase in mortality or progressive kidney disease (36,37). Moreover, a measure of markers for AKI showed no significant increase of any markers with increased creatinine (37).

Accordingly, ACE inhibitors and ARBs should not be discontinued for increases in serum creatinine (<30%) in the absence of volume depletion.

SURVEILLANCE

Both albuminuria and eGFR should be monitored annually to enable timely diagnosis of CKD, monitor progression of CKD, detect superimposed kidney diseases including AKI, assess risk of CKD complications, dose medications appropriately, and determine whether nephrology referral is needed. Among people with existing kidney disease, albuminuria and eGFR may change due to progression of CKD, development of a separate superimposed cause of kidney disease, AKI, or other effects of medications, as noted above. Serum potassium should also be monitored in individuals treated with diuretics because these medications can cause hypokalemia, which is associated with cardiovascular risk and mortality (38–40). Individuals with eGFR <60 mL/min/1.73 m^2 receiving ACE inhibitors, ARBs, or MRAs should have serum potassium measured periodically. Additionally, people with this lower range of eGFR should have their medication dosing verified, their exposure to nephrotoxins (e.g., nonsteroidal anti-inflammatory drugs and iodinated contrast) should be minimized, and they should be evaluated for potential CKD complications (**Table 11.2**).

There is a clear need for annual quantitative assessment of UACR. This is especially true after a diagnosis of albuminuria, institution of ACE inhibitors or ARB therapy to maximum tolerated doses, and achievement of blood pressure goals. Early changes in kidney function may be detected by increases in albuminuria before changes in eGFR (41), and this also significantly affects cardiovascular risk. Continued surveillance can assess both response to therapy and disease progression and may aid in assessing participation in ACE inhibitor or ARB therapy. In addition, in clinical trials of ACE inhibitor or ARB therapy in people with type 2 diabetes, reducing albuminuria to levels <300 mg/g creatinine or by >30% from baseline has been associated with improved kidney and cardiovascular outcomes, leading to the recommendation that medications should be titrated to maximize reduction in UACR (8). See **Table 11.3** for interventions that lower albuminuria.

Data from post hoc analyses demonstrate less benefit on cardiorenal outcomes at half doses of RAS blockade (42). In type 1 diabetes, remission of albuminuria may occur spontaneously, and cohort studies evaluating associations of change in albuminuria with clinical outcomes have reported inconsistent results (43,44).

The prevalence of CKD complications correlates with eGFR (40). When eGFR is <60 mL/min/1.73 m^2, screening for complications of CKD is indicated (**Table 11.2**). Early vaccination against hepatitis B virus is indicated in individuals likely to progress to ESKD (see Section 4, "Comprehensive Medical Evaluation and Assessment of

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Table 11.2—Screening for selected complications of chronic kidney disease

Complication	Physical and laboratory evaluation
Blood pressure >130/80 mmHg	Blood pressure, weight, BMI
Volume overload	History, physical examination, weight
Electrolyte abnormalities	Serum electrolytes
Metabolic acidosis	Serum electrolytes
Anemia	Hemoglobin; iron, iron saturation, ferritin testing if indicated
Metabolic bone disease	Serum calcium, phosphate, PTH, vitamin 25(OH)D

Complications of chronic kidney disease (CKD) generally become prevalent when estimated glomerular filtration rate falls below 60 mL/min/1.73 m^2 (stage G3 CKD or greater) and become more common and severe as CKD progresses. Evaluation of elevated blood pressure and volume overload should occur at every clinical contact possible; laboratory evaluations are generally indicated every 6–12 months for stage G3 CKD, every 3–5 months for stage G4 CKD, and every 1–3 months for stage G5 CKD, or as indicated to evaluate symptoms or changes in therapy. 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone.

Comorbidities," for further information on immunization).

Prevention

The only proven primary prevention interventions for CKD in people with diabetes are blood glucose (A1C goal of 7%) and blood pressure management. There is no evidence that renin-angiotensin-aldosterone system inhibitors or any other interventions prevent the development of CKD in the absence of hypertension or albuminuria. Thus, the American Diabetes Association does not recommend routine use of these medications solely for the purpose of prevention of the development of CKD. In 2023, the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) was published (45). This large prospective study compared liraglutide, sitagliptin, glimeperide, and insulin glargine with respect to achieving and maintaining A1C goals in people with type 2 diabetes treated with metformin monotherapy; kidney and cardiovascular end points were examined as secondary outcomes. A total of 5,047 participants were enrolled from July 2013 to August 2017 and were followed for an average of 5 years. Almost all participants did not have signs of kidney disease at the time of enrollment. No differences between the examined medications were observed, which suggests that there were no unique reno-protective effects among these medications for prevention. Of note, SGLT2 inhibitors were not included in the study, as these medications were not routinely available at the time the study started.

INTERVENTIONS

Nutrition

For people with stages 3–5 non–dialysis-dependent CKD, dietary protein intake should be ~0.8 g/kg body weight per day (the recommended daily allowance) (1). Compared with higher levels of dietary protein intake, this level slowed GFR decline with evidence of a greater effect over time. Higher levels of dietary protein intake (>20% of daily calories from protein or >1.3 g/kg/day) have been associated with increased albuminuria, more rapid kidney function loss, and CVD mortality and therefore should be avoided. Reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg/day is not recommended because it does not alter blood glucose levels, cardiovascular risk measures, or the course of GFR decline (46). Some organizations recommend a lower protein intake (0.6–0.8 g/kg/day). In particular, guidelines from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) (47) and the International Society of Renal Nutrition and Metabolism (48) recommend a lower protein intake level for reno-protection and state that this lower level is relatively safe. However, for CKD in diabetes, the expert grade is "opinion" only. The guidelines note that the evidence for lower protein intake in people with CKD has been published for only those without diabetes, which is graded Level 1A. Low-protein eating patterns should only be followed alongside guidance from a health care professional experienced in managing nutrition for people with CKD.

Restriction of dietary sodium (to <2,300 mg/day) may be useful to manage blood pressure and reduce cardiovascular risk (49,50), and individualization of dietary potassium may be necessary to manage serum potassium concentrations (28,38–40). These interventions may be most important for individuals with reduced eGFR, for whom urinary excretion of sodium and potassium may be impaired. For individuals on dialysis, higher levels of dietary protein intake should be considered since protein-energy wasting is a major problem for some individuals on dialysis (51). Recommendations for dietary sodium and potassium intake should be individualized based on comorbid conditions, medication use, blood pressure, and laboratory data.

Table 11.3—Interventions that lower albuminuria

- Blood glucose management
- Blood pressure management
- Treatment with ACE inhibitors or ARBs
- Smoking cessation
- Weight loss
- Changes in eating patterns (decreased salt intake and/or protein intake)
- Treatment with SGLT2 inhibitors, MRAs, or GLP-1 RAs

ARB, angiotensin receptor blocker; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MRA, mineralocorticoid receptor antagonist.

Glycemic Goals

Intensive lowering of blood glucose with the goal of achieving near-normoglycemia has been shown in large, randomized studies to delay the onset and progression of albuminuria and reduce eGFR in people with type 1 diabetes (52,53) and type 2 diabetes (1,54–59). Insulin alone was used to lower blood glucose in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study of type 1 diabetes, while a variety of agents were used in clinical trials of type 2 diabetes, supporting the conclusion that lowering blood glucose itself helps prevent CKD and its progression. The effects of glucose-lowering therapies on CKD have helped define A1C goals.

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The presence of CKD affects the risks and benefits of intensive lowering of blood glucose and a number of specific glucose-lowering medications. Adverse effects of intensive management of blood glucose levels (hypoglycemia and mortality) were increased among people with kidney disease at baseline (60). Moreover, there is a lag time of at least 2 years in type 2 diabetes to over 10 years in type 1 diabetes for the effects of intensive glucose control to manifest as improved eGFR outcomes (57,61,62). Therefore, in some people with prevalent CKD and substantial comorbidity, treatment may be less intensive (i.e., A1C goals may be higher) to decrease the risk of hypoglycemia (1,63). A1C levels are also less reliable at advanced CKD stages (64,65).

Blood Pressure and Use of ACE Inhibitors and Angiotensin Receptor Blockers

ACE inhibitors and ARBs remain a mainstay of management for people with CKD with albuminuria and for the treatment of hypertension in people with diabetes (with or without CKD in people with diabetes). Indeed, all the trials that evaluated the benefits of SGLT2 inhibition or nonsteroidal MRA effects were done in individuals who were being treated with an ACE inhibitor or ARB, in some trials up to maximum tolerated doses.

Hypertension is a strong risk factor for the development and progression of CKD (66). Antihypertensive therapy reduces the risk of albuminuria (67–70), and among people with type 1 or 2 diabetes with established CKD (eGFR $<$60 mL/min/1.73 m^2 and UACR $\geq$300 mg/g creatinine), ACE inhibitor or ARB therapy reduces the risk of progression to ESKD (71–80). Moreover, antihypertensive therapy reduces the risk of cardiovascular events (67).

A blood pressure level $<$130/80 mmHg is recommended to reduce CVD mortality and slow CKD progression among all people with diabetes. Lower blood pressure goals (e.g., $<$130/80 mmHg) should be considered based on individual anticipated benefits and risks. People with CKD are at increased risk of CKD progression (particularly those with albuminuria) and CVD; therefore, lower blood pressure goals may be suitable in some cases, especially in individuals with severely elevated albuminuria ($\geq$300 mg/g creatinine).

ACE inhibitors or ARBs are the preferred first-line agents for blood pressure treatment among people with diabetes, hypertension, eGFR $<$60 mL/min/1.73 m^2, and UACR $\geq$300 mg/g creatinine because of their proven benefits for prevention of CKD progression (71,72,74). ACE inhibitors and ARBs are considered to have similar benefits (75,76) and risks. In the setting of lower levels of albuminuria (30–299 mg/g creatinine), ACE inhibitor or ARB therapy at maximum tolerated doses in trials has reduced progression to more advanced albuminuria ($\geq$300 mg/g creatinine), slowed CKD progression, and reduced cardiovascular events but has not reduced progression to ESKD (74,77). While ACE inhibitors or ARBs are often prescribed for moderately increased albuminuria (30–299 mg/g creatinine) without hypertension, outcome trials have not been performed in this setting to determine whether they improve kidney outcomes. Moreover, two long-term, double-blind studies demonstrated no renoprotective effect of either ACE inhibitors or ARBs among people with type 1 and type 2 diabetes who were normotensive with or without high albuminuria (formerly microalbuminuria, 30–299 mg/g creatinine) (78,79).

It should be noted that ACE inhibitors and ARBs are commonly not dosed at maximum tolerated doses because of concerns that serum creatinine will rise. As previously noted, not maximizing these therapies for this reason would be considered suboptimal care. Note that in all clinical trials demonstrating efficacy of ACE inhibitors and ARBs in slowing kidney disease progression, the maximum tolerated doses were used—not very low doses that do not provide benefit. Moreover, there are now studies demonstrating outcome benefits on both mortality and slowed CKD progression in people with diabetes who have an eGFR $<$30 mL/min/1.73 m^2 (80). Additionally, when increases in serum creatinine reach 30% without associated hyperkalemia, RAS blockade should be continued (36,81).

Two recent large retrospective analyses provide additional support for the aggressive use of ACE inhibitors and ARBs in individuals with CKD. Ku et al. (82) reviewed 17 trials that included 11,800 individuals with CKD (defined as eGFR $<$60 mL/min/1.73 m^2); 82% had diabetes. The authors reported that a $<$13% decline in eGFR over a 3-month period or a $<$21% decline in a 1-month period was associated with better long-term kidney outcomes. Hattori et al. (83) evaluated 6,065 participants between 2005 and 2021 (approximately 40% had diabetes) with eGFR ranging from 10 to 60 mL/min/1.73 m^2 who had ACE inhibitors or ARBs stopped (usually due to hyperkalemia or AKI) and found that those who restarted the ACE inhibitor or ARB had better long-term kidney outcomes and lower mortality (there was no significant difference in hyperkalemia in those who restarted ACE inhibitors or ARBs). There is also an accompanying editorial that details the strengths and weaknesses of the studies (84).

In the absence of kidney disease, ACE inhibitors or ARBs are useful to manage blood pressure but have not proven superior to alternative classes of antihypertensive therapy, including thiazide-like diuretics and dihydropyridine calcium channel blockers (85). In a trial of people with type 2 diabetes and normal urinary albumin excretion, an ARB reduced or suppressed the development of albuminuria but increased the rate of cardiovascular events (86). In a trial of people with type 1 diabetes exhibiting neither albuminuria nor hypertension, ACE inhibitors or ARBs did not prevent the development of glomerulopathy assessed by kidney biopsy (78). This was further supported by a similar trial in people with type 2 diabetes (79).

Two clinical trials studied the combinations of ACE inhibitors and ARBs and found no benefits on CVD or CKD, and the medication combination had higher adverse event rates (hyperkalemia and/or AKI) (87,88). Therefore, the combined use of ACE inhibitors and ARBs should be avoided.

Direct Kidney Effects of Glucose-Lowering Medications

Some glucose-lowering medications also have effects on the kidney that are direct, i.e., not mediated through glycemia. For example, SGLT2 inhibitors reduce renal tubular glucose reabsorption, weight, systemic blood pressure, intraglomerular pressure, and albuminuria and slow GFR loss through mechanisms that appear independent of glycemia (31,89–92). Moreover, recent data support the notion that SGLT2 inhibitors reduce oxidative stress in the kidney by $>$50% and blunt increases in angiotensinogen as well as reduce NLRP3 inflammasome

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activity (92–94). Glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) have also been shown to improve kidney outcomes (95–100). Kidney effects should be considered when selecting agents for glucose lowering (see Section 9, "Pharmacologic Approaches to Glycemic Treatment").

Selection of Glucose-Lowering Medications for People With Chronic Kidney Disease

For people with type 2 diabetes and established CKD, special considerations for the selection of glucose-lowering medications include limitations to available medications when eGFR is diminished and a desire to mitigate risks of CKD progression, CVD, and hypoglycemia (101,102). Medication dosing may require modification with eGFR <60 mL/min/1.73 m^2 (1). **Figure 11.2** shows the American Diabetes Association and KDIGO consensus recommendation algorithm for medications in people with diabetes and CKD.

The FDA revised its guidance for the use of metformin in CKD in 2016 (103), recommending use of eGFR instead of serum creatinine to guide treatment and expanding the pool of people with kidney disease for whom metformin treatment should be considered. The revised FDA guidance states that *1*) metformin is contraindicated in individuals with an eGFR <30 mL/min/1.73 m^2, *2*) eGFR should be monitored while taking metformin, *3*) the benefits and risks of continuing treatment should be reassessed when eGFR falls to <45 mL/min/1.73 m^2 (104,105), *4*) metformin should not be initiated for individuals with an eGFR <45 mL/min/1.73 m^2, and *5*) metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in individuals with eGFR 30–60 mL/min/1.73 m^2.

A number of recent studies have shown cardiovascular protection from SGLT2 inhibitors and GLP-1 RAs as well as kidney protection from SGLT2 inhibitors and from GLP-1 RAs. Selection of which glucose-lowering medications to use should be based on the usual criteria of an individual's risks (cardiovascular and kidney in addition to glucose management) as well as considerations of effects on weight, other adverse effects, individual preferences, and cost.

SGLT2 inhibitors are recommended for people with eGFR ≥20 mL/min/1.73 m^2 and type 2 diabetes, as they slow CKD progression and reduce heart failure risk independent of glucose management (106). GLP-1 RAs are suggested for cardiovascular risk reduction if such risk is a predominant problem, as they reduce risks of CVD events and hypoglycemia and slow progression of CKD (100,107–110).

A number of large cardiovascular outcomes trials in people with type 2 diabetes

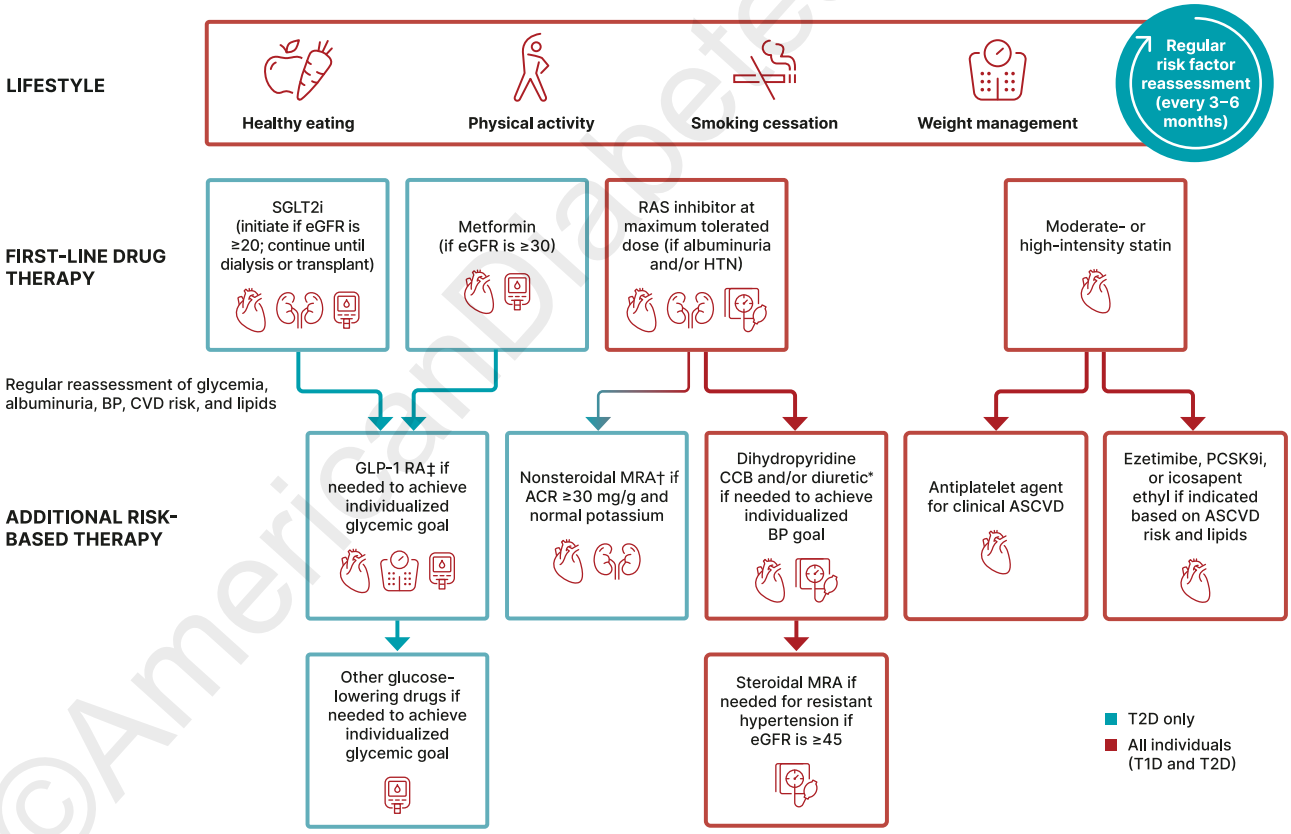

Figure 11.2—Holistic approach for improving outcomes in people with diabetes and CKD. Icons presented indicate the following benefits: BP cuff, BP lowering; glucose meter, glucose lowering; heart, cardioprotection; kidney, kidney protection; scale, weight management. eGFR is presented in units of mL/min/1.73 m^2. *ACEi or ARB (at maximal tolerated doses) should be first-line therapy for hypertension when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker or diuretic can also be considered; all three classes are often needed to attain BP targets. †Finerenone is currently the only ns-MRA with proven clinical kidney and cardiovascular benefits. ‡Semaglutide can be used as another first-line agent for people with CKD. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes. Adapted from de Boer et al. (1).

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at high risk for CVD or with existing CVD examined kidney effects as secondary outcomes. These trials include EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients], CANVAS (Canagliflozin Cardiovascular Assessment Study), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), and SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) (91,95,98,111). Specifically, compared with placebo, empagliflozin reduced the risk of incident or worsening nephropathy (a composite of progression to UACR >300 mg/g creatinine, doubling of serum creatinine, ESKD, or death from ESKD) by 39% and the risk of doubling of serum creatinine accompanied by eGFR ≤45 mL/min/1.73 m^2 by 44%; canagliflozin reduced the risk of progression of albuminuria by 27% and the risk of reduction in eGFR, ESKD, or death from ESKD by 40%; liraglutide reduced the risk of new or worsening nephropathy (a composite of persistent macroalbuminuria, doubling of serum creatinine, ESKD, or death from ESKD) by 22%; and semaglutide reduced the risk of new or worsening nephropathy (a composite of persistent UACR >300 mg/g creatinine, doubling of serum creatinine, or ESKD) by 36% (each $P < 0.01$). These analyses were limited by evaluation of study populations not selected primarily for CKD and examination of kidney effects as secondary outcomes.

Three large clinical trials of SGLT2 inhibitors have focused on people with CKD and assessment of primary kidney outcomes. Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), a placebo-controlled trial of canagliflozin among 4,401 adults with type 2 diabetes, UACR ≥300–5,000 mg/g creatinine, and eGFR range 30–90 mL/min/1.73 m^2 (mean eGFR 56 mL/min/1.73 m^2 with a mean albuminuria level of >900 mg/day), had a primary composite end point of ESKD, doubling of serum creatinine, or renal or cardiovascular death (29,112). It was stopped early due to positive efficacy and showed a 32% risk reduction for development of ESKD over control (29). Additionally, the development of the primary end point, which included dialysis for ≥30 days, kidney transplantation or eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days by central laboratory assessment, doubling from the baseline serum creatinine average sustained for ≥30 days by central laboratory assessment, or renal death or cardiovascular death, was reduced by 30%. This benefit was on background ACE inhibitor or ARB therapy in >99% of the participants (29). Moreover, in this advanced CKD group, there were clear benefits on cardiovascular outcomes demonstrating a 31% reduction in cardiovascular death or heart failure hospitalization and a 20% reduction in cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (29,110,113).

A second trial in advanced CKD in people with diabetes was the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) study (114). This trial examined a cohort similar to that in CREDENCE except 67.5% of the participants had type 2 diabetes and CKD (the other one-third had CKD without type 2 diabetes), and the end points were slightly different. The primary outcome was time to the first occurrence of any of the components of the composite, including ≥50% sustained decline in eGFR or reaching ESKD or cardiovascular death, or renal death. Secondary outcome measures included time to the first occurrence of any of the components of the composite kidney outcome (≥50% sustained decline in eGFR or reaching ESKD or renal death), time to the first occurrence of either of the components of the cardiovascular composite (cardiovascular death or hospitalization for heart failure), and time to death from any cause. The trial had 4,304 participants with a mean eGFR at baseline of 43.1 ± 12.4 mL/min/1.73 m^2 (range 25–75 mL/min/1.73 m^2) and a median UACR of 949 mg/g (range 200–5,000 mg/g). There was a significant benefit by dapagliflozin for the primary end point (hazard ratio [HR] 0.61 [95% CI 0.51–0.72]; $P < 0.001$) (114). The HR for the kidney composite of a sustained decline in eGFR of ≥50%, ESKD, or death from renal causes was 0.56 (95% CI 0.45–0.68; $P < 0.001$). The HR for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI 0.55–0.92; $P = 0.009$). Finally, all-cause mortality was decreased in the dapagliflozin group compared with the placebo group ($P < 0.004$).

The most recently published clinical trial was EMPA-KIDNEY (Study of Heart and Kidney Protection with Empagliflozin) (115). This study enrolled participants with kidney disease with an eGFR of at least 20 but less than 45 mL/min/1.73 m^2 or who had an eGFR of at least 45 but less than 90 mL/min/1.73 m^2 with a UACR of at least 200 mg/g creatinine. Approximately one-half of the 6,609 participants had diabetes. The empagliflozin-treated participants had lower risk of progression of kidney disease and lower risk of death from cardiovascular causes (HR 0.72 [95% CI 0.64–0.82]; $P < 0.001$).

With respect to cardiovascular outcomes, SGLT2 inhibitors have demonstrated reduced risk of heart failure hospitalizations and some also demonstrated cardiovascular risk reduction. GLP-1 RAs have clearly demonstrated cardiovascular benefits. (See Section 10, "Cardiovascular Disease and Risk Management," for further detailed discussion.)

Of note, while the glucose-lowering effects of SGLT2 inhibitors are blunted with eGFR <45 mL/min/1.73 m^2, the renal and cardiovascular benefits were still seen at eGFR levels as low as 20 mL/min/1.73 m^2 even with no significant change in glucose (29,31,52,63,98,111,114–116). Most participants with CKD in these trials also had diagnosed atherosclerotic cardiovascular disease (ASCVD) at baseline, although ∼28% of CANVAS participants with CKD did not have diagnosed ASCVD (32).

Based on evidence from the CREDENCE, DAPA-CKD, and EMPA-KIDNEY trials, as well as secondary analyses of cardiovascular outcomes trials with SGLT2 inhibitors, cardiovascular and renal events are reduced with SGLT2 inhibitor use in individuals with an eGFR of 20 mL/min/1.73 m^2, independent of glucose-lowering effects (110,113).

The recently published FLOW study demonstrated that the GLP-1 RA semaglutide had reno-protective effects in people with CKD (100). The study enrolled 3,533 participants with significant kidney disease defined by level of eGFR and/or by level of albuminuria (of note, all participants had an albuminuria level of at least 100 mg/g). The primary outcome was defined as the first major kidney disease event (onset of >50% in eGFR, onset of persistent eGFR of <15 mL/min/1.73 m^2, initiation of dialysis or transplant, renal death, and cardiovascular death). The study was stopped early due to reaching a prespecified outcome. There was a 24% lower HR for those taking semaglutide compared with the placebo group. Of note, cardiovascular deaths

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comprised about 38% of the events. When the cardiovascular deaths are removed from the analysis, the HR for kidney specific events was 21% lower in those taking semaglutide. Thus, the study supports a beneficial effect of semaglutide in slowing decline in kidney function as well as being cardioprotective in people with CKD and type 2 diabetes. Of note, the participants who took semaglutide had lower A1C, lower blood pressure, and more weight loss—all of which are beneficial for slowing decline in kidney function and reducing cardiovascular adverse events. Whether this beneficial combination of effects was the primary cause for the renoprotective outcomes or whether there is a unique reno-protective effect of semaglutide remains to be determined.

Adverse event profiles of these agents also must be considered. Please refer to **Table 9.2** for medication-specific factors, including adverse event information, for these agents. Additional clinical trials focusing on CKD and cardiovascular outcomes in people with CKD are ongoing and will be reported in the next few years.

For people with type 2 diabetes and CKD, the selection of specific agents may depend on comorbidity and CKD stage. SGLT2 inhibitors are recommended for individuals at high risk of CKD progression (i.e., with albuminuria or a history of documented eGFR loss) (**Fig. 9.3**). For people with type 2 diabetes and CKD, use of an SGLT2 inhibitor in individuals with eGFR ≥20 mL/min/1.73 m^2 is recommended to reduce CKD progression and cardiovascular events. The reason for the limit of eGFR is as follows. The major clinical trials for SGLT2 inhibitors that showed benefit for CKD in people with diabetes are CREDENCE, DAPA-CKD, and EMPA-KIDNEY. CREDENCE enrollment criteria included eGFR >30 mL/min/1.73 m^2 and UACR >300 mg/g (29,110). DAPA-CKD enrolled individuals with eGFR >25 mL/min/1.73 m^2 and UACR >200 mg/g. Subgroup analyses from DAPA-CKD (117) and analyses from the EMPEROR heart failure trials suggest that SGLT2 inhibitors are safe and effective at eGFR levels of >20 mL/min/1.73 m^2. The Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) enrolled 5,998 participants (118), and the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) enrolled 3,730 participants (119); enrollment criteria included eGFR >60 mL/min/1.73 m^2, but efficacy was seen at eGFR >20 mL/min/1.73 m^2 in people with heart failure. Most recently, the EMPA-KIDNEY trial showed efficacy in participants with eGFR as low as 20 mL/min/1.73 m^2 (115). Hence, the new recommendation is to use SGLT2 inhibitors in individuals with eGFR as low as 20 mL/min/1.73 m^2. In addition, the DECLARE-TIMI 58 trial suggested effectiveness in participants with normal urinary albumin levels (120). In sum, for people with type 2 diabetes and CKD, use of an SGLT2 inhibitor is recommended to reduce CKD progression and cardiovascular events in people with an eGFR ≥20 mL/min/1.73 m^2.

Of note, GLP-1 RAs may also be used at low eGFR for cardiovascular protection but may require dose adjustment (121).

Renal and Cardiovascular Outcomes of Mineralocorticoid Receptor Antagonists in Chronic Kidney Disease

MRAs historically have not been well studied in people with diabetes and CKD because of the risk of hyperkalemia (122,123). However, data that do exist suggest sustained benefit on albuminuria reduction. There are two different classes of MRAs, steroidal and nonsteroidal, with one group not extrapolatable to the other (124). Late in 2020, the results of the first of two trials, the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial, which examined the kidney effects of finerenone, demonstrated a significant reduction in CKD progression and cardiovascular events in people with diabetes and advanced CKD (33,125). This trial had a primary end point of time to first occurrence of the composite end point of onset of kidney failure, a sustained decrease of eGFR >40% from baseline over at least 4 weeks, or renal death. A prespecified secondary outcome was time to first occurrence of the composite end point of cardiovascular death or nonfatal cardiovascular events (myocardial infarction, stroke, or hospitalization for heart failure). Other secondary outcomes included all-cause mortality, time to all-cause hospitalizations, and change in UACR from baseline to month 4, and time to first occurrence of the following composite end point: onset of kidney failure, a sustained decrease in eGFR of ≥57% from baseline over at least 4 weeks, or renal death.

The double-blind, placebo-controlled trial randomized 5,734 people with CKD and type 2 diabetes to receive finerenone, a nonsteroidal MRA, or placebo. Eligible participants had a UACR of 30 to <300 mg/g, an eGFR of 25 to <60 mL/min/1.73 m^2, and diabetic retinopathy, or a UACR of 300–5,000 mg/g and an eGFR of 25 to <75 mL/min/1.73 m^2. The potassium level had to be ≤4.8 mmol/L. The mean age of participants was 65.6 years, and 30% were female. The mean eGFR was 44.3 mL/min/1.73 m^2, and the mean albuminuria was 852 mg/g (interquartile range 446–1,634 mg/g). The primary end point was reduced with finerenone compared with placebo (HR 0.82 [95% CI 0.73–0.93]; P = 0.001), as was the key secondary composite of cardiovascular outcomes (HR 0.86 [95% CI 0.75–0.99]; P = 0.03). Hyperkalemia resulted in 2.3% discontinuation in the study group compared with 0.9% in the placebo group. However, the study was completed, and there were no deaths related to hyperkalemia. Of note, 4.5% of the total group were being treated with SGLT2 inhibitors.

The Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial assessed the safety and efficacy of finerenone in reducing cardiovascular events among people with type 2 diabetes and CKD with elevated UACR (30 to <300 mg/g creatinine) and eGFR 25–90 mL/min/1.73 m^2 (126). The potassium level had to be ≤4.8 mmol/L The study randomized eligible subjects to either finerenone (n = 3,686) or placebo (n = 3,666). Participants with an eGFR of 25–60 mL/min/1.73 m^2 at the screening visit received an initial dose at baseline of 10 mg once daily, and if eGFR at screening was ≥60 mL/min/1.73 m^2, the initial dose was 20 mg once daily. An increase in the dose from 10 to 20 mg once daily was encouraged after 1 month, provided the serum potassium level was ≤4.8 mmol/L and eGFR was stable. The mean age of participants was 64.1 years (31% were female), and the median follow-up duration was 3.4 years. The median A1C was 7.7%, the mean systolic blood pressure was 136 mmHg, and the mean GFR was 67.8 mL/min/1.73 m^2. People with heart failure with a reduced ejection fraction and uncontrolled hypertension were excluded.

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The primary composite outcome was cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure. The finerenone group showed a 13% reduction in the primary end point compared with the placebo group (12.4% vs. 14.2%; HR 0.87 [95% CI 0.76–0.98]; *P* = 0.03). This benefit was primarily driven by a reduction in heart failure hospitalizations: 3.2% vs. 4.4% in the placebo group (HR 0.71 [95% CI 0.56–0.90]).

Of the secondary outcomes, the most noteworthy was a 36% reduction in ESKD: 0.9% vs. 1.3% in the placebo group (HR 0.64 [95% CI 0.41–0.995]). There was a higher incidence of hyperkalemia in the finerenone group, 10.8% vs. 5.3%, although only 1.2% of the 3,686 individuals on finerenone stopped the study due to hyperkalemia.

The FIDELITY prespecified pooled efficacy and safety analysis incorporated individuals from both the FIGARO-DKD and FIDELIO-DKD trials (*N* = 13,171) to allow for evaluation across the spectrum of severity of CKD, since the populations were different (with a slight overlap) and the study designs were similar (127). The analysis showed a 14% reduction in composite cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure for finerenone vs. placebo (12.7% vs. 14.4%; HR 0.86 [95% CI 0.78–0.95]; *P* = 0.0018).

It also demonstrated a 23% reduction in the composite kidney outcome, consisting of sustained ≥57% decrease in eGFR from baseline over ≥4 weeks, or renal death, for finerenone vs. placebo (5.5% vs. 7.1%; HR 0.77 [95% CI 0.670.88]; *P* = 0.0002).

The pooled FIDELITY trial analysis confirms and strengthens the positive cardiovascular and kidney outcomes with finerenone across the spectrum of CKD, irrespective of baseline ASCVD history (with the exclusion of those with heart failure with reduced ejection fraction).

Of note, there has not been a direct comparison of MRAs and SGLT2 inhibitors. At this time, they can be used interchangeably or together for the goal of slowing progression of CKD and providing cardiovascular protection. There have also been no studies directly comparing MRAs, SGLT2 inhibitors, and GLP-1 RAs. Health care professionals should use their best judgement as to which medication to prescribe initially and in combination. As noted, all of these studies included participants taking either an ACE inhibitor or an ARB, often at maximally tolerated doses.

REFERRAL TO A NEPHROLOGIST

Health care professionals should consider referral to a nephrologist if the individual with diabetes has continuously rising UACR levels and/or continuously declining eGFR, if there is uncertainty about the etiology of kidney disease, for difficult management issues (anemia, secondary hyperparathyroidism, significant increases in albuminuria despite good blood pressure management, metabolic bone disease, resistant hypertension, or electrolyte disturbances), or when there is advanced kidney disease (eGFR <30 mL/min/1.73 m^2) requiring discussion of renal replacement therapy for ESKD (1). The threshold for referral may vary depending on the frequency with which a health care professional encounters people with diabetes and kidney disease. Consultation with a nephrologist when stage 4 CKD develops (eGFR <30 mL/min/1.73 m^2) has been found to reduce cost, improve quality of care, and delay dialysis (128).

However, other specialists and health care professionals should also educate people with diabetes about the progressive nature of CKD, the kidney preservation benefits of proactive treatment of blood pressure and blood glucose, and the potential need for renal replacement therapy.

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12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes—2025

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, "Children and Adolescents."

DIABETIC RETINOPATHY

Recommendations

12.1 Implement strategies to help people with diabetes reach glycemic goals to reduce the risk or slow the progression of diabetic retinopathy. **A**

12.2 Implement strategies to help people with diabetes reach blood pressure and lipid goals to reduce the risk or slow the progression of diabetic retinopathy. **A**

Diabetic retinopathy is a highly specific neurovascular complication of both type 1 and type 2 diabetes, with prevalence strongly related to both the duration of diabetes and the level of glycemic management (1). Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years in developed countries. Glaucoma, cataracts, and other eye disorders occur earlier and more frequently in people with diabetes.

In addition to diabetes duration, factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycemia (2,3), nephropathy (4), hypertension (5), and dyslipidemia (6–8). Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy, reduce the need for future ocular surgical procedures, and potentially improve self-reported visual function (2,6,9–11). A meta-analysis of data from cardiovascular outcomes studies showed no association between glucagon-like peptide 1 receptor agonist (GLP-1 RA) treatment and retinopathy per se, except through the association between retinopathy and average A1C reduction at the 3-month and 1-year follow-up. Long-term impact of improved glycemic management on retinopathy was not studied in these trials. However, GLP-1 RAs including liraglutide, semaglutide, and dulaglutide have been shown to be

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associated with a risk of mildly worsening diabetic retinopathy in randomized trials (12,13). Further data from clinical studies with longer follow-up purposefully designed for diabetic retinopathy risk assessment, particularly including individuals with established diabetic retinopathy, are needed. Retinopathy status should be assessed when glucose-lowering therapies are intensified, such as those using GLP-1 RAs, since rapid reductions in A1C can be associated with initial worsening of retinopathy (14).

Screening

Recommendations

12.3 Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. **B**

12.4 People with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. **B**

12.5 If there is no evidence of retinopathy from one or more annual eye exams and glycemic indicators are within the goal range, then screening every 1–2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations by an ophthalmologist will be required more frequently. **B**

12.6 Programs that use retinal photography with remote reading or the use of U.S. Food and Drug Administration–approved artificial intelligence algorithms to improve access to diabetic retinopathy screening are appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **B**

12.7 Counsel individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant on the risk of development and/or progression of diabetic retinopathy. **B**

12.8 Individuals with preexisting type 1 or type 2 diabetes should receive an eye exam before pregnancy as well as in the first trimester and may need to be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy. **B**

Identifying individuals with diabetes-related eye disease is important because people with vision-threatening retinopathy may be asymptomatic. Additionally, current therapies can not only prevent vision loss but also help improve vision for many individuals. Prompt diagnosis allows triage of people with diabetes and timely intervention that may prevent vision loss in individuals who are asymptomatic despite advanced diabetes-related eye disease.

Diabetic retinopathy screening should be performed using validated approaches and methodologies. Youth with type 1 or type 2 diabetes are also at risk for complications and need to be screened for diabetic retinopathy (15–17) (see Section 14, "Children and Adolescents"). If diabetic retinopathy is evident on screening, prompt referral to an ophthalmologist is recommended. Subsequent examinations for individuals with type 1 or type 2 diabetes are generally repeated annually for individuals without or with mild retinopathy. Exams every 1–2 years may be cost-effective after one or more normal eye exams. In a population with well-managed type 2 diabetes, there was little risk of development of significant retinopathy within a 3-year interval after a normal examination (18), and less frequent intervals have been found in simulated modeling to be potentially effective in screening for diabetic retinopathy in individuals without diabetic retinopathy (19). However, it is important to adjust screening intervals based on the presence of specific risk factors for retinopathy onset and worsening retinopathy. More frequent examinations by the ophthalmologist will be required if retinopathy is progressing or risk factors such as not meeting glycemic goals, advanced retinopathy, or diabetic macular edema are present.

Retinal photography with remote reading by experts has great potential to provide screening services in areas where qualified eye care professionals are not readily available (20–22). High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care professional or reading center technician or by artificial intelligence (AI) programs that are U.S. Food and Drug Administration (FDA) approved for this purpose. Retinal photography may also enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for treatment (20,23,24). In-person exams are still necessary when the retinal photos are of unacceptable quality and for follow-up if abnormalities are detected. Retinal photos are not a substitute for dilated comprehensive eye exams, which should be performed at least initially and at yearly intervals thereafter or more frequently as recommended by an eye care professional. AI systems that detect more than mild diabetic retinopathy and diabetic macular edema that have been authorized for use by the FDA represent an alternative to traditional screening approaches (25). Three AI platforms have been approved by the FDA for diabetic retinopathy screening and examination: AEYE diagnostic screening technology, or AEYE-DS (AEYE Health); EyeArt AI screening system (Eyenuk); and LumineticsCore, formerly IDx-DR (Digital Diagnostics). These services are covered by most insurance plans. Prospective multicenter clinical trials on diagnostic accuracy have been published for each platform (26). However, the benefits and optimal utilization of this type of screening have yet to be fully determined. Results of all screening eye examinations should be documented and transmitted to the referring health care professional.

Type 1 Diabetes

Because retinopathy is estimated to take at least 5 years to develop after the onset of hyperglycemia, people with type 1 diabetes should have an initial dilated and comprehensive eye examination within 5 years after the diagnosis of diabetes (19).

Type 2 Diabetes

People with type 2 diabetes who may have had undiagnosed diabetes for years and have a significant risk of prevalent diabetic retinopathy at the time of diagnosis should have an initial dilated and comprehensive eye examination at the time of diagnosis.

Pregnancy

Individuals who develop gestational diabetes mellitus do not require eye examinations

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during pregnancy, since they do not appear to be at increased risk of developing diabetic retinopathy during pregnancy (27). However, individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the baseline prevalence and risk of development and/or progression of diabetic retinopathy. In a systematic review and meta-analysis of 18 observational studies of pregnant individuals with preexisting type 1 or type 2 diabetes, the prevalence of any diabetic retinopathy and proliferative diabetic retinopathy (PDR) in early pregnancy was 52.3% and 6.1%, respectively. The pooled progression rate per 100 pregnancies for new diabetic retinopathy development was 15.0 (95% CI 9.9–20.8), worsened nonproliferative diabetic retinopathy was 31.0 (95% CI 23.2–39.2), pooled sight-threatening progression rate from nonproliferative diabetic retinopathy to PDR was 6.3 (95% CI 3.3–10.0), and worsened PDR was 37.0 (95% CI 21.2–54.0), demonstrating that close follow-up should be maintained during pregnancy to prevent vision loss (28). In addition, rapid implementation of intensive glycemic management in the setting of retinopathy is associated with early worsening of retinopathy, and these individuals may also benefit from more frequent follow-up initially (29).

A systematic review and meta-analysis and a controlled prospective study demonstrate that pregnancy in individuals with type 1 diabetes may aggravate retinopathy and threaten vision, especially when glycemic management is suboptimal or retinopathy severity is advanced at the time of conception (28,29). Laser photocoagulation surgery can minimize the risk of vision loss during pregnancy for individuals with high-risk PDR or center-involved diabetic macular edema (29). The use of anti–vascular endothelial growth factor (anti-VEGF) injections in pregnant individuals may be justified only if the potential benefit outweighs the potential risk to the fetus and only if clearly indicated. Current anti-VEGF medications have been assigned to pregnancy category C by the FDA (animal studies have revealed evidence of embryo-fetal toxicity, but there are no controlled data in human pregnancy), and caution should be used in pregnant individuals with diabetes because of theoretical risks to the vasculature of the developing fetus.

Treatment

Recommendations

12.9 Promptly refer individuals with any level of diabetic macular edema, moderate or worse nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy [PDR]), or any PDR to an ophthalmologist who is knowledgeable and experienced in the management of diabetic retinopathy. **A**

12.10 Panretinal laser photocoagulation therapy is indicated to reduce the risk of vision loss in individuals with high-risk PDR and, in some cases, severe nonproliferative diabetic retinopathy. **A**

12.11 Intravitreous injections of anti–vascular endothelial growth factor (anti-VEGF) are a reasonable alternative to traditional panretinal laser photocoagulation for some individuals with PDR and also reduce the risk of vision loss in these individuals. **A**

12.12 Intravitreous injections of anti-VEGF are indicated as first-line treatment for most eyes with diabetic macular edema that involves the foveal center and impairs vision acuity. **A**

12.13 Macular focal/grid photocoagulation and intravitreal injections of corticosteroid are reasonable treatments in eyes with persistent diabetic macular edema despite previous anti-VEGF therapy or eyes that are not candidates for this first-line approach. **A**

12.14 The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. **A**

Two of the main motivations for screening for diabetic retinopathy are to prevent loss of vision and to intervene with treatment when vision loss can be prevented or reversed.

Photocoagulation Surgery

Two large trials, the Diabetic Retinopathy Study (DRS) in individuals with PDR and the Early Treatment Diabetic Retinopathy Study (ETDRS) in individuals with macular edema, provide the strongest support for the therapeutic benefits of laser photocoagulation surgery. The DRS (30) showed that panretinal photocoagulation surgery reduced the risk of severe vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes with the greatest benefit ratio in those with more advanced baseline disease (disc neovascularization or vitreous hemorrhage). Later, the ETDRS verified the benefits of panretinal photocoagulation for high-risk PDR and in older-onset individuals with severe nonproliferative diabetic retinopathy or less-than-high-risk PDR (31). Panretinal laser photocoagulation is still commonly used to manage proliferative diabetic retinopathy. A macular focal/grid laser photocoagulation technique was shown in the ETDRS to be effective in treating eyes with clinically significant macular edema from diabetes (31), but this is now largely considered a second-line treatment for diabetic macular edema.

Anti-VEGF Treatment

Data from the DRCR Retina Network (formerly the Diabetic Retinopathy Clinical Research Network) and others demonstrate that intravitreal injections of anti-VEGF agents are effective at regressing proliferative disease and lead to noninferior or superior visual acuity outcomes compared with panretinal laser over 2 years of follow-up (32,33). In addition, it was observed that individuals treated with ranibizumab tended to have less peripheral visual field loss, fewer vitrectomy surgeries for secondary complications from their proliferative disease, and a lower risk of developing diabetic macular edema (32). However, a potential drawback in using anti-VEGF therapy to manage proliferative disease is that individuals were required to have a greater number of visits and received a greater number of treatments than is typically required for management by panretinal laser, which may not be optimal for some individuals. Additionally, unlike panretinal laser, anti-VEGF therapy requires participation in scheduled follow-up. Individuals with nonintentional lapses in treatment are at risk for worse visual acuity and anatomic outcomes (34). The FDA has approved aflibercept and ranibizumab for the treatment of eyes with diabetic retinopathy. Other emerging therapies for retinopathy that may use sustained intravitreal delivery of pharmacologic agents are currently under investigation. Anti-VEGF treatment of eyes with nonproliferative diabetic retinopathy has been demonstrated to reduce subsequent development of retinal neovascularization and diabetic macular edema

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but has not been shown to improve visual outcomes over 2 years of therapy and therefore has not been widely adopted for this indication (35).

While the ETDRS (31) established the benefit of focal laser photocoagulation surgery in eyes with clinically significant macular edema (defined as retinal edema located at or threatening the macular center), current data from well-designed clinical trials demonstrate that intravitreal anti-VEGF agents provide more effective treatment for center-involved diabetic macular edema than monotherapy with laser (36,37). With ranibizumab and aflibercept, most individuals require administration of intravitreal therapy with anti-VEGF agents every 4–8 weeks during the first 12 months of treatment, with fewer injections needed in subsequent years to maintain remission from center-involved diabetic macular edema. Five anti-VEGF agents currently are used to treat eyes with center-involved diabetic macular edema, namely, bevacizumab, ranibizumab, aflibercept (2 mg and 8 mg), brolucizumab, and faricimab (1), and a comparative effectiveness study demonstrated that aflibercept provides vision outcomes superior to those of bevacizumab when eyes have moderate visual impairment (vision of 20/50 or worse) from diabetic macular edema (38). For eyes that have good vision (20/25 or better) despite diabetic macular edema, close monitoring with initiation of anti-VEGF therapy if vision worsens provides 2-year vision outcomes similar to those of immediate initiation of anti-VEGF therapy (39).

Eyes that have persistent diabetic macular edema despite anti-VEGF treatment may benefit from macular laser photocoagulation or intravitreal therapy with corticosteroids (40). Both of these therapies are also reasonable first-line approaches for individuals who are not candidates for anti-VEGF treatment due to systemic considerations such as pregnancy.

Adjunctive Therapy

Lowering blood pressure has been shown to decrease retinopathy progression, although strict goals (systolic blood pressure <120 mmHg) do not impart additional benefit (6). In individuals with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with early diabetic retinopathy at baseline (41–43). Several studies have shown an association with GLP-1 RA and lower intraocular pressure (44) as well as a reduced risk of glaucoma (45–47).

Visual Rehabilitation

Recommendations

12.15 People who experience vision loss from diabetes should be counseled on the availability and scope of vision rehabilitation care and provided, or referred for, a comprehensive evaluation of their visual impairment by a practitioner experienced in vision rehabilitation. **E**

12.16 People with vision loss from diabetes should receive educational materials and resources for eye care support in addition to self-management education (e.g., glycemic management and hypoglycemia awareness). **E**

In the U.S., ~12% of adults with diabetes have some level of vision impairment (48). They may have difficulty reaching their diabetes treatment goals and performing many other activities of daily living, which can lead to depression, anxiety, social isolation, and difficulties at home, in the workplace, or at school (49).

People with diabetes are at increased risk of chronic vision loss, subsequent functional decline, and resulting disability. Vision impairment has physical, psychological, behavioral, and social consequences that affect people with diabetes, their families, friends, and caregivers. Health care professionals and stakeholders may not be aware of the overall impact of vision loss on an individual's health and well-being. People with diabetic vision loss should be evaluated to determine their potential to benefit from comprehensive vision restoration. Vision rehabilitation can help people with vision loss achieve maximum function, independence, and quality of life.

NEUROPATHY

Screening

Recommendations

12.17 All people with diabetes should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **B**

12.18 Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All people with diabetes should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. **B**

12.19 Symptoms and signs of autonomic neuropathy should be assessed in people with diabetes starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes, and at least annually thereafter, and with evidence of other microvascular complications, particularly kidney disease and diabetic peripheral neuropathy. Screening can include asking about orthostatic dizziness, syncope, early satiety, erectile dysfunction, changes in sweating patterns, or dry cracked skin in the extremities. Signs of autonomic neuropathy include orthostatic hypotension, a resting tachycardia, or evidence of peripheral dryness or cracking of skin. **E**

Diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations. The early recognition and appropriate management of neuropathy in people with diabetes is important. Points to be aware of include the following:

1. Diabetic neuropathy is a diagnosis of exclusion. Non–diabetic neuropathies may be present in people with diabetes and may be treatable.
2. Up to 50% of diabetic peripheral neuropathy may be asymptomatic. If not recognized and if preventive foot care is not implemented, people with diabetes are at risk for injuries as well as diabetic foot ulcers (DFUs) and amputations.
3. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life.

Specific treatment to reverse the underlying nerve damage is currently not available. Glycemic management can effectively prevent diabetic peripheral neuropathy (DPN) and cardiovascular autonomic neuropathy (CAN) in type 1 diabetes (50,51) and may modestly slow their progression in type 2 diabetes (52), but it does not

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reverse neuronal loss. Treatments of other modifiable risk factors (including obesity, lipids, and blood pressure) can aid in prevention of DPN progression in type 2 diabetes and may reduce disease progression in type 1 diabetes (53–56). Therapeutic strategies (pharmacologic and nonpharmacologic) for the relief of painful DPN and symptoms of autonomic neuropathy can potentially reduce pain (57) and improve quality of life.

Diagnosis

Diabetic Peripheral Neuropathy

Individuals with a type 1 diabetes duration ≥5 years and all individuals with type 2 diabetes should be assessed annually for DPN using medical history and simple clinical tests (57). Symptoms vary according to the class of sensory fibers involved. The most common early symptoms are induced by the involvement of small fibers and include pain and dysesthesia (unpleasant sensations of burning and tingling). The involvement of large fibers may cause balance issues, numbness, and loss of protective sensation (LOPS). LOPS indicates the presence of distal sensory polyneuropathy and is a risk factor for diabetic foot ulceration. The following clinical tests may be used to assess small- and large-fiber function and protective sensation:

1. Small-fiber function: pinprick and temperature sensation.
2. Large-fiber function: lower-extremity reflexes, vibration perception, and 10-g monofilament.
3. Protective sensation: 10-g monofilament.

These tests not only screen for the presence of dysfunction but also predict future risk of complications. Electrophysiological testing or referral to a neurologist is rarely needed, except in situations where the clinical features are atypical (acute or subacute presentation, non–length dependent, asymmetric, and/or motor involvement) or the diagnosis is unclear.

In all people with diabetes and DPN, causes of neuropathy other than diabetes should be considered, including toxins (e.g., alcohol), neurotoxic medications (e.g., chemotherapy), vitamin B12 deficiency, hypothyroidism, kidney disease, malignancies (e.g., multiple myeloma, bronchogenic carcinoma), infections (e.g., HIV), chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (58). See the American Diabetes Association position statement "Diabetic Neuropathy" for more details (57).

Diabetic Autonomic Neuropathy

Individuals who have had type 1 diabetes for ≥5 years and all individuals with type 2 diabetes should be assessed annually for autonomic neuropathy (57). The symptoms and signs of autonomic neuropathy should be elicited carefully during the history and physical examination. Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating. Screening for symptoms of autonomic neuropathy includes asking about symptoms of orthostatic intolerance (dizziness, lightheadedness, or weakness with standing), syncope, exercise intolerance, constipation, diarrhea, urinary retention, urinary incontinence, or changes in sweat function. Further testing can be considered if symptoms are present and will depend on the end organ involved but might include cardiovascular autonomic testing, sweat testing, urodynamic studies, gastric emptying, or endoscopy or colonoscopy. Impaired counterregulatory responses to hypoglycemia in type 1 and type 2 diabetes can lead to impaired hypoglycemia awareness but are not directly linked to autonomic neuropathy.

Cardiovascular Autonomic Neuropathy

CAN is associated with mortality independent of other cardiovascular risk factors (59,60). In its early stages, CAN may be completely asymptomatic and detected only by decreased heart rate variability with deep breathing. Advanced disease may be associated with resting tachycardia (>100 bpm) and orthostatic hypotension (a fall in systolic or diastolic blood pressure by >20 mmHg or >10 mmHg, respectively, upon standing without an appropriate increase in heart rate). CAN treatment is generally focused on alleviating symptoms.

Gastrointestinal Neuropathies

Gastrointestinal neuropathies may involve any portion of the gastrointestinal tract, with manifestations including esophageal dysmotility, gastroparesis, constipation, diarrhea, and fecal incontinence. Gastroparesis should be suspected in individuals with erratic glycemic management or with upper gastrointestinal symptoms without another identified cause. Exclusion of reversible/iatrogenic causes such as medications or organic causes of gastric outlet obstruction or peptic ulcer disease (with esophagogastroduodenoscopy or a barium study of the stomach) is needed before considering a diagnosis of or specialized testing for gastroparesis. The diagnostic gold standard for gastroparesis is the measurement of gastric emptying with scintigraphy of digestible solids at 15-min intervals for 4 h after food intake. The use of ^{13}C octanoic acid breath test is an approved alternative.

Genitourinary Disturbances

Diabetic autonomic neuropathy may also cause genitourinary disturbances, including sexual dysfunction and bladder dysfunction. In men, diabetic autonomic neuropathy may cause erectile dysfunction and/or retrograde ejaculation (57). Female sexual dysfunction occurs more frequently in those with diabetes and presents as decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication (61). Lower urinary tract symptoms manifest as urinary incontinence and bladder dysfunction (nocturia, frequent urination, urination urgency, and weak urinary stream). Evaluation of bladder function should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

Treatment

Recommendations

12.20 Optimize glucose management to prevent or delay the development of neuropathy in people with type 1 diabetes **A** and to slow the progression of neuropathy in people with type 2 diabetes. **C** Optimize weight, blood pressure, and serum lipid management to reduce the risk or slow the progression of diabetic neuropathy. **B**

12.21 Assess and treat pain related to diabetic peripheral neuropathy **B** and symptoms of autonomic neuropathy to improve quality of life. **E**

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12.22 Gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and sodium channel blockers are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. **A** Opioids, including tramadol and tapentadol, should not be used for neuropathic pain treatment in diabetes given the potential for adverse events. **B**

Glycemic Management

Near-normal glycemic management, implemented early in the course of diabetes, has been shown to effectively delay or prevent the development of DPN and CAN in people with type 1 diabetes (62–65). Although the evidence for the benefit of near-normal glycemic management is not as strong for type 2 diabetes, some studies have demonstrated a modest slowing of progression without reversal of neuronal loss (52,66). Specific glucose-lowering strategies may have different effects. In a post hoc analysis, participants, particularly men, in the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial treated with insulin sensitizers had a lower incidence of distal symmetric polyneuropathy over 4 years than those treated with insulin or sulfonylurea (67). Additionally, recent evidence from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed benefit of intensive glucose and blood pressure management on the prevention of CAN in type 2 diabetes (68).

Weight Management

Obesity is consistently associated with neuropathy in cross-sectional and longitudinal studies (69). While obesity has been established as a risk factor for neuropathy, including in those with diabetes, treatments of obesity are less well studied. The Look AHEAD (Action for Health in Diabetes) randomized trial found that a lifestyle intervention primarily focused on dietary weight loss led to improvements in neuropathy symptoms but not neuropathy examination scores (53). Observational studies of metabolic surgery have also revealed improvements in neuropathy outcomes, but randomized trials are lacking (55,56). Weight loss medications have not been well studied to date with two negative trials (topiramate and exenatide). Trials investigating the impacts of exenatide and topiramate on DPN and CAN measurements led to no substantial weight loss (70,71). Exercise often leads to a small reduction in weight and may also have positive effects on diabetic neuropathy through other mechanisms. Two systematic reviews have shown that exercise interventions improve diabetic neuropathy outcomes, including symptoms, examination findings, balance, and functional assessments, but the strength of the evidence is low (72,73).

Lipid Management

Dyslipidemia is a key factor in the development of neuropathy in people with type 2 diabetes and may contribute to neuropathy risk in people with type 1 diabetes (74,75). Although the evidence for a relationship between lipids and neuropathy development has become increasingly clear in type 2 diabetes, the optimal therapeutic intervention has not been identified. Positive effects of physical activity, weight loss, and metabolic surgery have been reported in individuals with DPN, but use of conventional lipid-lowering pharmacotherapy (such as statins or fenofibrates) does not appear to be effective in treating or preventing DPN development (76).

Blood Pressure Management

There are multiple reasons for blood pressure management in people with diabetes, and neuropathy progression (especially in type 2 diabetes) has now been added to this list. Although data from many studies have supported the role of hypertension in the risk of neuropathy development, a meta-analysis of data from 14 countries in the International Prevalence and Treatment of Diabetes and Depression (INTERPRET-DD) study revealed hypertension as an independent risk factor for DPN development with an odds ratio of 1.58 (95% CI 1.18–2.12) (77). In the ACCORD trial, intensive blood pressure intervention also decreased CAN risk by 25% (68).

Neuropathic Pain

Neuropathic pain can be severe and can impact quality of life, affect sleep, limit mobility, and contribute to depression and anxiety (78). No compelling evidence exists in support of glycemic or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes, which leaves only pharmaceutical interventions (79). A recent guideline by the American Academy of Neurology recommends that the initial treatment of pain should also focus on the concurrent treatment of both sleep and mood disorders because of increased frequency of these problems in individuals with DPN (80).

Several pharmacologic therapies exist for treatment of pain in diabetes. The American Academy of Neurology (AAN) update suggested that gabapentinoids, serotonin-norepinephrine reuptake inhibitors (SNRIs), sodium channel blockers, and tricyclic antidepressants (TCAs) all could be considered in the treatment of pain in DPN (80). These AAN recommendations offer a supplement to a recent American Diabetes Association pain monograph (81). A head-to-head trial suggested therapeutic equivalency for TCAs, SNRIs, and gabapentinoids in the treatment of pain in DPN (82). The trial also supported the role of combination therapy over monotherapy for the treatment of pain in DPN.

Gabapentinoids. Gabapentinoids include several calcium channel $\alpha 2$-δ subunit ligands. Several high-quality and medium-quality studies support the role of pregabalin in treatment of pain in DPN. One high-quality study and many small studies support the role of gabapentin in the treatment of pain in DPN. Medium-quality studies suggest that mirogabalin has a small effect on pain in DPN (80). Adverse effects may be more severe in older individuals (83) and may be attenuated by lower starting doses and more gradual titration.

SNRIs. SNRIs include duloxetine, venlafaxine, and desvenlafaxine, all selective SNRIs. Two high-quality studies and five medium-quality studies support the role of duloxetine in the treatment of pain in DPN. A high-quality study supports the role of venlafaxine in the treatment of pain in DPN. Only one medium-quality study supports a possible role for desvenlafaxine for treatment of pain in DPN (80). Adverse events may be more severe in older people but may be attenuated with lower doses and slower titration of duloxetine.

Tricyclic Antidepressants. TCAs have been studied for treatment of pain. Most of the relevant data were acquired from trials of amitriptyline and include two high-quality studies and two medium-quality

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studies supporting the effectiveness of amitryiptylinein the treatment of painful DPN (80,82). Anticholinergic side effects may be dose limiting and restrict use in individuals ≥65 years of age.

Sodium Channel Blockers. Sodium channel blockers include lamotrigine, lacosamide, carbamazepine, oxcarbazepine, and valproic acid. Five medium-quality studies support the role of sodium channel blockers in treating pain in DPN (80).

Capsaicin. Capsaicin has received FDA approval for treatment of pain in DPN using an 8% patch, with one high-quality study reported. One medium-quality study of 0.075% capsaicin cream has been reported. In individuals with contraindications to oral pharmacotherapy or who prefer topical treatments, the use of topical capsaicin can be considered.

Lidocaine 5% Plaster/Patch. Lidocaine patches have limited data supporting their use in DPN and are not effective in more widespread distribution of pain (although they may be of use in individuals with nocturnal neuropathic foot pain). Lidocaine patches cannot be used for more than 12 h in a 24-h period (84).

Opioids. Several randomized controlled trials (RCTs) have demonstrated that opioids (dextromethorphan, oxycodone, morphine sulfate) can reduce pain in individuals with DPN (84). However, evidence for the long-term efficacy of opioids in neuropathic pain is lacking. In fact, the Centers for Disease Control and Prevention (CDC) performed a systematic review that found no studies of opioids for chronic pain have evaluated long-term outcomes, including pain, function, and quality of life (85). Moreover, CDC and AAN reviews have documented the long-term harms from opioids, including abuse, addiction, fractures, heart attacks, motor vehicle accidents, overdose, and mortality (85,86). The current evidence balancing risks and benefits has led the AAN to recommend against opioids for the treatment of painful DPN (80).

Tapentadol and Tramadol. Tapentadol and tramadol exert their analgesic effects through both μ-opioid receptor agonism (opioid) and norepinephrine and serotonin reuptake inhibition. Given that opioids and SNRIs are both effective for painful DPN, it is not surprising that these SNRI and opioid agents are effective in the treatment of pain in DPN too (80). However, the effect size is similar to that of other effective therapies, such as SNRIs, and these medications have the same risks as other opioids listed above. In fact, tramadol has been shown to be associated with all-cause mortality with an effect size similar to that of codeine (87). Similar to other opioids, risks likely outweigh benefits, and the AAN guidelines also recommend against their use for painful DPN (80).

Orthostatic Hypotension

Treating orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most individuals require both nonpharmacologic measures (e.g., ensuring adequate salt intake, avoiding medications that aggravate hypotension, or using compressive garments over the legs and abdomen) and pharmacologic measures. Physical activity and exercise should be encouraged to avoid deconditioning, which is known to exacerbate orthostatic intolerance, and volume repletion with fluids and salt is critical. Additionally, supine blood pressure tends to be much higher in these individuals, often requiring treatment of blood pressure at bedtime with shorter-acting drugs that also affect baroreceptor activity such as guanfacine or clonidine, shorter-acting calcium blockers (e.g., isradipine), or shorter-acting β-blockers such as atenolol or metoprolol tartrate. Alternatives can include enalapril if an individual is unable to tolerate preferred agents (88–90). Midodrine and droxidopa are approved by the FDA for the treatment of orthostatic hypotension.

Gastroparesis

Treatment of diabetic gastroparesis may be very challenging. A small-particle diet may provide some symptom relief (91–93). In addition, foods with small particle size may improve key symptoms (94). Withdrawing drugs with adverse effects on gastrointestinal motility, including opioids, anticholinergics, TCAs, GLP-1 RAs, and pramlintide, may also improve intestinal motility (91,95). However, the risk of removal of GLP-1 RAs should be balanced against their potential benefits. In cases of severe gastroparesis, pharmacologic interventions are needed. Only metoclopramide, a prokinetic agent, is approved by the FDA for the treatment of gastroparesis (96). However, the level of evidence regarding the benefits of metoclopramide for the management of gastroparesis is weak, and given the risk for serious adverse effects (extrapyramidal signs such as acute dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia), its use in the treatment of gastroparesis beyond 12 weeks is no longer recommended by the FDA. It should be reserved for severe cases that are unresponsive to other therapies (95). Other treatment options include domperidone (available outside the U.S.) and erythromycin, which is only effective for short-term use due to tachyphylaxis (96). Gastric electrical stimulation using a surgically implantable device has received approval from the FDA, although there are very limited data on DPN and the results do not support gastric stimulation as an effective therapy in diabetic gastroparesis (97).

Erectile Dysfunction

In addition to treatment of hypogonadism if present, treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process but may improve a person's quality of life.

FOOT CARE

Recommendations

12.23 Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputations. **A**

12.24 The examination should include inspection of the skin, assessment of foot deformities, neurological assessment (10-g monofilament testing or Ipswich touch test with at least one additional assessment: pinprick, temperature, or vibration), and vascular assessment, including pulses in the legs and feet. **B**

12.25 Individuals with evidence of sensory loss or prior ulceration or amputation should have their feet inspected at every visit. **A**

12.26 Obtain a prior history of ulceration, amputation, Charcot foot, angioplasty or vascular surgery, cigarette

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smoking, retinopathy, and renal disease and assess current symptoms of neuropathy (pain, burning, numbness) and vascular disease (leg fatigue, claudication). B

12.27 Initial screening for peripheral arterial disease (PAD) should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time. Individuals with a history of leg fatigue, claudication, and rest pain relieved with dependency or decreased or absent pedal pulses should be referred for ankle-brachial index with toe pressures and for further vascular assessment as appropriate. B

12.28 An interprofessional approach facilitated by a podiatrist in conjunction with other appropriate team members is recommended for individuals with foot ulcers and high-risk feet (e.g., those on dialysis, those with Charcot foot, those with a history of prior ulcers or amputation, and those with PAD). B

12.29 Refer individuals who smoke and have a history of prior lower-extremity complications, loss of protective sensation, structural abnormalities, or PAD to foot care specialists for ongoing preventive care and lifelong surveillance. B These individuals should also be provided with information on the importance of smoke cessation and referred for counseling on smoke cessation. A

12.30 Provide general preventive foot self-care education to all people with diabetes, including those with loss of protective sensation, on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems. B

12.31 The use of specialized therapeutic footwear is recommended for people with diabetes at high risk for ulceration, including those with loss of protective sensation, foot deformities, ulcers, callous formation, poor peripheral circulation, or history of amputation. B

12.32 For chronic diabetic foot ulcers that have failed to heal with optimal standard care alone, adjunctive treatment with randomized controlled trial–proven advanced agents should be considered. Considerations might include negative-pressure wound therapy, placental membranes, bioengineered skin substitutes, several acellular matrices, autologous fibrin and leukocyte platelet patches, and topical oxygen therapy. A

Foot ulcerations and amputations are common complications associated with diabetes. These may be the consequences of several factors, including peripheral neuropathy, PAD, and foot deformities. They represent major causes of morbidity and mortality in people with diabetes. Early recognition of at-risk feet, preulcerative lesions, and prompt treatment of ulcerations and other lower-extremity complications can delay or prevent adverse outcomes.

Early recognition requires an understanding of those factors that put people with diabetes at increased risk for ulcerations and amputations. Factors that are associated with the at-risk foot include the following:

- Poor glycemic management
- Peripheral neuropathy/LOPS
- PAD
- Foot deformities (bunions, hammertoes, Charcot joint, etc.)
- Preulcerative corns or calluses
- Prior ulceration
- Prior amputation
- Smoking
- Retinopathy
- Nephropathy (particularly individuals on dialysis or posttransplant)

Identifying the at-risk foot begins with a detailed history documenting diabetes management, smoking history, exercise tolerance, history of claudication or rest pain, and prior ulcerations or amputations. A thorough examination of the feet should be performed annually in all people with diabetes and more frequently in at-risk individuals (98). The examination should include assessment of skin integrity, assessment for LOPS using the 10-g monofilament along with at least one other neurological assessment tool, pulse examination of the dorsalis pedis and posterior tibial arteries, and assessment for foot deformities such as bunions, hammertoes, and prominent metatarsals, which increase plantar foot pressures and increase risk for ulcerations. At-risk individuals should be assessed at each visit and should be referred to foot care specialists for ongoing preventive care and surveillance. The physical examination can stratify people with diabetes into different categories and determine the frequency of these visits (99) (**Table 12.1**).

Evaluation for Loss of Protective Sensation

The presence of peripheral sensory neuropathy is the single most common component cause for foot ulceration. In a multicenter trial, peripheral neuropathy was found to be a component cause in 78% of people with diabetes with ulcerations and that the triad of peripheral sensory neuropathy, minor trauma, and foot deformity was present in >63% of participants (100). All people with diabetes should undergo a comprehensive foot examination at least annually or more frequently for those in higher-risk categories (98,99).

LOPS is vital to risk assessment. One of the most useful tests to determine LOPS is the 10-g monofilament test. Studies have shown that clinical examination and the 10-g monofilament test are the two most sensitive tests in identifying the foot at risk for ulceration (101). The monofilament test should be performed with at least one other neurologic assessment tool (e.g., pinprick, temperature perception, ankle reflexes, or vibratory perception with a 128-Hz tuning fork or similar device). Absent monofilament sensation and one other abnormal test confirms the presence of LOPS. Further neurological testing, such as nerve conduction, electromyography, nerve biopsy, or intraepidermal nerve fiber density biopsies, are rarely indicated for the diagnosis of peripheral sensory neuropathy (57).

Evaluation for Peripheral Arterial Disease

Initial screening for PAD should include a history of leg fatigue, claudication, and rest pain relieved with dependency. Physical examination for PAD should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time (98,102). Any individual exhibiting signs and symptoms of PAD should be referred for noninvasive arterial studies in the form of Doppler ultrasound with pulse volume recordings. While ankle-brachial indices will be calculated, they should be interpreted carefully, as they are known to be inaccurate in people

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Table 12.1—International Working Group on Diabetic Foot risk stratification system and corresponding foot screening frequency

Category	Ulcer risk	Characteristics	Examination frequency*
0	Very low	No LOPS and no PAD	Annually
1	Low	LOPS or PAD	Every 6–12 months
2	Moderate	LOPS + PAD, or LOPS + foot deformity, or PAD + foot deformity	Every 3–6 months
3	High	LOPS or PAD and one or more of the following: • History of foot ulcer • Amputation (minor or major) • End-stage renal disease	Every 1–3 months

Adapted with permission from Schaper et al. (99). LOPS, loss of protective sensation; PAD, peripheral artery disease. *Examination frequency suggestions are based on expert opinion and person-centered requirements.

with diabetes due to noncompressible vessels. Toe systolic blood pressure tends to be more accurate. Toe systolic blood pressure <30 mmHg is suggestive of PAD and an inability to heal foot ulcerations (103). Individuals with abnormal pulse volume recording tracings and toe pressures <30 mmHg with foot ulcers should be referred for immediate vascular evaluation. Due to the high prevalence of PAD in people with diabetes, the Society for Vascular Surgery and the American Podiatric Medical Association guidelines recommend that all people with diabetes >50 years of age should undergo screening via noninvasive arterial studies (102, 104). If normal, these should be repeated every 5 years (102).

Education for People With Diabetes

All people with diabetes (and their caregivers), particularly those with the aforementioned high-risk conditions, should receive general foot care education, including appropriate management strategies (105–107). This education should be provided to all newly diagnosed people with diabetes as part of an annual comprehensive examination and to individuals with high-risk conditions at every visit. Recent studies have shown that while education improves knowledge of diabetic foot problems and self-care of the foot, it does not improve behaviors associated with active participation in their overall diabetes care and the achievement of personal health goals (108). Evidence also suggests that while education for people with diabetes and their families is important, the knowledge is quickly forgotten and needs to be reinforced regularly (109).

Individuals considered at risk should understand the implications of foot deformities, LOPS, and PAD; the proper care of the foot, including nail and skin care; and the importance of daily foot inspections. Individuals with LOPS should be educated on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems. People with diabetes should also be educated on the importance of referrals to foot care specialists. A recent study showed that people with diabetes and foot disease lacked awareness of their risk status and why they were being referred to an interprofessional team of foot care specialists. Further, they exhibited a variable degree of interest in learning further about foot complications (110).

Individuals' understanding of these issues and their physical ability to conduct proper foot surveillance and care should be assessed. Those with visual difficulties, physical constraints preventing movement, or cognitive problems that impair their ability to assess the condition of the foot and to institute appropriate responses will need other people, such as family members, to assist with their care.

The selection of appropriate footwear and footwear behaviors at home should also be discussed (e.g., no walking barefoot, avoiding open-toed shoes). Therapeutic footwear with custom-made orthotic devices have been shown to reduce peak plantar pressures (107). Most studies use reduction in peak plantar pressures as an outcome as opposed to ulcer prevention. Certain design features of the orthoses, such as rocker soles and metatarsal accommodations, can reduce peak plantar pressures more significantly than insoles alone. A systematic review, however, showed there was no significant reduction in ulcer incidence after 18 months compared with standard insoles and extra-depth shoes. Further, it was also noted that evidence to prevent first ulcerations was nonexistent (111).

Treatment

Treatment recommendations for people with diabetes will be determined by their risk category. No-risk or low-risk individuals often can be managed with education and self-care. People in the moderate- to high-risk category should be referred to foot care specialists for further evaluation and regular surveillance as outlined in **Table 12.1**. This category includes individuals with LOPS, PAD, and/or structural foot deformities, such as Charcot foot, bunions, or hammertoes. Individuals with any open ulceration or unexplained swelling, erythema, or increased skin temperature should be referred urgently to a foot care specialist or interprofessional team.

Initial treatment recommendations should include daily foot inspection, use of moisturizers for dry, scaly skin, and avoidance of self-care of ingrown nails and calluses. Well-fitted athletic or walking shoes with customized pressure-relieving orthoses should be part of initial recommendations for people with increased plantar pressures (as demonstrated by plantar calluses). Individuals with deformities such as bunions or hammertoes may require specialized footwear such as extra-depth shoes. Those with even more significant deformities, as in Charcot joint disease, may require custom-made footwear. For recalcitrant deformities or for

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recurrent ulcerations not amenable to conservative footwear therapy alone, appropriate surgical reconstruction by an experienced diabetic foot surgeon should be considered (112,113).

Special consideration should be given to individuals with neuropathy who present with a warm, swollen, red foot with or without a history of trauma and without an open ulceration. These individuals require a thorough workup for possible Charcot neuroarthropathy (114,115). Foot and ankle X-rays should be performed in all individuals presenting with the above clinical findings. Early diagnosis and treatment of this condition is of paramount importance in preventing deformities and instability that can lead to ulceration and amputation. These individuals require total non–weight-bearing and urgent referral to a foot care specialist for further management. Surgical reconstruction of these complex limb-threatening deformities has assumed an important role in recent years, with many surgeries yielding high levels of success and limb salvage (113,116,117). Nonetheless, such procedures need to be approached by experienced surgeons with an appreciation not only for the complexities of the deformity but also for the complexities of the individuals themselves.

There have been a number of developments in the treatment of ulcerations over the years (118). These include negative-pressure therapy, growth factors, bioengineered tissue, acellular matrix tissue, stem cell therapy, hyperbaric oxygen therapy, and, most recently, topical oxygen therapy (119–121). While there is literature to support many modalities currently used to treat diabetic foot wounds, robust RCTs are often lacking. However, it is agreed that the initial treatment and evaluation of ulcerations include the following five basic principles of ulcer treatment:

- Offloading of plantar ulcerations
- Debridement of necrotic, nonviable tissue
- Revascularization of ischemic wounds when necessary
- Management of infection: soft tissue or bone
- Use of physiologic, topical dressings

However, despite following the above principles, some ulcerations will become chronic and fail to heal. Careful evaluation is necessary to determine if there are associated deformities predisposing to high plantar pressures that need to be addressed with surgical offloading procedures to expedite healing (112,122,123). Additionally, underlying osteomyelitis must be ruled out as a cause for the nonhealing ulcer and treated as necessary. Once these complicating factors have been addressed, adjunctive advanced wound therapy can play an important role. When to use advanced wound therapy has been the subject of much discussion, as the therapy is often quite expensive. It has been determined that if a wound fails to show a reduction of 50% or more after 4 weeks of appropriate wound management (i.e., the five basic principles above), consideration should be given to the use of advanced wound therapy (124). Treatment of these chronic wounds is best managed in an interprofessional setting.

Evidence to support advanced wound therapy is challenging to produce and to assess. Randomization of trial participants is difficult, as there are many variables that can affect wound healing. In addition, many RCTs exclude certain cohorts of people, e.g., individuals with chronic renal disease or those on dialysis. Finally, blinding of participants and clinicians is not always possible. Meta-analyses and systematic reviews of observational studies are used to determine the clinical effectiveness of these modalities. Such studies can augment formal RCTs by including a greater variety of participants in various clinical settings who are typically excluded from the more rigidly structured clinical trials.

Advanced wound therapy can be classified into nine broad categories (118) (**Table 12.2**). Topical growth factors, acellular matrix tissues, and bioengineered cellular therapies are commonly used in offices and wound care centers to expedite healing of chronic, more superficial ulcerations. Numerous clinical reports and retrospective studies have demonstrated the clinical effectiveness of each of these modalities. Over the years, there has been increased evidence to support the use of these modalities. Nonetheless, use of those products or agents with robust RCTs or systematic reviews should generally be preferred over those without level 1 evidence (**Table 12.2**).

Negative-pressure wound therapy was first introduced in the early to mid-1990s. It has become especially useful in wound preparation for skin grafts and flaps and assists in the closure of deep, large wounds (125,126). A variety of types exist in the marketplace and range from electrically powered to mechanically powered in different sizes depending upon the specific wound requirements.

Electrical stimulation, pulsed radiofrequency energy, and extracorporeal shockwave therapy are biophysical modalities that are believed to upregulate growth factors or cytokines to stimulate wound healing, while low-frequency noncontact ultrasound is used to debride wounds. However, most of the studies advocating the use of these modalities have been retrospective observational studies or poor-quality RCTs.

Hyperbaric oxygen therapy is the delivery of oxygen through a chamber, either individual or multiperson, with the intention of increasing tissue oxygenation to increase tissue perfusion and neovascularization, combat resistant bacteria, and stimulate wound healing. While there had been great interest in this modality being able to expedite healing of chronic diabetic foot ulcers (DFUs), there is one RCT with positive results that reported increased healing rates at 9 and 12 months compared with control participants (127). More recent studies with significant design deficiencies and participant dropouts have failed to provide corroborating evidence that hyperbaric oxygen therapy should be widely used for managing nonhealing DFUs (128,129). While there may be some benefit in prevention of amputation in selected chronic neuroischemic ulcers, recent studies have shown no benefit in healing DFUs in the absence of ischemia and/or infection (120,130).

Topical oxygen therapy has been studied rather vigorously in recent years, with several high-quality RCTs and at least five systematic reviews and meta-analyses all supporting its efficacy in healing chronic DFUs at 12 weeks (119,121,131–135). Three types of topical oxygen devices are available, including continuous-delivery, low-constant-pressure, and cyclical-pressure modalities. Importantly, topical oxygen therapy devices provide for home-based therapy and replace the need for daily visits to specialized centers. Very high participation with very few reported adverse events combined with improved healing rates makes this therapy another attractive option for advanced wound care.

If DFUs fail to heal despite appropriate standard or surgical wound care, adjunctive

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Table 12.2—Categories of advanced wound therapies

Negative-pressure wound therapy
Standard electrically powered
Mechanically powered
Oxygen therapies
Hyperbaric oxygen therapy
Topical oxygen therapy
Oxygen-releasing sprays, dressings
Biophysical
Electrical stimulation, diathermy
Pulsed electromagnetic fields, pulsed radiofrequency energy
Low-frequency noncontact ultrasound
Extracorporeal shock wave therapy
Growth factors
Becaplermin: platelet-derived growth factor
Fibroblast growth factor
Epidermal growth factor
Autologous blood products
Platelet-rich plasma
Leukocyte, platelet, fibrin multilayered patches
Whole blood clot
Acellular matrix tissues
Xenograft dermis
Bovine dermis
Xenograft acellular matrices
Small intestine submucosa
Porcine urinary bladder matrix
Ovine forestomach
Equine pericardium
Fish skin graft
Bovine collagen
Bilayered dermal regeneration matrix
Human dermis products
Human pericardium
Placental tissues
Amniotic tissues/amniotic fluid
Umbilical cord
Bioengineered allogeneic cellular therapies
Bilayered skin equivalent (human keratinocytes and fibroblasts)
Dermal replacement therapy (human fibroblasts)
Stem cell therapies
Autogenous: bone marrow–derived stem cells
Allogeneic: amniotic matrix with mesenchymal stem cells
Miscellaneous active dressings
Hyaluronic acid, honey dressings, etc.
Sucrose octasulfate dressing

Adapted with permission from Frykberg and Banks (118).

advanced therapies should be instituted and are best managed in an interprofessional manner. Once healed, all individuals should be enrolled in a formal comprehensive prevention program focused on reducing the incidence of recurrent ulcerations and subsequent amputations (98,136,137).

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13. Older Adults: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Recommendations

13.1 Assess the medical, psychological, functional (self-management abilities), and social domains in older adults with diabetes to provide a framework to determine goals and therapeutic approaches for diabetes management. **B**

13.2 Screen at least annually for geriatric syndromes (e.g., cognitive impairment, depression, urinary incontinence, falls, persistent pain, and frailty), hypoglycemia, and polypharmacy in older adults with diabetes, as they may affect diabetes management and diminish quality of life. **B**

Diabetes is a highly prevalent health condition in the aging population. Over 29% of people over the age of 65 years have diabetes (1,2). The number of older adults living with these conditions is expected to increase rapidly in the coming decades. Diabetes in older adults is a highly heterogeneous condition. While type 2 diabetes predominates in the older population as in the younger population, improvements in insulin delivery, technology, and care over the last few decades have led to increasing numbers of people with childhood and adult-onset type 1 diabetes surviving and thriving into their later decades.

Diabetes management in older adults requires regular assessment of medical, psychological, functional, and social domains. When assessing older adults with diabetes, it is important to accurately categorize the type of diabetes as well as other factors, including diabetes duration, the presence of complications, and treatment-related concerns, such as fear of hypoglycemia. Screening for diabetes complications in older adults should be individualized and periodically revisited, as the results of screening tests may impact treatment goals and therapeutic approaches (3–5). Older adults with diabetes have higher rates of functional disability, accelerated muscle loss, mobility impairment, frailty, and coexisting illnesses, such as hypertension, chronic kidney disease, coronary heart disease, stroke, and premature death than those without diabetes. At the same time, older adults with diabetes also require greater caregiver support and are at greater risk than other older adults for

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.*

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several common geriatric syndromes such as cognitive impairment, depression, urinary incontinence, injurious falls, persistent pain, and frailty as well as polypharmacy (1). These conditions may impact older adults' diabetes self-management abilities and quality of life if left unaddressed (2,6,7). See Section 4, "Comprehensive Medical Evaluation and Assessment of Comorbidities," for the full range of issues to consider when caring for older adults with diabetes. The Institute for Healthcare Improvement has developed an evidence-based "4Ms" framework for age-friendly health care that is being adopted by many health systems caring for older adults. The key elements of this approach to the care of older adults are Mentation, Medications, Mobility, and What Matters Most (person centered), with the understanding that any one of the components may affect another domain (8). This approach has been conceptualized to address person-specific issues that may be interrelated and affect diabetes management in older individuals in **Fig. 13.1**.

The comprehensive assessment described above provides a framework to determine goals and therapeutic approaches (9–11), including whether referral for diabetes self-management education is appropriate (when complicating factors arise or when transitions in care occur) or whether the current plan is too complex for the individual's self-management ability or for the care partners providing care (12). Particular attention should be paid to complications that can develop over short periods of time and/or would significantly impair functional status, such as visual and lower-extremity complications. Please refer to the American Diabetes Association (ADA) consensus report "Diabetes in Older Adults" for details (3).

NEUROCOGNITIVE FUNCTION

Recommendation

13.3 Screening for early detection of mild cognitive impairment or dementia should be performed for adults 65 years of age or older at the initial visit, annually, and as appropriate. **B**

Older adults with diabetes are at higher risk of cognitive decline and institutionalization (13,14). Presentation of cognitive impairment ranges from subtle executive dysfunction to memory loss to overt dementia. People with diabetes have higher incidences of all-cause dementia, Alzheimer disease, and vascular dementia than people without diabetes (15). Both hyperglycemia and hypoglycemia are associated with a decline in cognitive function (16–18), and longer duration of diabetes is associated with worsening cognitive function. A newly recognized clinical entity, diabetes-related dementia, is emerging as distinct from Alzheimer disease and vascular dementia. Diabetes-related dementia is characterized by a slower progression of dementia, absence of typical neuroimaging findings, advanced age, elevated A1C levels, long duration of diabetes, high frequency of insulin use, frailty, sarcopenia, and dynapenia (loss of muscle strength not caused by neurologic or muscular diseases) (18). Ongoing studies are evaluating whether lifestyle interventions may help to maintain cognitive function in older adults (19). However, studies on diabetes prevention or intensive glycemic and blood pressure management have not demonstrated a reduction in cognitive decline (20,21). A recent systematic review and meta-analysis showed that glucose-lowering drugs, such as thiazolidinediones, glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and sodium–glucose cotransporter 2 (SGLT2) inhibitors, have shown small benefits on slowing progression of cognitive decline (22). Cardiovascular risk factors are also associated with an increased risk of cognitive decline and

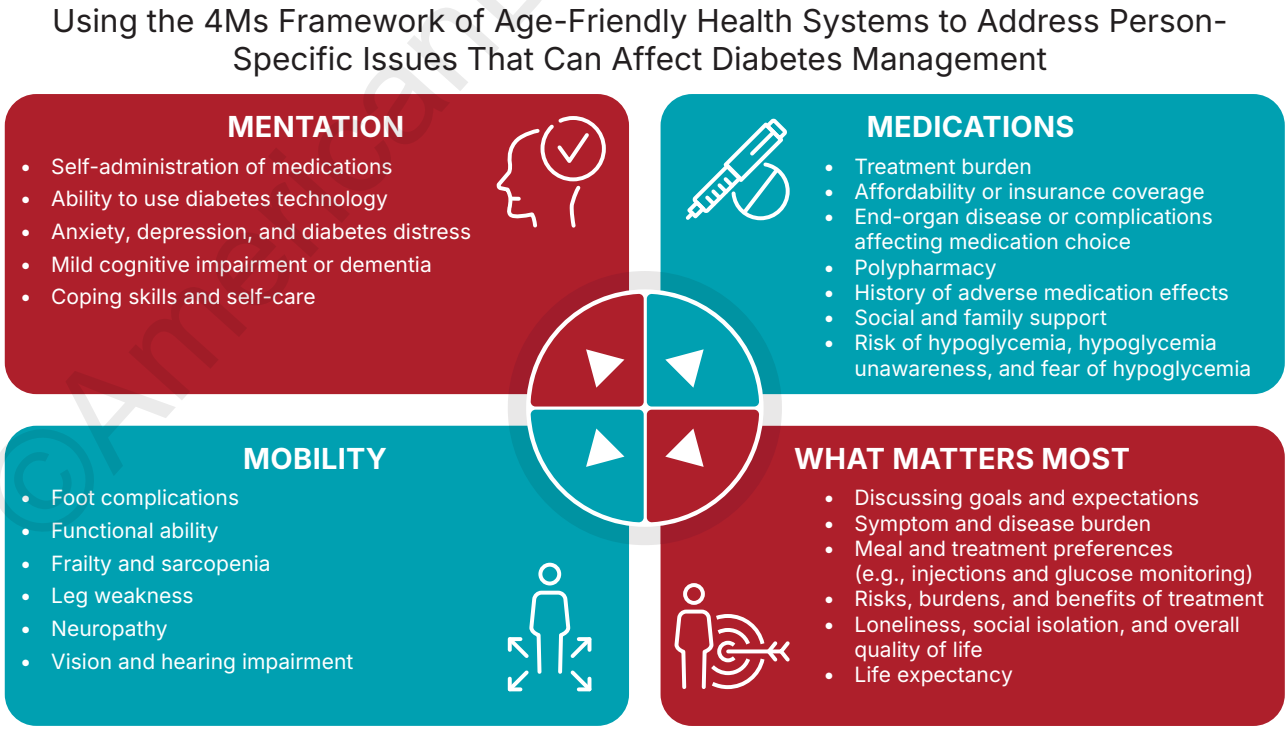

Figure 13.1—Using the 4Ms framework of age-friendly health systems to address person-specific issues that can affect diabetes management.

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dementia. Management of blood pressure and cholesterol lowering with statins have been associated with a reduced risk of incident dementia and are, thus, particularly important in older adults with diabetes.

Recently, the U.S. Food and Drug Administration (FDA) approved two new anti-amyloid monoclonal antibodies for the treatment of early Alzheimer disease (23,24). While these drugs lower the amyloid burden in the brain and appear to slow cognitive decline, the slowing is modest and of unclear significance and duration. In addition, a substantial minority of individuals developed imaging abnormalities consistent with brain edema or hemorrhage. Whether these drugs will provide net benefit for older adults with diabetes remains to be determined.

Identifying cognitive impairment early has important implications for diabetes care. The presence of cognitive impairment can make it challenging for health care professionals to help people with diabetes reach individualized glycemic, blood pressure, and lipid goals. Cognitive dysfunction may make it difficult for individuals to perform complex self-care tasks (25), such as monitoring glucose and administering and adjusting insulin doses. Also, it can hinder their ability to appropriately maintain the timing and nutritional content of their meals. These factors increase risk for hypoglycemia, which, in turn, can worsen cognitive function and have multiple other adverse effects in older individuals with diabetes. When clinicians are providing care for people with cognitive dysfunction, it is critical to simplify care plans and to ascertain and engage the appropriate support structure to assist individuals in all aspects of care.

Older adults with diabetes should be carefully screened and monitored for cognitive impairment (2). Several simple assessment tools are available to screen for cognitive impairment (25,26), such as the Mini-Mental State Examination (27), Mini-Cog (28), and the Montreal Cognitive Assessment (29), which may help to identify individuals requiring neuropsychological evaluation, particularly when dementia is suspected (i.e., in those experiencing memory loss, a decrease in executive function, and declines in their basic and instrumental activities of daily living). Annual screening is indicated for adults 65 years of age or older for early detection of mild cognitive impairment or dementia (4,30). Screening for cognitive impairment should also be considered when an individual presents with a significant decline in clinical status due to increased problems with self-care activities and medication management, such as errors in calculating insulin dose, difficulty counting carbohydrates, skipped meals, skipped insulin doses, and difficulty recognizing, preventing, or treating hypoglycemia. People who screen positive for cognitive impairment should receive diagnostic assessment as appropriate, including referral to a behavioral health professional for formal cognitive and neuropsychological evaluation if indicated and feasible (31).

HYPOGLYCEMIA

Recommendations

13.4 Ascertain and address episodes of hypoglycemia at routine visits because older adults with diabetes have a greater risk of hypoglycemia, especially when treated with hypoglycemic agents (e.g., sulfonylureas, meglitinides, and insulin). **B**

13.5 Recommend continuous glucose monitoring (CGM) for older adults with type 1 diabetes to improve glycemic outcomes, reduce hypoglycemia, and reduce treatment burden. **A**

13.6 Offer CGM for older adults with type 2 diabetes on insulin therapy to improve glycemic outcomes and reduce hypoglycemia. **B**

13.7 Consider the use of automated insulin delivery systems, **A** mechanical insulin delivery systems, **E** and other advanced insulin delivery devices such as connected pens **E** to reduce risk of hypoglycemia for older adults, based on individual ability and support system.

Older adults may be at higher risk of hypoglycemia for many reasons, including irregular meal intake, insulin deficiency necessitating insulin therapy, and worsening kidney function (32). As described above, older adults have higher rates of unidentified cognitive impairment and dementia, leading to difficulties in performing complex self-care activities (e.g., glucose monitoring and insulin dose adjustment). Cognitive decline has been associated with increased risk of hypoglycemia, and conversely, severe hypoglycemia has been linked to increased risk of dementia (33–35). Therefore, as discussed in Recommendation 13.3, it is important to routinely screen older adults for cognitive impairment and dementia and discuss findings with the individuals and their care partners.

People with diabetes and their care partners should be routinely queried about their history of hypoglycemic events, impaired hypoglycemia awareness, and fear of hypoglycemia as discussed in Section 6, "Glycemic Goals and Hypoglycemia." Older adults can also be stratified for future risk for hypoglycemia with validated risk calculators (e.g., Kaiser Hypoglycemia Model for adults with type 2 diabetes) (36) and with consideration of hypoglycemia risk factors (**Table 6.5**). An important step to mitigate hypoglycemia risk is to determine whether the person with diabetes is skipping meals or inadvertently repeating doses of their medications. Glycemic goals and pharmacologic treatments may need to be adjusted to minimize the occurrence of hypoglycemic events (2). This recommendation is supported by results from multiple randomized controlled trials, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and the Veterans Affairs Diabetes Trial (VADT), which showed that intensive treatment protocols aimed to achieve an A1C $<6.0\%$ with complex drug plans significantly increased the risk for hypoglycemia requiring assistance compared with standard treatment (37,38). However, these intensive treatment plans included extensive use of insulin and minimal use of GLP-1 RAs, and they preceded the availability of SGLT2 inhibitors.

Use of Continuous Glucose Monitoring and Advanced Insulin Delivery Devices

For older adults with type 1 diabetes, continuous glucose monitoring (CGM) is a useful approach to predicting and reducing the risk of hypoglycemia (39). In the Wireless Innovation in Seniors with Diabetes Mellitus (WISDM) trial, adults over 60 years of age with type 1 diabetes were randomized to CGM or standard blood glucose monitoring. Over 6 months, use of CGM resulted in a small but statistically significant reduction in time spent with hypoglycemia (glucose level <70 mg/dL) compared with standard blood glucose monitoring (adjusted treatment difference -1.9% [-27 min/day]; 95% CI -2.8% to

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−1.1% [−40 to −16 min/day]; $P < 0.001$) (40,41). Among secondary outcomes, time spent in range between 70 and 180 mg/dL increased by 8% (95% CI 6.0–11.5) and glycemic variability (%CV) decreased. In the 6-month trial extension, these benefits were sustained for up to a year (42). These and other short-term trials are supported by observational data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study indicating that among older adults (mean age 58 years) with long-standing type 1 diabetes, routine CGM and insulin pump use was associated with fewer hypoglycemic events and hyperglycemic excursions and lower A1C levels (43). While the current evidence base for older adults is primarily in type 1 diabetes, the evidence demonstrating the clinical benefits of CGM for people with type 2 diabetes using insulin is growing (44) (see Section 7, "Diabetes Technology"). The DIAMOND (Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes) study demonstrated that in adults ≥60 years of age with either type 1 or type 2 diabetes using multiple daily injections of insulin, CGM use was associated with improved A1C and reduced glycemic variability (45). An analysis of the results of the MOBILE study, which focused on adults aged ≥65 years and compared CGM with blood glucose meter monitoring, showed that the mean A1C change at 8 months was greater in older adults than in younger adults (−0.65% vs. –0.35%) with type 2 diabetes treated with basal insulin and oral glucose-lowering agents. Similarly, the increase in time in range (TIR) at 8 months was greater in the older adult group than in the younger adult group (19% vs. 12%, $P = 0.01$) and the decrease in time above range was greater in the older adult group as well, which shows that CGM benefits extend to older adults with type 2 diabetes who are non-intensively treated (46). Older adults with physical or cognitive limitations who require monitoring of blood glucose by a surrogate or reside in group homes or assisted living facilities are other populations for which CGM may play a useful role.

The availability of accurate CGM devices that can communicate with insulin pumps through Bluetooth has enabled the development of advanced insulin delivery algorithms for pumps. These algorithms fall into two categories: predictive low-glucose suspend algorithms that automatically shut off insulin delivery if a hypoglycemic event is imminent and hybrid closed-loop algorithms that automatically adjust insulin infusion rates based on feedback from a CGM to keep glucose levels in a goal range. Advanced insulin delivery devices have been shown to improve glycemic outcomes in both children and adults with type 1 diabetes. Most trials of these devices have included people with type 1 diabetes but relatively few older adults; however, data from two small randomized controlled trials in older adults are available. The Older Adult Closed Loop (ORACL) trial in 30 older adults (mean age 67 years) with type 1 diabetes found that an automated insulin delivery (AID) strategy was associated with significant improvements in TIR compared with sensor-augmented pump therapy (47). Moreover, they found small but significant decreases in hypoglycemia with the AID strategy. Boughton et al. (48) reported results of an open-label, crossover design clinical trial in 37 older adults (≥60 years) in which 16 weeks of treatment with a hybrid closed-loop advanced insulin delivery system was compared with sensor-augmented pump therapy. They found that hybrid closed-loop insulin delivery improved the proportion of time glucose was in range largely due to decreases in hyperglycemia. In contrast to the ORACL study, no significant differences in hypoglycemia were observed. Both studies enrolled older individuals whose blood glucose was relatively well managed (mean A1C ∼7.4%), and both used a crossover design comparing hybrid closed-loop insulin delivery to sensor-augmented pump therapy. A recent randomized controlled trial of older adults with type 2 diabetes using multiple daily injections who were unable to manage insulin therapy on their own revealed an increase of TIR of 27% over 12 weeks of AID use in addition to tailored home health care services (49).

These trials provide the first evidence that older individuals with long-standing type 1 and type 2 diabetes can successfully use advanced insulin delivery technologies to improve glycemic outcomes, as has been seen in younger populations. A recent real world evidence analysis of a Medicare population (n = 4,243, 89% with type 1 diabetes, mean age 67.4 years) also indicated that initiating hybrid closed-loop insulin delivery was associated with improvements in mean glucose and a 10% increase in TIR (50). Use of such technologies should be periodically reassessed, as the burden may outweigh the benefits in those with declining cognitive or functional status.

TREATMENT GOALS

Recommendations

13.8a Older adults with diabetes who are otherwise healthy with few and stable coexisting chronic illnesses and intact cognitive and functional status should have lower glycemic goals (such as A1C <7.0–7.5% [<53–58 mmol/mol]) and/or time in range [TIR] 70–180 mg/dL [3.9–10.0 mmol] of ∼70% and time below range ≤70 mg/dL [3.9 mmol/L] of ≤4%) if CGM is used. **C**

13.8b Older adults with diabetes and intermediate or complex health are clinically heterogeneous with variable life expectancy. Selection of glycemic goals should be individualized and should prioritize avoidance of hypoglycemia, with less stringent goals (such as A1C <8.0% [<64 mmol/mol] and/or TIR 70–180 mg/dL [3.9–10.0 mmol] of ∼50% and time below range <70 mg/dL [3.9 mmol/L] of <1%) for those with significant cognitive and/or functional limitations, frailty, severe comorbidities, and a less favorable risk-to-benefit ratio of diabetes medications. **C**

13.8c Older adults with very complex or poor health receive minimal benefit from stringent glycemic goals. Clinicians should focus on avoiding hypoglycemia and symptomatic hyperglycemia rather than achieving stringent glycemic goals. **C**

13.9 Screening for diabetes complications should be individualized in older adults with diabetes. Particular attention should be paid to complications that would lead to impairment of functional status or quality of life. **C**

13.10 Treatment of hypertension to individualized goal levels is indicated in most older adults with diabetes. **B**

13.11 Treatment of other cardiovascular risk factors should be individualized in older adults with diabetes, considering the time frame of benefit. Lipid-lowering therapy and antiplatelet agents may benefit those with life expectancies at least equal to the time frame of primary prevention or secondary intervention trials. **E**

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The care of older adults with diabetes is complicated by their clinical, cognitive, and functional heterogeneity and their varied prior experience with disease management. Some older individuals may have developed diabetes years earlier and have significant complications, others are newly diagnosed and may have had years of undiagnosed diabetes with resultant complications, and still, other older adults may have truly recent-onset disease with few or no complications (51). Some older adults with diabetes have other underlying chronic conditions, substantial diabetes-related comorbidity, limited cognitive or physical functioning, or frailty (52,53). Other older individuals with diabetes have little comorbidity and are active.

Life expectancy is affected by the age of the individual, disease burden, and degree of disability. Multiple prognostic tools for life expectancy for older adults are available (54,55). Notably, the Life Expectancy Estimator for Older Adults with Diabetes (LEAD) tool was developed and validated among older adults with diabetes, and a high risk score was strongly associated with having a life expectancy of $<$5 years (56). These data may be a useful starting point to inform decisions about selecting less stringent glycemic goals (56,57). Older adults also vary in their preferences for the intensity and mode of glucose management (58). Health care professionals caring for older adults with diabetes must take this heterogeneity into consideration when setting and prioritizing treatment goals (10,11) (**Table 13.1**). In addition, older adults with diabetes should be assessed for disease treatment and self-management knowledge, health literacy, and mathematical literacy (numeracy) at the onset and throughout treatment. See **Fig. 6.2** for individual/disease-related factors to consider when determining individualized glycemic goals.

A1C results may be inaccurate in those who have received blood transfusions and who have medical conditions that impact red blood cell turnover (see Section 2, "Diagnosis and Classification of Diabetes," for additional details on the limitations of A1C) (59). Conditions affecting red blood cell turnover that are common in older adults include end-stage kidney disease, recent significant blood loss, and erythropoietin therapy. In these instances, blood glucose monitoring and/or CGM should be used for glycemic goal setting (**Table 13.1**). Serum glycated protein assays such as fructosamine may also be useful for glycemic monitoring in conjunction with other measures (see Section 6, "Glycemic Goals and Hypoglycemia") (60–62).

Older Adults With Good Functional Status and Without Complications

There are few long-term studies in older adults demonstrating the benefits of intensive glycemic, blood pressure, and lipid management. Older adults who can be expected to live long enough to realize the benefits of long-term intensive diabetes management, who have good cognitive and physical function, and who choose to do so via shared decision-making may be treated using therapeutic interventions and goals similar to those for younger adults with diabetes (**Table 13.1**).

As for all people with diabetes, diabetes self-management education and ongoing diabetes self-management support are vital components of diabetes care for older adults and their caregivers. Self-management knowledge and skills should be reassessed following a significant clinical change or hospitalization, when treatment plan changes are made, or when an individual's functional abilities diminish. In addition, declining or impaired ability to perform diabetes self-care behaviors may be an indication that an older person with diabetes needs a referral for cognitive and physical functional assessment, using age-normalized evaluation tools, as well as help establishing a support structure for diabetes care (3,31).

Older Adults With Complications and Reduced Functionality

Older adults with diabetes categorized as having complex or intermediate health (**Table 13.1**) are heterogeneous with respect to their function and life expectancy (63–65). Based on concepts of competing mortality and time to benefit, some people in this category with shorter life expectancy will have less benefit from glucose lowering and should have less stringent glycemic goals (66). This is especially true for individuals with advanced diabetes complications, life-limiting comorbid illnesses, frailty, or substantial cognitive or functional impairments. These individuals are also more likely to experience serious adverse effects of therapeutics, such as hypoglycemia (67). However, those with poorly managed diabetes may be subject to acute complications of diabetes, including dehydration, poor wound healing, and hyperglycemic crises. Glycemic goals should, at a minimum, avoid these consequences. Factors to consider for individualizing glycemic goals are outlined in **Fig. 6.2** and **Fig. 13.1** (4Ms framework). Clinicians should also consider the balance of risks and benefits of an individual's diabetes medications, including disease-specific benefits (such as reducing symptomatic heart failure or stabilizing chronic kidney disease) and burdens such as hypoglycemia risk, tolerability, difficulties of administration, inadequate support system, and financial cost. In addition, attention to oral health, vision and hearing loss, foot care, fall prevention, and early detection of depression will improve quality of life.

While **Table 13.1** provides overall guidance for identifying complex and very complex individuals, there is not yet global consensus on geriatric people classification. Ongoing empiric research on the classification of older adults with diabetes based on comorbid illness has repeatedly found three major classes of individuals: a healthy, a geriatric, and a cardiovascular class (10,63,68). The geriatric class has the highest prevalence of obesity, hypertension, arthritis, and incontinence, and the cardiovascular class has the highest prevalence of myocardial infarctions, heart failure, and stroke. Compared with the healthy class, the cardiovascular class has the highest risk of frailty and subsequent mortality. Additional research is needed to develop a reproducible classification scheme to distinguish the natural history of disease as well as differential response to glucose management and specific glucose-lowering agents (69).

Vulnerable Older Adults at the End of Life

For people with diabetes receiving palliative care and end-of-life care, the focus should be to avoid hypoglycemia and symptomatic hyperglycemia while reducing the burdens of glycemic management. Thus, as organ failure develops, the treatment plan will have to be deintensified and one or more agents will need to be discontinued. At the end of life, most agents for type 2 diabetes may be removed (70). There is, however, no consensus for the management of type 1 diabetes in this scenario (71). Consultation with a geriatric specialist might be warranted to

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Table 13.1—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes

Characteristics and health status of person with diabetes	Rationale	Reasonable A1C goal*	Reasonable CGM goals	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.0–7.5% (<53–58 mmol/mol)	TIR 70–180 mg/dL (3.9–10.0 mmol) of ~70%, and TBR <70 mg/dL (3.9 mmol/L) of <4%)	80–130 mg/dL (4.4–7.2 mmol/L)	80–180 mg/dL (4.4–10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses† or two or more ADL impairments or mild to moderate cognitive impairment)	Variable life expectancy. Individualize goals, considering: • Severity of comorbidities • Cognitive and functional limitations • Frailty • Risk-to-benefit ratio of diabetes medications • Individual preference	<8.0% (<64 mmol/mol)	TIR 70–180 mg/dL (3.9–10.0 mmol) of ~50% and TBR <70 mg/dL (3.9 mmol/L) of <1%	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses‡ or moderate to severe cognitive impairment or two or more ADL impairments)	Limited remaining life expectancy makes benefit minimal	Avoid reliance on A1C; glucose management decisions should be based on avoiding hypoglycemia and symptomatic hyperglycemia		100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<140/90 mmHg	Consider likelihood of benefit with statin

This table represents a consensus framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes. The characteristic categories are general concepts. Not every individual will clearly fall into a particular category. Consideration of individual and care partner preferences, care partner engagement, abilities, and resources is an important aspect of treatment individualization. Additionally, an individual's health status and preferences may change over time. ADL, activities of daily living; CGM, continuous glucose monitoring; LTC, long-term care; TBR, time below range; TIR, time in range. *A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden. †Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. "Multiple" means at least three, but many individuals may have five or more (77). ‡The presence of a single end-stage chronic illness, such as stage 3–4 heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy. Adapted from Kirkman et al. (3).

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assist with complex medical and functional issues as well as advance care planning. See the section END-OF-LIFE CARE below for additional information.

Beyond Glycemic Management

Although minimizing hyperglycemia may be important in older individuals with diabetes, greater reductions in morbidity and mortality are likely to result from a clinical focus on comprehensive cardiovascular risk factor modification. There is strong evidence from clinical trials of the value of treating hypertension in older adults (72,73), with treatment of hypertension to individualized target levels indicated in most. There is less evidence for lipid-lowering therapy and aspirin therapy, although the benefits of these interventions for primary and secondary prevention are likely to apply to older adults whose life expectancies equal or exceed the time frames of the clinical trials (74). In the case of statins, the follow-up time of clinical trials ranged from 2 to 6 years. While the time frame of trials can be used to inform treatment decisions, a more specific concept is the time to benefit for a therapy. For statins, a meta-analysis of the previously mentioned trials showed that the time to benefit is 2.5 years (75).

LIFESTYLE MANAGEMENT

Recommendations

13.12 Recommend healthful eating with adequate protein intake for older adults with diabetes. Recommend regular exercise, including aerobic activity, weight-bearing exercise, and/or resistance training as tolerated in those who can safely engage in such activities. **B**

13.13 For older adults with type 2 diabetes, overweight or obesity, and capacity to exercise safely, an intensive lifestyle intervention focused on dietary changes, physical activity, and modest weight loss (e.g., 5–7%) should be considered for its benefits on quality of life, mobility and physical functioning, and cardiometabolic risk. **A**

Lifestyle management in older adults should be tailored to frailty status. Diabetes in the aging population is associated with reduced muscle strength, poor muscle quality, and accelerated loss of muscle mass, which may result in sarcopenia or dynapenia (76) and/or osteopenia (77,78). Diabetes is also recognized as an independent risk factor for frailty. Frailty is characterized by decline in physical performance and an increased risk of negative health outcomes due to physiologic vulnerability and functional or psychosocial stressors. Inadequate nutritional intake, particularly inadequate protein intake, can increase the risk of sarcopenia and frailty in older adults. Special attention should be paid to malnutrition or the risk of malnutrition in older adults with diabetes given its association with sarcopenia (79,80). Malnutrition is also associated with decreases in activities of daily living, grip strength, physical performance of lower limbs, cognition, and quality of life (81–83). See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for a description of malnutrition and screening recommendations. Management of malnutrition, sarcopenia, and frailty in diabetes includes optimal nutrition with adequate protein intake combined with an exercise program that includes aerobic, weight-bearing, and resistance training. The benefits of a structured exercise program (as in the Lifestyle Interventions and Independence for Elders [LIFE] study) in frail older adults include reducing sedentary time, preventing mobility disability, and reducing frailty (84). The goal of these programs is not weight loss but enhanced functional status. For nonfrail older adults with type 2 diabetes and overweight or obesity, an intensive lifestyle intervention designed to reduce weight is beneficial across multiple outcomes. The Look AHEAD (Action for Health in Diabetes) trial is described in Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes." Look AHEAD specifically excluded individuals with a low functional status. It enrolled people between 45 and 74 years of age and required that they be able to perform a maximal exercise test (85,86). While the Look AHEAD trial did not achieve its primary outcome of reducing cardiovascular events, the intensive lifestyle intervention had multiple clinical benefits that are important to the quality of life of older adults. Benefits included weight loss, improved physical fitness, increased HDL cholesterol, lowered systolic blood pressure, reduced A1C levels, reduced waist circumference, and reduced need for medications (87). Additionally, several subgroups, including participants who lost at least 10% of baseline body weight at year 1, had improved cardiovascular outcomes (88). Risk factor management was improved with reduced utilization of antihypertensive medications, statins, and insulin (89). In age-stratified analyses, older adults in the trial (60 to early 70s) had similar benefits compared with younger people (90,91). In addition, lifestyle intervention produced benefits on aging relevant outcomes, such as reductions in multimorbidity and improvements in physical function and quality of life (92–95).

PHARMACOLOGIC THERAPY

Recommendations

13.14 Select medications with low risk of hypoglycemia in older adults with type 2 diabetes, specifically for those with hypoglycemia risk factors. **B**

13.15 Overtreatment of diabetes is common in older adults and should be avoided. **B**

13.16a Deintensify hypoglycemia-causing medications (e.g., insulin, sulfonylureas, or meglitinides) or switch to a medication class with low hypoglycemia risk for individuals who are at high risk for hypoglycemia, using individualized glycemic goals. **B**

13.16b In older adults with diabetes, deintensify diabetes medications for individuals for whom the harms and/or burdens of treatment may be greater than the benefits, within individualized glycemic goals. **E**

13.16c Simplify complex treatment plans (especially insulin) to reduce the risk of hypoglycemia and polypharmacy and decrease the treatment burden if it can be achieved within the individualized glycemic goals. **B**

13.16d In older adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment plan should include agents that reduce cardiovascular and kidney disease risk, irrespective of glycemia. **A**

13.17 Consider costs of care and coverage when developing treatment plans in order to reduce risk of cost-related barriers to medication taking and self-management behaviors. **B**

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Special care is required in prescribing and monitoring pharmacologic therapies in older adults (96), who are at high risk of polypharmacy, have difficulties in maintaining prescribed medication plans, and may have cognitive impairment and functional impairment. Therapeutic choices should take into consideration whether older adults with diabetes live independently, have an engaged care partner, or live in a skilled nursing facility, assisted living facility, or group home. See **Fig. 9.3** for general recommendations regarding glucose-lowering treatment for adults with type 2 diabetes and **Table 9.2** for person- and drug-specific factors to consider when selecting glucose-lowering agents. Cost may be an especially important consideration, as older adults tend to be on many medications and live on fixed incomes (97). Accordingly, the costs of care and insurance coverage rules should be considered when developing treatment plans to reduce the risk of cost-related barriers to use (98,99). See **Table 9.3** and **Table 9.4** for median monthly cost in the U.S. of noninsulin glucose-lowering agents and insulin, respectively. It is important to match complexity of the treatment plan to the self-management ability of older adults with diabetes and their available social and medical support. Many older adults with diabetes struggle to maintain the frequent blood glucose monitoring and insulin injection plans they previously followed, perhaps for many decades, as they develop medical conditions that may impair their ability to follow their treatment plan safely. Individualized glycemic goals should be established (**Fig. 6.2** and **Table 13.1**) and periodically adjusted based on coexisting chronic illnesses, cognitive function, functional status, life expectancy, and risk of complications (2). Intensive glycemic management with medication plans including insulin and sulfonylureas in older adults with complex medical conditions has been identified as overtreatment and found to be very common in clinical practice (100–104) and may increase the risk of mortality (37). Ultimately, the determination of whether a person is considered overtreated requires an elicitation of the person's perceptions of the current medication burden and preferences for treatments. For those seeking to simplify their diabetes medication plan, deintensification of plans in individuals taking noninsulin glucose-lowering medications can be achieved by either lowering the dose or discontinuing some medications, as long as individualized glycemic goals are maintained (105). When older adults are found to have an insulin plan with complexity beyond their self-management abilities, lowering the dose of insulin may not be adequate (106). Simplification of the insulin plan to match an individual's self-management abilities and their available social and medical support in these situations has been shown to reduce hypoglycemia and disease-related distress without worsening glycemic outcomes (107–110). **Figure 13.2** depicts an algorithm that can be used to simplify the insulin administration plan (109). There are now multiple studies evaluating deintensification protocols in diabetes as well as hypertension, demonstrating that deintensification is safe and possibly beneficial for older adults (105). **Table 13.2** provides examples of and rationale for situations where deintensification and/or insulin plan simplification may be appropriate in older adults.

Metformin

Metformin is a treatment option for older adults with type 2 diabetes if prescription guidelines are followed carefully. Metformin may be used safely in individuals with an estimated glomerular filtration rate (eGFR) $\geq$30 mL/min/1.73 m^2 (111), while lower doses may be used in those with an eGFR 30–45 mL/min/1.73 m^2. eGFR should be monitored every 3 to 6 months in those at risk for decline in kidney function. However, it is contraindicated in those with advanced renal insufficiency and should be used with caution in those with hypoperfusion, hypoxemia, impaired hepatic function, or heart failure because of the increased risk of lactic acidosis. Metformin may be temporarily discontinued before procedures including imaging studies using iodinated contrast, during hospitalizations, and when acute illness may compromise renal or liver function. Additionally, metformin can cause gastrointestinal side effects and a reduction in appetite that can be problematic for some older adults. The daily dose should be slowly increased to minimize gastrointestinal side effects, and reduction or elimination of metformin may be necessary for those experiencing persistent gastrointestinal side effects. For those taking metformin long term, monitoring for vitamin B12 deficiency should be considered (112). Extended-release formulation may be used as an alternative to immediate-release formulation in older adults experiencing difficulties in maintaining medication plans or gastrointestinal effects.

Pioglitazone

Pioglitazone, if used at all, should be used very cautiously in older adults on insulin therapy as well as in those with or at risk for heart failure, fluid retention, weight gain, osteoporosis, falls or fractures, and/or macular edema (113,114). Lower doses of pioglitazone in combination therapy may mitigate these side effects.

Insulin Secretagogues

Sulfonylureas and other insulin secretagogues such as the meglitinides (repaglinide and nateglinide) are associated with hypoglycemia, bone loss (115), and fracture risk (116) and should be used with caution. If used, sulfonylureas with a shorter duration of action, such as glipizide, are preferred, and frequency of hypoglycemia monitored at each visit. Glyburide is a longer-acting sulfonylurea and should be avoided in older adults (117). Many antimicrobials (most commonly fluroquinolones and sulfamethoxazole-trimethoprim) interact with sulfonylureas to increase the effective sulfonylurea dose, which may precipitate hypoglycemia (118–120). Sulfonylureas should be reduced or temporarily discontinued in these circumstances.

Incretin-Based Therapies

Oral dipeptidyl peptidase 4 (DPP-4) inhibitors have few side effects and minimal risk of hypoglycemia, but their cost may be a barrier to some older adults. DPP-4 inhibitors are relatively weak agents and do not reduce or increase major adverse cardiovascular outcomes generally, and there is no interaction by age-group (121). A challenge of interpreting the age-stratified analyses of this drug class and other cardiovascular outcomes trials is that while most of these analyses were prespecified, they were not powered to detect differences. In general, these medications may be useful in older adults with mild hyperglycemia or with high risk of hypoglycemia, or when metformin is contraindicated. Among DPP-4 inhibitors, linagliptin may be used as alternative to metformin in older adults with low GFR.

GLP-1 RAs have demonstrated cardiovascular benefits among people with

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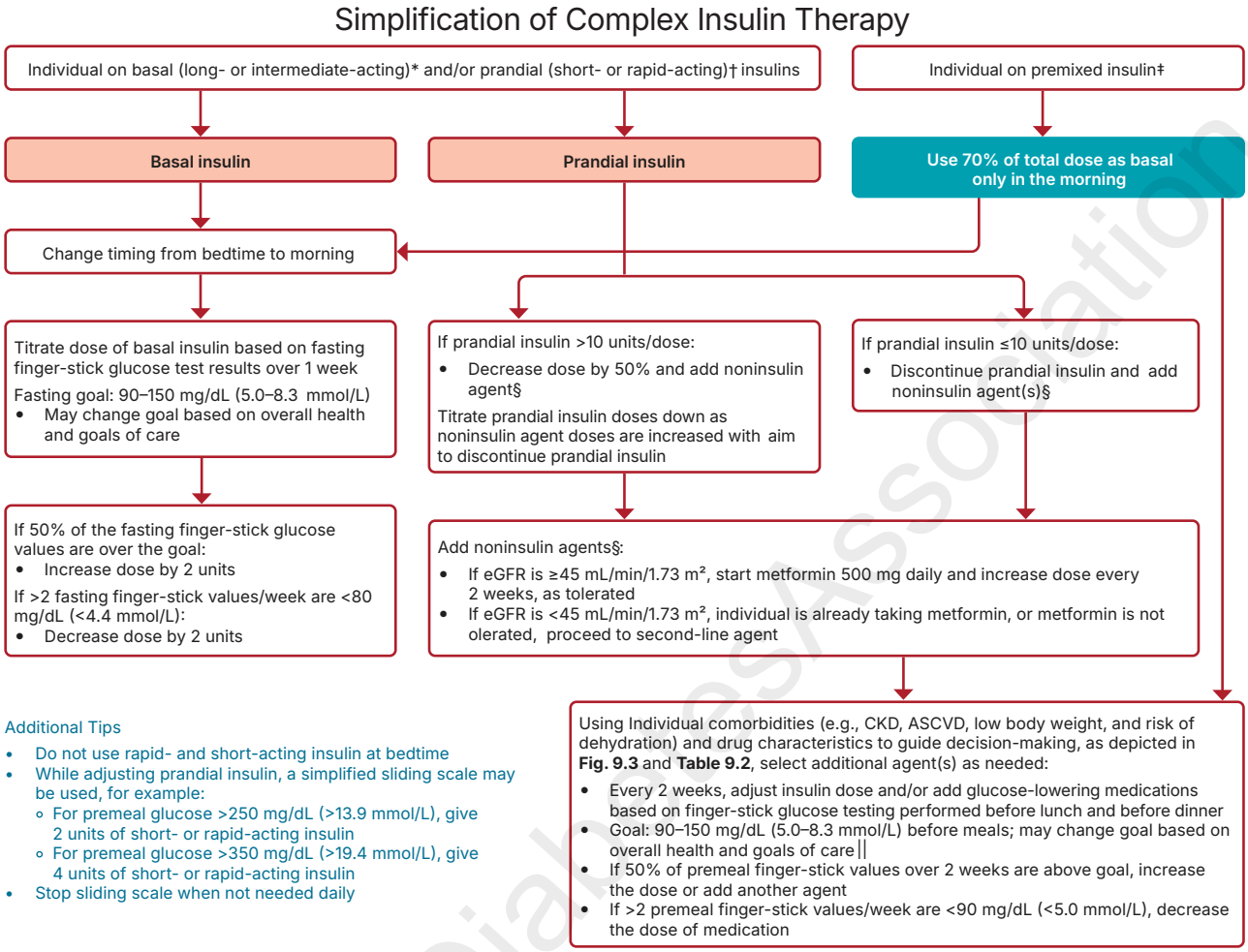

Figure 13.2—Algorithm to simplify insulin administration plans in older individuals. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate. *Basal insulins: glargine U-100 and U-300, detemir, degludec, and human NPH. †Prandial insulins: short-acting (regular human insulin) or rapid-acting (lispro, aspart, and glulisine). ‡Premixed insulins: 70/30, 75/25, and 50/50 products. §Examples of noninsulin agents include metformin, sodium–glucose cotransporter 2 inhibitors, dipeptidyl peptidase 4 inhibitors, and glucagon-like peptide 1 receptor agonists. ||See **Table 13.1**. Figure was adapted with permission from Munshi et al. (109).

diabetes and established atherosclerotic cardiovascular disease (ASCVD) and those at higher ASCVD risk, and newer trials are expanding our understanding of their benefits in other populations (122). See Section 9, "Pharmacologic Approaches to Glycemic Treatment," and Section 10, "Cardiovascular Disease and Risk Management," for a more extensive discussion regarding the specific indications for this class of agents. In a systematic review and meta-analysis of GLP-1 RA trials, these agents have been found to reduce major adverse cardiovascular events, cardiovascular deaths, stroke, and myocardial infarction to the same degree for people over and under 65 years of age (123). While the evidence for this class of agents for older adults continues to grow, there are a number of practical issues that should be considered specifically for older people. These drugs are injectable agents (with the exception of oral semaglutide) (124), which require visual, motor, and cognitive skills for appropriate administration, although most of them have a weekly dosing schedule. GLP-1 RAs may also be associated with nausea, vomiting, diarrhea, or constipation and should be titrated slowly. Given the gastrointestinal side effects of this class, GLP-1 RAs are not preferred in older adults experiencing unexplained weight loss or undernutrition or in those who have recurrent gastrointestinal problems. GLP-1 RAs should be avoided especially in people with problematic constipation, significant gastroparesis, recurrent ileus, or bowel obstruction. Individuals should be monitored regularly for excessive weight loss.

Tirzepatide is a novel dual-acting glucose-dependent insulinotropic polypeptide and GLP-1 RA administered as a once-weekly subcutaneous injection. In phase 3 trials, tirzepatide decreased A1C and weight—generally to a greater extent than other glucose-lowering drugs including semaglutide and insulin—with no significant differences in the safety or efficacy in older compared with younger individuals (125). As the adverse effect profile of tirzepatide is similar to that for GLP-1 RAs, the same precautions for older adults apply (125).

Sodium–Glucose Cotransporter 2 Inhibitors

SGLT2 inhibitors are administered orally, which may be convenient for older adults with diabetes. In those with established ASCVD, these agents have shown cardiovascular benefits (122). This class of agents has also been found to be beneficial for

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Table 13.2—Considerations for treatment plan simplification and deintensification/deprescribing in older adults with diabetes

Characteristics and health status of person with diabetes	Reasonable glycemic goal	Rationale/considerations	When may medication plan simplification be required?	When may treatment deintensification be required?
Healthy (few chronic illnesses, intact cognitive and function)	A1C <7.0–7.5% (<53–58 mmol/mol)	• Healthy individuals can perform complex tasks for glycemic management • During acute illness, individuals may be at risk for administration or dosing errors	• Severe or recurrent hypoglycemia on insulin therapy, regardless of A1C • Wide glucose excursions • Cognitive or functional decline following acute illness	• Severe or recurrent hypoglycemia on insulin, sulfonylureas, or meglitinides, regardless of A1C • Wide glucose excursions • Polypharmacy
Complex/intermediate (multiple chronic illnesses or two or more ADL impairments or mild to moderate cognitive impairment)	A1C <8.0% (<64 mmol/mol)	• Comorbidities may affect self-management abilities and capacity to avoid hypoglycemia	• Severe or recurrent hypoglycemia on insulin therapy, regardless of A1C • Unable to manage complexity of insulin plan • Significant change in social circumstances, such as loss of care partner, change in living situation, or financial difficulties	• Severe or recurrent hypoglycemia on insulin, sulfonylureas, or meglitinides regardless of A1C • Wide glucose excursions • Polypharmacy
Community-dwelling individuals receiving short-term care in a skilled nursing facility	Avoid reliance on A1C, glucose goal 100–200 mg/dL (5.6–11.1 mmol/L)	• Glycemic management is important for recovery, wound healing, hydration, and avoidance of infections • Recovery from acute illness may impair cognitive function • More support may be needed on transition to home	• Consider reinstating prehospitalization treatment if it increased in complexity during hospitalization	• Weight loss, anorexia, short-term cognitive decline, and/or loss of physical functioning
Very complex/poor health (LTC or end-stage chronic illnesses or moderate to severe cognitive impairment or two or more ADL impairments)	Avoid reliance on A1C and avoid hypoglycemia and symptomatic hyperglycemia	• No benefits of tight glycemic goals in this population • Hypoglycemia should be avoided • Most important outcomes are maintenance of cognitive and functional status	• The individual would like to decrease the number of injections and finger-stick blood glucose monitoring • The individual has an inconsistent eating pattern	• Cognitive dysfunction, depression, anorexia, or inconsistent eating pattern while taking sulfonylureas or meglitinides • Taking any diabetes medications without clear benefits
At the end of life	Avoid hypoglycemia and symptomatic hyperglycemia	• Goal is to provide comfort and avoid tasks or interventions that cause pain or discomfort • Care partners are important in providing medical care and maintaining quality of life	• Pain or discomfort caused by treatment (e.g., injections or finger sticks) • Excessive stress of care partners due to treatment complexity	• Taking any diabetes medications without clear benefits in improving symptoms and/or comfort

Treatment plan simplification refers to changing strategy to decrease the complexity of a medication plan (e.g., fewer administration times and fewer blood glucose checks) and decreasing the need for calculations (such as sliding-scale insulin calculations or insulin-carbohydrate ratio calculations). Deintensification/deprescribing refers to decreasing the dose or frequency of administration of a treatment or discontinuing a treatment altogether. ADL, activities of daily living; LTC, long-term care. Created using information from Munshi et al. 2016 (109) and 2017 (161).

people with heart failure and to slow the progression of chronic kidney disease. See Section 9, "Pharmacologic Approaches to Glycemic Treatment," and Section 10, "Cardiovascular Disease and Risk Management," for a more extensive discussion regarding the indications for this class of agents. Stratified analyses of the trials of this drug class indicate that older adults

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have similar or greater benefits than younger people (126–128). SGLT2 inhibitors are generally well tolerated among older adults, although thoughtful selection is needed to avoid adverse effects in individuals at elevated risk (129). SGLT2 inhibitors may cause clinically significant volume depletion, for which older adults are at greater risk, and should be used cautiously in older adults who are frail or prone to orthostasis (130). SGLT2 inhibitors cause a higher rate of genital mycotic infections, especially in women, and may need to be discontinued if this effect becomes burdensome (131). Their use is also associated with a small increase in urinary tract infections; caution should be used in people with recurrent or severe urinary tract infections (131). Because SGLT2 inhibitors typically increase urine volume, symptoms of urinary incontinence should be queried before and after SGLT2 inhibitor initiation (132). Euglycemic diabetic ketoacidosis is a rare but potentially serious phenomenon associated with treatment with SGLT2 inhibitors, especially in those with multimorbidity who reside in post-acute and long-term care (PALTC) settings, with infection being the most common trigger (132,133). There is emerging data that SGLT2 inhibitor use may cause an increase in osteoporotic bone fractures, and although more data are needed, clinicians should consider minimizing SGLT2 inhibitor use in older adults at high fracture risk.

Insulin Therapy

The use of insulin therapy requires that individuals or their caregivers have good visual and motor skills and cognitive ability to manage the appropriate insulin dose using insulin pens or syringes. Insulin therapy relies on the ability of the older person with diabetes to administer insulin on their own or with the assistance of a care partner, to monitor glucose levels, and, eventually, to recognize and treat hypoglycamia. Insulin doses should be titrated to meet individualized glycemic goals and to avoid hypoglycemia.

Once-daily basal insulin injection therapy is associated with minimal side effects and may be a reasonable option in many older adults (134). When choosing a basal insulin, long-acting insulin analogs have been found to be associated with a lower risk of hypoglycemia compared with NPH insulin in the Medicare population. Multiple daily injections of insulin may be too complex for an older person with advanced diabetes complications, life-limiting coexisting chronic illnesses, or limited functional status or social support. Moreover, if affordable, use of insulin pens should be prefered to syringes, mostly in older adults with functional impairment. **Figure 13.2** provides a potential approach to simplification of insulin plans.

Other Factors to Consider

The needs of older adults with diabetes and their care partners should be evaluated to construct a tailored care plan. Inadequate social support and reduced access to long-term services and support may reduce these individuals' quality of life and increase the risk of functional dependency (7). The living situation must be considered as it may affect diabetes management and support needs. Social and instrumental support networks (e.g., adult children and care partners) that provide instrumental or emotional support for older adults with diabetes should be included in diabetes management discussions and shared decision-making.

The need for ongoing support of older adults becomes even greater when transitions to acute care and long-term care (LTC) become necessary. Unfortunately, these transitions can lead to discontinuity in goals of care, errors in dosing, and changes in nutrition and activity (135). Older adults in assisted living facilities may not have support to administer their own medications, whereas those living in a nursing home for short-term rehabilitation or LTC may rely on first-line care partners including nursing and care professionals with variable clinical expertise. Those receiving palliative care (with or without hospice) may require an approach that emphasizes comfort and symptom management while deemphasizing strict metabolic and blood pressure management.

SPECIAL CONSIDERATIONS FOR OLDER ADULTS WITH TYPE 1 DIABETES

Due in part to the success of modern diabetes management, people with type 1 diabetes are living longer, and the population of these people over 65 years of age is growing (136–138). Many of the recommendations in this section regarding a comprehensive geriatric assessment and personalization of goals and treatments are directly applicable to older adults with type 1 diabetes; however, this population has unique challenges and requires distinct treatment considerations (139). Insulin is an essential life-preserving therapy for people with type 1 diabetes, unlike for those with type 2 diabetes. To avoid diabetic ketoacidosis, older adults with type 1 diabetes need some form of basal insulin even when they are unable to ingest meals. Insulin may be delivered through an insulin pump or injections. CGM is approved for use by Medicare and can play a critical role in improving A1C, reducing glycemic variability, and reducing risk of hypoglycemia (45) (see Section 7, "Diabetes Technology," and Section 9, "Pharmacologic Approaches to Glycemic Treatment"). In older people with type 1 diabetes, administration of insulin may become more difficult as complications, cognitive impairment, and functional impairment arise. This increases the importance of care partners in the lives of these individuals. Many older people with type 1 diabetes require placement in PALTC settings (i.e., nursing homes and skilled nursing facilities), and unfortunately staff in these settings are less familiar with CGM devices, insulin pumps, or advanced insulin delivery devices. Nevertheless, a feasibility study in LTC facilities showed that CGM can be useful in older adults with diabetes, although it requires substantial staff training (140). Furthermore, an observational study of older adults with diabetes living in LTC facilities using CGM revealed a high prevalence of hypoglycemia both in people using insulin and in those using sulfonylureas, thus showing that this population of older adults in LTC facilities are at increased risk for hypoglycemia (141). Therefore, using CGM can provide useful and more prompt information on hypoglycemia in this vulnerable population. Of note, a recent randomized controlled trial in LTC facilities showed that real-time CGM use for up to 60 days was safe and effective in guiding insulin doses compared with BGM by point of care. There were no differences in TIR, time below range, or mean glucose levels (142). Some staff may be less knowledgeable about the differences between type 1 and type 2 diabetes. Diabetic ketoacidosis may be mistaken for sepsis, end-organ failure, or other electrolyte abnormalities. In these instances, the individual or their family may be more familiar with their diabetes management plan than the staff or health care professionals. Education of

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relevant support staff and health care professionals in rehabilitation and PALTC settings regarding insulin dosing and use of pumps and CGM is recommended as part of general diabetes education (see Recommendations 13.18 and 13.19).

TREATMENT IN POST-ACUTE AND LONG-TERM CARE SETTINGS

Recommendations

13.18 Recommend diabetes education/training (including that for CGM devices, insulin pumps, and advanced insulin delivery systems) for the staff of long-term care and rehabilitation facilities to improve the management of older adults with diabetes. **E**

13.19 People with diabetes residing in long-term care facilities need careful assessment of mobility, mentation, medications, and management preferences to establish individualized glycemic goals and to make appropriate choices of glucose-lowering agents and devices (including CGM devices, insulin pumps, and advanced insulin delivery systems) based on their clinical and functional status. **E** See **Fig. 13.1** for the 4Ms framework to address person-specific issues that affect diabetes management in older individuals.

Management of diabetes in the LTC setting is unique. Individualization of health care is important for all people with diabetes; however, practical guidance is needed for health care professionals as well as the LTC staff and care partners (143,144). Training should include diabetes detection and institutional quality assessment. PALTC facilities should develop their own policies and procedures for prevention, recognition, and management of hypoglycemia. With the increased longevity of populations, the care of people with diabetes and its complications in PALTC is an area that warrants greater study.

Resources

Staff of PALTC facilities should receive appropriate diabetes education to improve the management of older adults with diabetes. Treatments for each person with diabetes should be individualized. Special management considerations include the need to avoid both hypoglycemia and the complications of hyperglycemia (2,145). For more information, see the ADA position statement "Management of Diabetes in Long-term Care and Skilled Nursing Facilities" (135,143,144).

Nutritional Considerations

An older adult residing in a PALTC facility may have irregular and unpredictable meal consumption, undernutrition, anorexia, and impaired swallowing. Furthermore, therapeutic nutrition plans or modified food consistencies may inadvertently lead to decreased food intake and contribute to unintentional weight loss and undernutrition. Meals tailored to a person's culture, preferences, and personal goals may increase quality of life, satisfaction with meals, and nutrition status (146). It may be helpful to give insulin immediately after meals to ensure that the dose is appropriate for the amount of carbohydrate the individual consumed in the meal.

Hypoglycemia

Older adults with diabetes in PALTC are especially vulnerable to hypoglycemia. They have a disproportionately high number of clinical complications and comorbidities that can increase hypoglycemia risk: impaired cognitive and renal function, slowed hormonal regulation and counterregulation, suboptimal hydration, variable appetite and nutritional intake, requirement for feeding assistance, polypharmacy, and slowed intestinal absorption (147). Oral agents may achieve glycemic outcomes similar to basal insulin in PALTC populations (100,148). CGM may be a useful approach to monitoring for hypoglycemia among individuals treated with insulin in LTC, but the data are limited.

Another consideration for the PALTC setting is that unlike in the hospital setting, health care professionals are not required to evaluate individuals daily. According to federal guidelines, at a minimum, assessments should be done at least every 30 days for the first 90 days after admission and then at least once every 60 days and as clinically indicated. Although in practice individuals may actually be seen more frequently, the concern is that these individuals may have poorly managed glucose levels or wide excursions without the practitioner being notified. Health care professionals may adjust treatment plans by telephone, fax, or in person directly at the PALTC facilities, provided they are given timely notification of blood glucose management issues from a standardized alert system.

The following alert strategy could be considered:

1. Call a health care professional immediately in cases of low blood glucose levels (<70 mg/dL [<3.9 mmol/L]). However, treatment of hypoglycemia should not be delayed.
2. Call as soon as possible when
   a) glucose values are 70–100 mg/dL (3.9–5.6 mmol/L) (treatment plan may need to be adjusted),
   b) two or more blood glucose values >250 mg/dL (>13.9 mmol/L) are observed within a 24-h period accompanied by a significant change in clinical status,
   c) glucose values are consistently >250 mg/dL (>13.9 mmol/L) within a 24-h period,
   d) glucose values are consistently >300 mg/dL (>16.7 mmol/L) over 2 consecutive days,
   e) any reading is too high for the glucose monitoring device, or
   f) the individual is sick, with symptomatic hyperglycemia, vomiting, fever, lethargy, or poor oral intake.

END-OF-LIFE CARE

Recommendations

13.20 When palliative care is needed in older adults with diabetes, health care professionals should initiate conversations with people with diabetes and their care partners regarding the goals and intensity of care. Strict glucose and blood pressure management are not necessary, and simplification of medication plans can be considered. Similarly, the intensity of lipid management can be relaxed, and withdrawal of lipid-lowering therapy may be appropriate. **E**

13.21 Prioritize the overall comfort, prevention of distressing symptoms, and preservation of quality of life and dignity as primary goals for diabetes management at the end of life. **C**

Management of the older adult receiving palliative medicine or hospice care at the end of life is a unique situation. Overall, palliative medicine promotes comfort, symptom management and prevention

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(pain, hypoglycemia, hyperglycemia, and dehydration), and preservation of dignity and quality of life in older adults with limited life expectancy (145,149).

In the setting of palliative care, health care professionals should initiate conversations with people with diabetes and their care partners regarding the goals and intensity of diabetes care; strict glucose and blood pressure management may not be consistent with achieving comfort and quality of life. Avoidance of severe hypertension and hyperglycemia aligns with the goals of palliative care. In a multicenter trial, withdrawal of statins among people with diabetes in palliative care was found to improve quality of life (150–152). The evidence for the safety and efficacy of deintensification protocols in older adults is growing for both glucose and blood pressure management (104,153) and is clearly relevant for palliative care. An individual has the right to refuse testing and treatment, whereas health care professionals may consider withdrawing treatment and limiting diagnostic testing, including a reduction in the frequency of blood glucose monitoring (154,155). CGM could be considered when frequent blood glucose testing is burdensome but monitoring for hypoglycemia and hyperglycemia is needed. Glycemic goals should aim to prevent hypoglycemia and hyperglycemia. Treatment interventions need to be mindful of quality of life. Careful monitoring of oral intake is warranted. The decision process may need to involve the individual, family, and care partners, leading to a care plan that is both convenient and effective for the goals of care (156). The pharmacologic therapy may include oral agents as first line, followed by a simplified insulin plan. If needed, basal insulin can be implemented, accompanied by oral agents and without rapid-acting insulin. Agents that can cause gastrointestinal symptoms such as nausea or excess weight loss may not be good choices in this setting. As symptoms progress, some agents may be slowly tapered and discontinued.

Different categories have been proposed for diabetes management in those with advanced disease (70).

1. A stable individual: Continue with the person's previous medication plan, with a focus on *1*) the prevention of hypoglycemia and *2*) the management of hyperglycemia using blood glucose monitoring, keeping levels below the renal threshold of glucose, and hyperglycemia-mediated dehydration. There is no role for A1C monitoring.
2. An individual with organ failure: Preventing hypoglycemia is of greatest significance. Dehydration must be prevented and treated. In people with type 1 diabetes, insulin administration may be reduced as the oral intake of food decreases but should not be stopped. For those with type 2 diabetes, agents that may cause hypoglycemia should be reduced in dose. The main goal is to avoid hypoglycemia, allowing for glucose values in the upper level of the desired goal range.
3. A dying individual: For people with type 2 diabetes, the discontinuation of all medications may be a reasonable approach, as these individuals are unlikely to have any oral intake. In people with type 1 diabetes, there is no consensus, but a small amount of basal insulin may maintain glucose levels and prevent acute hyperglycemic complications and symptom burden.

Finally, diabetes health care professionals are well positioned to support people with diabetes in advance care planning. Health care professionals can assist people with diabetes in clarifying and documenting their values, preferences, and goals for care in an advance care plan (157). Advance care plans are guides and decision aids to help health care professionals and care partners make difficult treatment decisions when the person with diabetes is no longer able to make decisions for themselves. Research shows that people with diabetes want to discuss end-of-life care plans with their health care professional (158). Two validated tools exist to support health care professionals in this process: the Supportive and Palliative Care Indicators Tool (159) and the Gold Standards Framework Proactive Identification Guidance (160).

In conclusion, the management of diabetes in older adults at the end of life necessitates a person-centered approach that prioritizes comfort, symptom management, quality of life, and the preservation of dignity.

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14. Children and Adolescents: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

The management of diabetes in children and adolescents (individuals <18 years of age) cannot simply be derived from care routinely provided to adults with diabetes. The epidemiology, pathophysiology, developmental considerations, and response to therapy in pediatric diabetes are often different from those of adult diabetes. There are also differences in recommended care for children and adolescents with type 1 diabetes, type 2 diabetes, and other forms of diabetes. This section is divided into two major parts: the first part addresses care for children and adolescents with type 1 diabetes, and the second part addresses care for children and adolescents with type 2 diabetes. Monogenic diabetes (neonatal diabetes and maturity-onset diabetes of the young) and cystic fibrosis-related diabetes, which are often present in youth, are discussed in Section 2, "Diagnosis and Classification of Diabetes." **Table 14.1*A*** and **Table 14.1*B*** provide an overview of the recommendations for screening and treatment of complications and related conditions in pediatric type 1 diabetes and type 2 diabetes, respectively. In addition to comprehensive diabetes care, youth with diabetes should receive age-appropriate and developmentally appropriate pediatric care, including immunizations as recommended by the Centers for Disease Control and Prevention (CDC) (1). To ensure continuity of care as a person with diabetes becomes an adult, guidance is provided at the end of this section on the transition from pediatric to adult diabetes care.

Due to the nature of pediatric clinical research, the recommendations for children and adolescents with diabetes are less likely to be based on clinical trial evidence. However, expert opinion and a review of available and relevant experimental data are summarized in the American Diabetes Association (ADA) position statements "Type 1 Diabetes in Children and Adolescents" (2) and "Evaluation and Management of Youth-Onset Type 2 Diabetes" (3). Finally, other sections in the Standards of Care may have recommendations that apply to youth with diabetes and are referenced in the narrative of this section.

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.*

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Table 14.1*A*—Recommendations for screening and treatment of complications and related conditions in pediatric type 1 diabetes

	Thyroid disease	Celiac disease	Hypertension	Nephropathy	Retinopathy	Neuropathy	Dyslipidemia
Corresponding recommendations	14.29 and 14.30	14.31–14.33	14.34–14.37	14.43 and 14.44	14.45–14.47	14.48	14.38–14.42
Method	Thyroid-stimulating hormone; consider antithyroglobulin and antithyroid peroxidase antibodies	IgA tTG if total IgA normal; IgG tTG and deamidated gliadin antibodies if IgA deficient	Blood pressure monitoring	Albumin-to-creatinine ratio; random sample acceptable initially	Dilated fundoscopy or retinal photography	Foot exam with foot pulses, pinprick, 10-g monofilament sensation tests, vibration, and ankle reflexes	Lipid profile, nonfasting acceptable initially
When to start	Soon after diagnosis	Soon after diagnosis	At diagnosis	Puberty or ≥10 years old, whichever is earlier, and diabetes duration of 5 years	Puberty or ≥11 years old, whichever is earlier, and diabetes duration of 3–5 years	Puberty or ≥10 years old, whichever is earlier, and diabetes duration of 5 years	Soon after diagnosis; preferably after glycemia has improved and ≥2 years old
Follow-up frequency	Every 1–2 years if thyroid antibodies negative; more often if symptoms develop or presence of thyroid antibodies	Within 2 years and then at 5 years after diagnosis; sooner if symptoms develop	Every visit	If normal, annually; if abnormal, repeat with confirmation in two of three samples over 6 months (first morning void is recommended)	If normal, every 2 years; consider less frequently (every 4 years) if A1C <8% and eye professional agrees	If normal, annually	If LDL <100 mg/dL, repeat at 9–11 years old; then, if <100 mg/dL, every 3 years
Goal	NA	NA	<90th percentile for age, sex, and height; if ≥13 years old, <120/80 mmHg	Albumin-to-creatinine ratio <30 mg/g	No retinopathy	No neuropathy	LDL <100 mg/dL
Treatment	Appropriate treatment of underlying thyroid disorder	After confirmation, start gluten-free diet	Lifestyle modification for elevated blood pressure (90th to <95th percentile for age, sex, and height or, if ≥13 years old, 120–129/<80 mmHg); lifestyle modification and ACE inhibitor or ARB* for hypertension (≥95th percentile for age, sex, and height or, if ≥13 years old, ≥130/80 mmHg)	Optimize glycemia and blood pressure; ACE inhibitor* if albumin-to-creatinine ratio is elevated in two of three samples over 6 months	Optimize glycemia; treatment per ophthalmology	Optimize glycemia; referral to neurology	If abnormal, optimize glycemia and medical nutrition therapy; if after 6 months LDL >160 mg/dL or >130 mg/dL with cardiovascular risk factor(s), initiate statin therapy (for those aged >10 years)*

ARB, angiotensin receptor blocker; NA, not applicable; tTG, tissue transglutaminase. *Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and medication should be avoided in individuals of childbearing age who are not using reliable contraception.

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Table 14.1*B*—Recommendations for screening and treatment of complications and related conditions in pediatric type 2 diabetes

	Hypertension	Nephropathy	Neuropathy	Retinopathy	Dyslipidemia	Metabolic dysfunction–associated steatotic liver disease	Obstructive sleep apnea	Polycystic ovary syndrome (for adolescent female individuals)
Corresponding recommendations	14.72–14.75	14.76–14.80	14.81 and 14.82	14.83–14.86	14.93–14.97	14.87 and 14.88	14.89	14.90 and 14.91
Method	Blood pressure monitoring	Albumin-to-creatinine ratio; random sample acceptable initially	Foot exam with foot pulses, pinprick, 10-g monofilament sensation tests, vibration, and ankle reflexes	Dilated fundoscopy	Lipid profile	AST and ALT measurement	Screening for symptoms	Screening for symptoms; laboratory evaluation if positive symptoms
When to start	At diagnosis	At diagnosis	At diagnosis	At or soon after diagnosis	Soon after diagnosis, preferably after glycemia has improved	At diagnosis	At diagnosis	At diagnosis
Follow-up frequency	Every visit	If normal, annually; if abnormal, repeat with confirmation in two of three samples over 6 months	If normal, annually	If normal, annually or every 2 years if glycemic goals are achieved	Annually	Annually	Every visit	Every visit
Goal	<90th percentile for age, sex, and height; if ≥13 years old, <130/80 mmHg	<30 mg/g	No neuropathy	No retinopathy	LDL <100 mg/dL, HDL >35 mg/dL, triglycerides <150 mg/dL	NA	NA	NA
Treatment	Lifestyle modification for elevated blood pressure (90th to <95th percentile for age, sex, and height or, if ≥13 years old, 120–129/<80 mmHg); lifestyle modification and ACE inhibitor or ARB* for hypertension (≥95th percentile for age, sex, and height or, if ≥13 years, ≥130/80 mmHg)	Optimize glycemia and blood pressure; ACE inhibitor* if albumin-to-creatinine ratio is elevated in two of three samples over 6 months	Optimize glycemia; referral to neurology	Optimize glycemia; treatment per ophthalmology	If abnormal, optimize glycemia and medical nutrition therapy; if LDL >130 mg/dL after 6 months, initiate statin therapy (for those aged >10 years);* if triglycerides >400 mg/dL fasting or >1,000 mg/dL nonfasting, begin fibrate	Refer to gastroenterology for persistently elevated or worsening transaminases	If positive symptoms, refer to sleep specialist and polysomnogram	If no contraindications, oral contraceptive pills; medical nutrition therapy; metformin

ARB, angiotensin receptor blocker; NA, not applicable; tTG, tissue transglutaminase. *Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and medication should be avoided in individuals of childbearing age who are not using reliable contraception.

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TYPE 1 DIABETES

Type 1 diabetes is the most common form of diabetes in youth (4), although there are more adults living with and diagnosed with type 1 diabetes (5). The health care professional must consider the unique aspects of care and management of children and adolescents with type 1 diabetes, such as changes in insulin sensitivity related to physical growth and sexual maturation, ability to provide self-care, supervision in the childcare and school environment, neurological vulnerability to hypoglycemia and hyperglycemia in young children, and possible adverse neurocognitive effects of diabetic ketoacidosis (DKA) (6,7). Attention to family dynamics, developmental stages, and physiologic differences related to sexual maturity is essential in developing and implementing an optimal diabetes treatment plan (8). Additionally, more people (adults and youth) with type 1 diabetes are experiencing obesity than in the past, which adds to the complexity of living with and managing type 1 diabetes (9).

An interprofessional team trained in pediatric diabetes management and sensitive to the challenges of children and adolescents with type 1 diabetes and their families should provide diabetes-specific care for this population. It is essential that diabetes self-management education and support (DSMES), medical nutrition therapy (MNT), and psychosocial and behavioral support be provided at diagnosis and routinely (e.g., at each follow-up visit) thereafter in a developmentally appropriate format that builds on prior knowledge by a team of health care professionals experienced with the biological, educational, nutritional, behavioral, and emotional needs of the growing child and family. The diabetes team, considering the youth's developmental and psychosocial needs, should ask about and discuss diabetes management responsibilities with youth and parents or caregivers on an ongoing basis.

Diabetes Self-Management Education and Support

Recommendation

14.1 Youth with type 1 diabetes and their parents or caregivers (for individuals aged <18 years) should receive culturally sensitive and developmentally appropriate individualized diabetes self-management education and support (DSMES) according to national standards at diagnosis and routinely thereafter. **B**

Self-management in pediatric diabetes involves both the youth and their parents or adult caregivers. No matter how sound the medical plan is, it will only be effective if the family and/or affected individuals can implement it. Family involvement is a vital component of optimal diabetes management throughout childhood and adolescence. As parents or caregivers are critical to diabetes self-management in youth, diabetes care requires an approach that places the youth and their parents or caregivers at the center of the care model. The pediatric diabetes care team must be capable of evaluating the educational, behavioral, emotional, and psychosocial factors that impact treatment plan implementation and must work with the youth and family to overcome barriers or redefine goals as appropriate. As the youth grows, develops, and acquires the need and desire for greater independent self-care skills, DSMES requires periodic and routine (e.g., at each follow-up visit) reassessment. The pediatric diabetes team should work with the youth and their parents or caregivers to ensure there is not a premature transfer of self-management tasks to the youth during this time. In addition, it is important to assess the educational needs and skills of, and provide training to, daycare workers, school nurses, and school personnel who are responsible for the care and supervision of the child with diabetes (2,10,11).

Nutrition Therapy

Recommendations

14.2 Individualized medical nutrition therapy (MNT) is recommended for youth with type 1 diabetes as an essential component of the overall treatment plan. **A**

14.3 Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is a key component to optimizing glycemic management. **B**

14.4 Advise youth with type 1 diabetes and their caregivers to strive for an eating pattern emphasizing key nutrition principles (including nonstarchy vegetables, whole fruits, legumes, fish and other lean protein, whole grains, nuts and seeds, and low-fat dairy products, and minimize consumption of red meat, sugar-sweetened beverages, sweets, refined grains, and processed foods). **B**

14.5 Meal composition impacts postprandial glucose excursions. Education on the impact of high-fat and high-protein meals and the adjustment of insulin dosing is necessary. **A**

14.6 Strongly advise comprehensive nutrition education at diagnosis, and at least annually as needed, by an experienced registered dietitian nutritionist to assess the eating pattern in relation to weight status, age-appropriate growth, and cardiovascular disease risk factors. **E**

Nutrition management should be individualized: family habits, food preferences, religious or cultural needs, finances, schedules, physical activity, and the youth's and family's abilities in numeracy, literacy, and self-management should be considered. Visits with a registered dietitian nutritionist, preferably experienced in working with pediatric populations with diabetes, should include assessment for changes in food preferences over time, access to food, growth and development, weight status, cardiovascular risk, and potential for disordered eating. Following recommended eating patterns is associated with better glycemic outcomes in youth with type 1 diabetes (12).

Although carbohydrate content is the primary variable for calculation of mealtime insulin doses, meals with higher fat and protein content can cause early hypoglycemia and delayed postprandial glucose excursions. Some adjustments in insulin dosing, including an increase in the calculated dose and a split dose, will improve postprandial glucose management (13–17).

Physical Activity and Exercise

Recommendations

14.7 Physical activity is recommended for all youth with type 1 diabetes with the goal of 60 min of moderate- to vigorous-intensity aerobic activity daily, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days per week. **C**

14.8 Advise frequent glucose monitoring before, during, and after exercise,

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via blood glucose meter and/or continuous glucose monitoring (CGM), to prevent, detect, and treat hypoglycemia and hyperglycemia associated with exercise. C

14.9 Youth and their parents or caregivers should receive education on goals and management of glycemia before, during, and after physical activity, individualized according to the type and intensity of the planned physical activity. C

14.10 Youth and their parents or caregivers should be educated on strategies to prevent hypoglycemia during, after, and overnight following physical activity and exercise. Treatment for hypoglycemia should be accessible before, during, and after engaging in activity. C

Physical activity and structured exercise positively impact metabolic and psychological health in children with type 1 diabetes (18). While it can have positive effects on insulin sensitivity, physical fitness, strength building, cardiorespiratory fitness, weight management, social interaction, mood, self-esteem building, and the creation of healthful habits for adulthood, it also has the potential to cause both hypoglycemia and hyperglycemia.

See below for strategies to mitigate hypoglycemia risk and minimize hyperglycemia associated with exercise. For an in-depth discussion, see previously published reviews and guidelines (19–23).

Overall, it is recommended that all youth participate in 60 min of moderate-intensity (e.g., brisk walking and dancing) to vigorous-intensity (e.g., running and jumping rope) aerobic activity daily, including resistance and flexibility training (24). Although uncommon in the pediatric population, youth should be medically evaluated for comorbid conditions or diabetes complications that may restrict participation in an exercise program. As hyperglycemia can occur before, during, and after physical activity, it is important to ensure the elevated glucose level is not related to insulin deficiency, as that can lead to worsening hyperglycemia with exercise and ketosis risk. Intense activity should be postponed with marked hyperglycemia (glucose ≥350 mg/dL [≥19.4 mmol/L]), moderate to large urine ketones, and/or β-hydroxybutyrate (B-OHB) >1.5 mmol/L. Caution may be needed when B-OHB levels are ≥0.6 mmol/L (12,19).

Prevention and treatment of hypoglycemia associated with physical activity includes decreasing prandial insulin for the meal or snack before exercise and/or increasing food intake. Youth on insulin pumps without automated insulin delivery (AID) can lower basal rates by ∼10–50% or more or suspend for 1–2 h during exercise (25). Decreasing basal rates or long-acting insulin doses by ∼20% after exercise may reduce delayed exercise-induced hypoglycemia (26). Accessible rapid-acting carbohydrates and frequent blood glucose monitoring before, during, and after exercise, with or without continuous glucose monitoring (CGM), maximize safety with exercise. Using AID systems may improve time in range (TIR) (70–180 mg/dL) during exercise, and youth can use brand-specific settings that are more conservative or increase the glycemic goal to prevent hypoglycemia (27).

Blood glucose goals prior to physical activity and exercise are 126–180 mg/dL (7.0–10.0 mmol/L) but should be individualized based on the type, intensity, and duration of activity (19,21). The accuracy of CGM systems varies depending on the type of exercise (28–30). Consider additional carbohydrate intake during and/or after exercise, depending on duration and intensity of physical activity, to prevent hypoglycemia. For low- to moderate-intensity aerobic activities (30–60 min), and if the youth is fasting, 10–15 g of carbohydrate may prevent hypoglycemia (21). After insulin boluses (relative hyperinsulinemia), consider 0.5–1.0 g of carbohydrates/kg per hour of exercise (∼30–60 g), similar to carbohydrate requirements for optimizing performance in athletes without type 1 diabetes (31,32).

For children and adolescents with type 1 diabetes and obesity, physical activity and exercise are key components of diabetes care. Obesity is equally common in youth with or without type 1 diabetes. Having obesity is associated with a higher frequency of cardiovascular risk factors, and it disproportionately affects youth from racial and ethnic minoritized groups (e.g., Black and Latino youth) (9,33–36). Therefore, diabetes health care professionals should monitor weight status and encourage a healthy eating pattern, physical activity, and healthy weight as key components of pediatric type 1 diabetes care.

School and Child Care

As a large portion of a youth's day is spent in school and/or daycare, training of school or daycare personnel to provide care in accordance with the child's individualized diabetes medical management plan is essential for optimal diabetes management and safe access to all school- or daycare–sponsored opportunities (11,37,38). In addition, federal and state laws require schools, daycare facilities, and other entities to provide needed diabetes care to enable the child to safely access the school or daycare environment. Refer to the ADA position statements "Diabetes Care in the School Setting" (11) and "Care of Young Children With Diabetes in the Childcare and Community Setting" (38) and the ADA's Safe at School website (diabetes.org/resources/know-your-rights/safe-at-school-state-laws) for additional details.

Psychosocial Care

Recommendations

14.11 At diagnosis and during routine follow-up care, screen youth with type 1 diabetes for psychosocial concerns (e.g., diabetes distress, depressive symptoms, and disordered eating), family factors, and behavioral health concerns that could impact diabetes management with age-appropriate standardized and validated tools. Refer to a qualified behavioral health professional, preferably experienced in childhood diabetes, when indicated. B

14.12 Behavioral health professionals should be considered integral members of the pediatric diabetes interprofessional team. E

14.13 Encourage developmentally appropriate family involvement in diabetes management tasks for children and adolescents, recognizing that premature or unsupportive transfer of diabetes care responsibility to the youth can contribute to diabetes distress, lower engagement in diabetes self-management behaviors, and deterioration in glycemia. A

14.14 Health care professionals should screen for food security, housing stability, health literacy, financial barriers, and social or community support and apply that information to treatment decisions. E

14.15 Health care professionals should consider asking youth and their parents

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or caregivers about social adjustment (peer relationships) and school performance to determine whether further intervention is needed. **B**

14.16 Offer adolescents time by themselves with their health care professional(s) at a developmentally appropriate age. **E**

14.17 Starting at puberty, preconception counseling should be incorporated into routine diabetes care for all individuals of childbearing potential. **A**

Rapid and dynamic cognitive, developmental, and emotional changes occur during childhood, adolescence, and emerging adulthood. Diabetes management during childhood and adolescence places substantial burdens on the youth and family, necessitating ongoing assessment of psychosocial status, social determinants of health, and diabetes distress in the youth and the parents or caregivers during routine diabetes visits (39–41). It is important to consider the impact of diabetes on quality of life as well as the development of behavioral health problems related to diabetes distress, symptoms of depression, symptoms of anxiety, fear of hypoglycemia (and hyperglycemia), disordered eating behaviors, and eating disorders (39,42).

Consider screening youth for diabetes distress, generally starting at 7 or 8 years of age (42), using validated tools for youth and their parents or caregivers (43). The U.S. Preventive Services Task Force recommends screening for depression in youth aged 12–18 years (44). Additional times to consider screening for depression include when youth are not meeting treatment goals or when there are significant changes in medical status or life circumstances. The U.S. Preventive Services Task Force also recommends screening for anxiety in youth aged 8–18 years (45). Parents or caregivers and youth at risk for hypoglycemia or fear of hypoglycemia, especially if they have experienced severe and/or frequent hypoglycemic events, should be screened for fear of hypoglycemia; youth as young as 6 years old can provide reliable self-reports for fear of hypoglycemia (46). Lastly, health care professionals should consider screening for disordered eating behaviors when signs and symptoms (e.g., unexplained weight loss, hyperglycemia, and DKA) and/or behavioral and emotional indicators (e.g., secrecy around eating and excessive concern about weight) are present using available screening tools (47). Youth with type 1 diabetes have an increased risk of disordered eating behavior as well as clinical eating disorders, with serious short-term and long-term negative effects on diabetes outcomes and health in general. It is important to recognize the unique and dangerous disordered eating behavior of insulin omission for weight management in type 1 diabetes (48).

Given the complexity of psychosocial concerns in the management of type 1 diabetes in youth, collaboration between the diabetes health care team and a behavioral health professional, ideally with expertise in diabetes, is recommended. Early detection of diabetes distress, depression, anxiety, fear of hypoglycemia, and disordered eating can facilitate effective treatment options and help minimize adverse effects on diabetes management and disease outcomes (39,42). When psychological symptoms are identified, referral to a behavioral health professional, ideally with experience in pediatric diabetes, may be warranted. Such professionals can provide individualized, evidence-based behavioral health care services, including cognitive-behavioral, mindfulness-based, and other interventions (49), to improve psychosocial functioning in youth with type 1 diabetes (50–52).

The complexities of diabetes management require ongoing parental involvement in care throughout childhood and adolescence. Developmentally appropriate, supportive family teamwork between the growing youth and parent(s) can help maintain engagement in self-management behaviors and reduce deterioration in glycemia (53,54). It is appropriate to inquire about diabetes-specific family relationships, including family teamwork and conflict, during visits; health care professionals can both help families negotiate a plan and refer to an appropriate behavioral health professional for more in-depth support (55). Such professionals can conduct further assessment and deliver evidence-based behavioral interventions to support developmentally appropriate, collaborative family involvement in diabetes self-management (50,52). Monitoring of social adjustment (peer relationships) and school performance can facilitate both well-being and academic achievement (56,57). Diabetes management and glycemic levels may be related to academic progress and students' functioning in the school setting, which highlights the need for appropriate accommodations and access to diabetes-related support in school (58).

Shared decision-making with youth regarding the adoption of management plan components and self-management behaviors can improve diabetes self-efficacy, participation in diabetes care, and glycemic outcomes (9,59). For example, well-designed decision aids can engage youth in comprehensive, unbiased conversations with their diabetes care team about treatment options (60). Other examples include creating self-care contracts (61) and technology-integrated care that uses blood glucose records shared with the care team to facilitate shared decision-making (62). Importantly, health care professionals working with youth who are not yet able to provide legal consent must balance clinical oversight with promoting developmentally appropriate independence. Recommendations include providing education tailored to the developmental stage, encouraging gradual responsibility with self-care, guiding parental involvement as responsibilities change, teaching self-advocacy to prepare for transitions in care, and incorporating psychosocial support at all stages (57,63). Although cognitive abilities vary, the ethical position often adopted is the "mature minor rule," whereby children after age 12 or 13 years who appear to be mature have the right to consent or withhold consent to general medical treatment, except in cases in which refusal would significantly endanger health (64).

Beginning at the onset of puberty or at diagnosis of diabetes, all individuals with childbearing potential should receive education about the effective use of contraception to prevent unplanned pregnancy, as risks of fetal malformations are associated with elevated A1C. Preconception counseling using developmentally appropriate educational and behavioral strategies enables individuals of childbearing potential to make well-informed decisions (65). Preconception counseling resources tailored for adolescents are available at no cost through the ADA (66). Refer to the ADA position statement "Psychosocial Care for People With Diabetes" for further details (42).

The presence of a behavioral health professional on pediatric interprofessional teams highlights the importance

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of attending to the psychosocial issues of diabetes. These psychosocial factors are significantly related to self-management difficulties, elevated A1C, reduced quality of life, and higher rates of acute and chronic diabetes complications.

Glycemic Monitoring, Insulin Delivery, and Goals

Recommendations

14.18 All youth with type 1 diabetes should monitor glucose levels multiple times daily (up to 10 times/day by blood glucose meter or CGM), including prior to meals and snacks, at bedtime, and as needed for safety in specific situations such as physical activity, driving, or the presence of symptoms of hypoglycemia. **B**

14.19 Real-time CGM **A** or intermittently scanned CGM **C** should be offered for diabetes management at diagnosis or as soon as possible in youth with diabetes on multiple daily injections or insulin pump therapy who are capable of using the device safely (either by themselves or with caregivers). The choice of device should be made based on the individual's and family's circumstances, desires, and needs.

14.20 Automated insulin delivery (AID) systems should be offered for diabetes management to youth with type 1 diabetes who are capable of using the device safely (either by themselves or with caregivers). The choice of device should be made based on the individual's and family's circumstances, desires, and needs. **A**

14.21 Insulin pump therapy alone should be offered for diabetes management to youth on multiple daily injections with type 1 diabetes who are capable of using the device safely (either by themselves or with caregivers) if unable to use AID systems. The choice of device should be made based on the individual's and family's circumstances, desires, and needs. **A**

14.22 Students must be supported at school in the use of diabetes technology, including CGM, insulin pumps, connected insulin pens, and AID systems, as prescribed by their diabetes care team. **E**

14.23 A1C goals must be individualized and reassessed over time. An A1C of <7% (<53 mmol/mol) is appropriate for many children and adolescents. **B**

14.24 Less stringent A1C goals (such as <7.5% [<58 mmol/mol]) may be appropriate for youth who cannot articulate symptoms of hypoglycemia; have hypoglycemia unawareness; lack advanced insulin delivery technology and/or CGM; cannot check blood glucose regularly; or have nonglycemic factors that increase A1C (e.g., high glycators). **B**

14.25 Even less stringent A1C goals (such as <8% [<64 mmol/mol]) may be appropriate for individuals with a history of severe hypoglycemia or limited life expectancy or where the harms of treatment are greater than the benefits. **B**

14.26 Health care professionals may reasonably suggest more stringent A1C goals (such as <6.5% [<48 mmol/mol]) for selected individuals if they can be achieved without significant hypoglycemia, excessive weight gain, negative impacts on well-being, or undue burden of care or in those who have nonglycemic factors that decrease A1C (e.g., lower erythrocyte life span). Lower goals may also be appropriate during the honeymoon phase. **B**

14.27 CGM metrics derived from CGM use over the most recent 14 days (or longer for youth with more glycemic variability), including time in range (70–180 mg/dL [3.9–10.0 mmol/L]), time below range (<70 mg/dL [<3.9 mmol/L] and <54 mg/dL [<3.0 mmol/L]), and time above range (>180 mg/dL [>10.0 mmol/L] and >250 mg/dL [>13.9 mmol/L]), are recommended to be used in conjunction with A1C whenever possible. **E**

Current standards for diabetes management reflect the need to minimize hyperglycemia as safely as possible. The Diabetes Control and Complications Trial (DCCT), which did not enroll children <13 years of age, demonstrated that near normalization of blood glucose levels was more difficult to achieve in adolescents than in adults. Nevertheless, the increased use of basal-bolus plans, insulin pumps, frequent blood glucose monitoring, CGM, AID systems, goal setting, and improved education has been associated with more children and adolescents reaching the blood glucose goals recommended by the ADA (67,68), particularly in families in which the parents or caregivers as well as the child with diabetes participate jointly to perform the required diabetes-related tasks.

Lower A1C in adolescence and young adulthood is associated with a lower risk and rate of microvascular and macrovascular complications (69–71) and demonstrates the effects of metabolic memory (72–75).

In addition, type 1 diabetes can be associated with adverse effects on cognition during childhood and adolescence (6,76), and neurocognitive imaging differences related to hyperglycemia in children provide another motivation for achieving glycemic goals (6). Several factors, including young age, severe hypoglycemia at <6 years of age, DKA, and chronic hyperglycemia (76,77), contribute to adverse effects on brain development and function. However, meticulous use of therapeutic modalities such as rapid- and long-acting insulin analogs, technological advances (e.g., CGM, sensor-augmented pump therapy, and AID systems), and intensive self-management education now make it more feasible to achieve glycemic goals while reducing the incidence of severe hypoglycemia (78–99). Please refer to Section 7, "Diabetes Technology," for more information on technology to support people with diabetes.

Recent data with newer devices and insulins indicate that the risk of hypoglycemia with lower A1C is less than it was before (100–108). In addition, achieving lower A1C levels is likely facilitated by setting lower A1C goals (109). Lower goals may be possible during the honeymoon phase of type 1 diabetes. Special consideration should be given to the risk of hypoglycemia in young children (aged <6 years) who are often unable to recognize, articulate, and/or manage hypoglycemia. However, registry data indicate that lower A1C goals can be achieved in children, including those aged <6 years, without increased risk of severe hypoglycemia (101). Recent data have demonstrated that the use of real-time CGM lowered A1C and increased TIR in adolescents and young adults and was associated with a lower risk of hypoglycemia (110). Please refer to Section 6, "Glycemic Goals and Hypoglycemia," for more information on glycemic assessment.

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A strong relationship exists between the frequency of blood glucose monitoring and glycemic management (97–99, 111,112). Glucose levels for all children and adolescents with type 1 diabetes should be monitored multiple times daily by blood glucose monitoring and/or CGM. Recent data on children and adults suggest that use of CGM soon after type 1 diabetes diagnosis is associated with improved A1C (84,85,113). In the U.S., real-time CGM is approved for nonadjunctive use in children aged 2 years and older, and intermittently scanned CGM is approved for nonadjunctive use in children aged 4 years and older. Parents, caregivers, and youth should be offered initial and ongoing education and support for CGM use. Behavioral support may further improve ongoing CGM use (114). Metrics derived from CGM include percent TIR, time below target range, and time above target range (115). While studies indicate a relationship between TIR and A1C (116,117), it is still uncertain what the ideal goal TIR should be for children, and further studies are needed. Please refer to Section 7, "Diabetes Technology," for more information on the use of blood glucose meters, CGM, and insulin pumps. More information on insulin injection technique can be found in Section 9, "Pharmacologic Approaches to Glycemic Treatment."

Key Concepts in Setting Glycemic Goals

- Glycemic goals should be individualized, and lower goals may be reasonable based on a benefit-risk assessment.
- Blood glucose goals should be modified in children with frequent hypoglycemia or hypoglycemia unawareness.
- Postprandial blood glucose values should be measured when there is a discrepancy between preprandial blood glucose values and A1C levels and to assess preprandial insulin doses in those on basal-bolus or pump plans.

Autoimmune Conditions

Recommendation

14.28 Assess for additional autoimmune conditions soon after the diagnosis of type 1 diabetes and if clinically relevant. **B**

Because of the increased frequency of other autoimmune diseases in type 1 diabetes, screening for thyroid dysfunction and celiac disease should be considered (118–122). Periodic screening in asymptomatic individuals has been recommended, but the optimal frequency of screening is unclear.

Although much less common than thyroid dysfunction and celiac disease, other autoimmune conditions, such as Addison disease (primary adrenal insufficiency), autoimmune hepatitis, autoimmune gastritis, dermatomyositis, and myasthenia gravis, occur more commonly in the population with type 1 diabetes than in the general pediatric population and should be assessed and monitored as clinically indicated. In addition, relatives of youth with type 1 diabetes should be offered testing for islet autoantibodies through research studies (e.g., TrialNet) and national programs for early diagnosis of preclinical type 1 diabetes (stages 1 and 2).

Thyroid Disease

Recommendations

14.29 Consider testing children with type 1 diabetes for antithyroid peroxidase and antithyroglobulin antibodies soon after diagnosis. **B**

14.30 Measure thyroid-stimulating hormone concentrations at diagnosis when clinically stable or soon after optimizing glycemia. If normal, suggest rechecking every 1–2 years or sooner if the youth has positive thyroid antibodies or develops symptoms or signs suggestive of thyroid dysfunction, thyromegaly, an abnormal growth rate, or unexplained glycemic variability. **B**

Autoimmune thyroid disease is the most common autoimmune disorder associated with diabetes, occurring in 17–30% of individuals with type 1 diabetes (119,123,124). At the time of diagnosis, ~25% of children with type 1 diabetes have thyroid autoantibodies (125), the presence of which is predictive of thyroid dysfunction—most commonly hypothyroidism, although hyperthyroidism occurs in ~0.5% of people with type 1 diabetes (126,127). For thyroid autoantibodies, a study from Sweden indicated that antithyroid peroxidase antibodies were more predictive than antithyroglobulin antibodies in multivariate analysis (128). Thyroid function tests may be misleading (euthyroid sick syndrome) if performed at the time of diagnosis owing to the effect of previous hyperglycemia, ketosis or ketoacidosis, weight loss, etc. Therefore, if performed at diagnosis and slightly abnormal, thyroid function tests should be repeated soon after a period of metabolic stability and achievement of glycemic goals. Subclinical hypothyroidism may be associated with an increased risk of symptomatic hypoglycemia and dyslipidemia (129,130) and a reduced linear growth rate. Hyperthyroidism alters glucose metabolism and usually causes deterioration of glycemia.

Celiac Disease

Recommendations

14.31 Screen youth with type 1 diabetes for celiac disease by measuring IgA tissue transglutaminase (tTG) antibodies, with documentation of normal total serum IgA levels, soon after the diagnosis of diabetes, or IgG tTG and deamidated gliadin antibodies if IgA is deficient. **B**

14.32 Repeat screening for celiac disease within 2 years of diabetes diagnosis and then again after 5 years and consider more frequent screening in youth who have symptoms or a first-degree relative with celiac disease. **B**

14.33 Individuals with confirmed celiac disease should be placed on a gluten-free diet for treatment and to avoid complications. Youth and their caregivers should also have a consultation with a registered dietitian nutritionist experienced in managing both diabetes and celiac disease. **B**

Celiac disease is an immune-mediated disorder that occurs with increased frequency in people with type 1 diabetes (1.6–16.4% of individuals compared with 0.3–1% in the general population) (118,121,122, 131–134). Screening people with type 1 diabetes for celiac disease is further justified by its association with osteoporosis, iron deficiency, growth failure, and potential increased risk of retinopathy and albuminuria (135–137).

Screening for celiac disease includes measuring serum levels of IgA and tissue transglutaminase (tTG) IgA antibodies, or, with IgA deficiency, screening can include measuring tTG IgG antibodies or deamidated gliadin peptide IgG antibodies. Because most cases of celiac disease are diagnosed within the first 5 years after the diagnosis of type 1 diabetes, screening should be considered at the

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time of diagnosis and repeated at 2 and then 5 years (132) or if clinical symptoms indicate, such as poor growth or increased hypoglycemia (135).

Although celiac disease can be diagnosed more than 10 years after diabetes diagnosis, there are insufficient data after 5 years to determine the optimal screening frequency. Measurement of tTG antibody should be considered at other times in individuals with symptoms suggestive of celiac disease (132). Monitoring for symptoms should include an assessment of linear growth and weight gain (135). A small-bowel biopsy in antibody-positive children is recommended to confirm the diagnosis (138). European guidelines on screening for celiac disease in children (not specific to children with type 1 diabetes) suggest that biopsy may not be necessary in symptomatic children with high antibody titers (i.e., >10 times the upper limit of normal) provided that further testing is performed (verification of endomysial antibody positivity on a separate blood sample). Whether this approach may be appropriate for asymptomatic children in high-risk groups remains an open question, though evidence is emerging (139). It is also advisable to check for celiac disease–associated HLA types in individuals who are diagnosed without a small intestinal biopsy. In symptomatic children with type 1 diabetes and confirmed celiac disease, gluten-free diets reduce symptoms and rates of hypoglycemia (140). The challenging eating plan restrictions associated with having both type 1 diabetes and celiac disease place a significant burden on individuals. Therefore, a biopsy to confirm the diagnosis of celiac disease is recommended, especially in asymptomatic children, before establishing a diagnosis of celiac disease and endorsing significant eating plan changes.

Management of Cardiovascular Risk Factors

Hypertension Screening

Recommendation

14.34 Blood pressure should be measured at every routine visit. In youth with high blood pressure (blood pressure ≥90th percentile for age, sex, and height or, in adolescents aged ≥13 years, blood pressure ≥120/80 mmHg) on three separate measurements, ambulatory blood pressure monitoring should be strongly considered. **B**

Hypertension Treatment

Recommendations

14.35 Treatment of elevated blood pressure (defined as 90th to <95th percentile for age, sex, and height or, in adolescents aged ≥13 years, 120–129/<80 mmHg) is lifestyle modification focused on healthy nutrition, physical activity, sleep, and, if appropriate, weight management. **C**

14.36 After excluding other causes, in addition to lifestyle modification, ACE inhibitors or angiotensin receptor blockers should be started for treatment of confirmed hypertension (defined as blood pressure consistently ≥95th percentile for age, sex, and height or, in adolescents aged ≥13 years, ≥130/80 mmHg). Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception. **B**

14.37 The goal of treatment is blood pressure <90th percentile for age, sex, and height or, in adolescents aged ≥13 years, <130/80 mmHg. **C**

Blood pressure measurements should be performed using the appropriate size cuff with the youth seated and relaxed. Elevated blood pressure should be confirmed on at least three separate days, and ambulatory blood pressure monitoring should be considered. Evaluation should proceed as clinically indicated (141,142). Treatment is generally initiated with an ACE inhibitor, but an angiotensin receptor blocker can be used if the ACE inhibitor is not tolerated (e.g., due to cough) (143).

Dyslipidemia Screening

Recommendations

14.38 Initial lipid profile should be performed soon after diagnosis, preferably after glycemia has improved and age is ≥2 years. If initial LDL cholesterol is ≤100 mg/dL (≤2.6 mmol/L), subsequent testing should be performed at 9–11 years of age. **B** Initial testing may be done with a nonfasting lipid level with confirmatory testing with a fasting lipid panel.

14.39 If LDL cholesterol values are within the accepted risk level (<100 mg/dL [<2.6 mmol/L]), a lipid profile repeated every 3 years is reasonable. **E**

Dyslipidemia Treatment

Recommendations

14.40 If lipids are abnormal, initial therapy should consist of optimizing glycemia and MNT to limit the amount of calories from fat to 25–30% and saturated fat to <7%, limit cholesterol to <200 mg/day, avoid *trans* fats, and aim for ~10% calories from monounsaturated fats. **A**

14.41 Consider age-approved statins, in addition to MNT and lifestyle changes, for youth with type 1 diabetes who have LDL cholesterol ≥130 mg/dL (≥3.4 mmol/L). **E** Individuals of childbearing age should receive reproductive counseling, and lipid-lowering medications should be avoided in most individuals of childbearing age who are not using reliable contraception. **B**

14.42 The goal of therapy is an LDL cholesterol value <100 mg/dL (<2.6 mmol/L). **E**

Population-based studies estimate that 14–45% of children with type 1 diabetes have two or more atherosclerotic cardiovascular disease risk factors (144–146), and the prevalence of cardiovascular disease (CVD) risk factors increase with age (146) and among racial and ethnic minoritized groups (33), with girls having a higher risk burden than boys (145).

Pathophysiology. The atherosclerotic process begins in childhood, and although atherosclerotic cardiovascular disease events are not expected to occur during childhood, observations using a variety of methodologies show that youth with type 1 diabetes may have subclinical CVD within the first decade of diagnosis (147–149). Studies of carotid intima media thickness have yielded inconsistent results (142,143).

Screening. Diabetes predisposes the individual to the development of accelerated arteriosclerosis. Lipid evaluation for these individuals contributes to risk assessment and identifies an important proportion of those with dyslipidemia. Therefore, initial screening should be done soon after diagnosis. If the initial screen is normal, subsequent screening may be done at 9–11 years of age, which is a stable time

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for lipid assessment in children (150). Children with a primary lipid disorder (e.g., familial hyperlipidemia) should be referred to a lipid specialist. Non-HDL cholesterol level has been identified as a significant predictor of the presence of atherosclerosis—as powerful as any other lipoprotein cholesterol measure in children and adolescents. For both children and adults, non-HDL cholesterol level seems to be more predictive of persistent dyslipidemia and, therefore, atherosclerosis and future events than total cholesterol, LDL cholesterol, or HDL cholesterol level alone. A major advantage (151) of non-HDL cholesterol is that it can be accurately calculated in a nonfasting state and therefore is practical to obtain in clinical practice as a screening test (152). Youth with type 1 diabetes have a high prevalence of lipid abnormalities (144,151). Even if normal, screening should be repeated within 3 years, as A1C and other cardiovascular risk factors can change dramatically during adolescence (153).

Treatment. Pediatric lipid guidelines provide some guidance relevant to children with type 1 diabetes and secondary dyslipidemia (142,154,155); however, there are few studies on modifying lipid levels in children with type 1 diabetes. A 6-month trial of nutritional counseling produced a significant improvement in lipid levels (156); likewise, a lifestyle intervention trial with 6 months of exercise in adolescents demonstrated improvement in lipid levels (157). Data from the SEARCH for Diabetes in Youth (SEARCH) study show that improved glucose over a 2-year period is associated with a more favorable lipid profile; however, improved glycemia alone will not normalize lipids in youth with type 1 diabetes and dyslipidemia (158).

Although intervention data are sparse, the American Heart Association categorizes children with type 1 diabetes in the highest tier for cardiovascular risk and recommends both lifestyle and pharmacologic treatment for those with elevated LDL cholesterol levels (159,160). Initial therapy should include a nutrition plan that restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day (150). Data from randomized clinical trials in children as young as 7 months of age indicate that this nutrition plan is safe and does not interfere with normal growth and development.

Long-term safety and cardiovascular outcome efficacy of statin therapy have been established for children with familial hypercholesterolemia (161). At the time of this writing, rosuvastatin is indicated for children as young as 6 years old (162). Statins should be avoided in individuals of childbearing age who are not using reliable contraception (see Section 15, "Management of Diabetes in Pregnancy," for more information). The multicenter, randomized, placebo-controlled Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) provides safety data on pharmacologic treatment with an ACE inhibitor and statin in adolescents with type 1 diabetes (142).

Microvascular Complications

Nephropathy Screening

Recommendation

14.43 Annual screening for albuminuria with a random (morning sample preferred to avoid effects of exercise) spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the youth has had diabetes for 5 years. **B**

Nephropathy Treatment

Recommendation

14.44 An ACE inhibitor or an angiotensin receptor blocker, titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio (>30 mg/g) is documented (two of three urine samples obtained over a 6-month interval following efforts to improve glycemia and normalize blood pressure). **E** Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception. **B**

Data from 7,549 participants <20 years of age in the T1D Exchange clinic registry emphasize the importance of meeting glycemic and blood pressure goals, particularly as diabetes duration increases, to reduce the risk of diabetic kidney disease. The data also underscore the importance of routine screening to ensure early diagnosis and timely treatment of albuminuria (163). An estimation of glomerular filtration rate (GFR), calculated with GFR-estimating equations using serum creatinine, height, age, and sex (164), should be considered at baseline and repeated as indicated based on clinical status, age, diabetes duration, and therapies. Improved methods are needed to screen for early GFR loss, since estimated GFR is inaccurate at GFR >60 mL/min/1.73 m^2 (164,165). The AdDIT study in adolescents with type 1 diabetes demonstrated the safety of ACE inhibitor treatment, but the treatment did not change the albumin-to-creatinine ratio over the course of the study (142).

Retinopathy

Recommendations

14.45 An initial dilated and comprehensive eye examination is recommended once youth have had type 1 diabetes for 3–5 years, provided they are aged ≥11 years or puberty has started, whichever is earlier. **B**

14.46 After the initial examination, repeat dilated and comprehensive eye examination every 2 years. Less frequent examinations, every 4 years, may be acceptable on the advice of an eye care professional and based on risk factor assessment, including a history of A1C <8% (<64 mmol/mol). **B**

14.47 Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **B**

Retinopathy (like albuminuria) most commonly occurs after the onset of puberty and after 5–10 years of diabetes duration (166). It is currently recognized that there is a low risk of development of vision-threatening retinal lesions prior to 12 years of age (167,168). A 2019 publication based on the follow-up of the DCCT adolescent cohort supports a lower frequency of eye examinations than previously recommended, particularly in adolescents with A1C closer to the goal range (169,170). Autonomous artificial intelligence screening for diabetic retinopathy has been shown to increase access to this routine

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health maintenance (171). Referrals should be made to eye care professionals with expertise in diabetic retinopathy and experience in counseling pediatric individuals and families on the importance of prevention, early detection, and intervention.

Neuropathy

Recommendation

14.48 Consider an annual comprehensive foot exam at the start of puberty or at age ≥10 years, whichever is earlier, once the youth has had type 1 diabetes for 5 years. The examination should include inspection, assessment of foot pulses, pinprick, and 10-g monofilament sensation tests, testing of vibration sensation using a 128-Hz tuning fork, and ankle reflex tests. **B**

Diabetic neuropathy rarely occurs in prepubertal children or after only 1–2 years of diabetes (166), although data suggest a prevalence of distal peripheral neuropathy of 7% in 1,734 youth with type 1 diabetes and association with the presence of CVD risk factors (172,173). A comprehensive foot exam, including inspection, palpation of dorsalis pedis and posterior tibial pulses, and determination of proprioception, vibration, and monofilament sensation, should be performed annually along with an assessment of symptoms of neuropathic pain (173). Foot inspection can be performed at each visit to educate youth regarding the importance of foot care (see Section 12, "Retinopathy, Neuropathy, and Foot Care").

TYPE 2 DIABETES

For information on risk-based screening for type 2 diabetes and prediabetes in youth, please refer to Section 2, "Diagnosis and Classification of Diabetes." For additional support for these recommendations, see the ADA position statement "Evaluation and Management of Youth-Onset Type 2 Diabetes" (3).

The prevalence of type 2 diabetes in youth has continued to increase over the past 20 years (4). The CDC published projections for type 2 diabetes prevalence using the SEARCH database. Assuming a 2.3% annual increase, the prevalence in those under 20 years of age will quadruple in 40 years (174,175).

Evidence suggests that type 2 diabetes in youth is different not only from type 1 diabetes but also from type 2 diabetes in adults and has unique features, such as a more rapidly progressive decline in β-cell function and accelerated development of diabetes complications (3,176). Long-term follow-up data from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study reported most individuals with type 2 diabetes diagnosed as youth had microvascular complications by young adulthood (177). Type 2 diabetes disproportionately impacts youth from historically marginalized communities and can occur in complex psychosocial and cultural environments, which may make it difficult to implement and sustain healthy lifestyle changes and self-management behaviors (9,178–181). Additional risk factors associated with type 2 diabetes in youth include obesity and excess adiposity (182), family history of diabetes possibly mediated by shared genetics, lifestyle, and environmental factors (183), female sex, maternal gestational diabetes mellitus (184), and adverse social determinants of health (176).

As with type 1 diabetes, youth with type 2 diabetes spend much of the day in school. Therefore, close communication with and the cooperation of school personnel are essential for optimal diabetes management and safety and maximal academic opportunities.

Screening and Diagnosis

Recommendations

14.49 Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or ≥10 years of age, whichever occurs earlier, in youth with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more additional risk factors for diabetes (see **Table 2.5** for evidence grading of other risk factors).

14.50 If screening is normal, repeat screening at a minimum of 2-year intervals **E** or more frequently if BMI is increasing. **C**

14.51 Fasting plasma glucose, 2-h plasma glucose during a 75-g oral glucose tolerance test, and A1C can be used to test for prediabetes or diabetes in children and adolescents. **B**

14.52 Children and adolescents with overweight or obesity in whom the diagnosis of type 2 diabetes is being considered should have a panel of pancreatic autoantibodies tested to exclude the possibility of autoimmune type 1 diabetes. **B**

In recent years, incidence and prevalence of type 2 diabetes in adolescents have increased dramatically, especially in historically marginalized communities (185). A few studies suggest oral glucose tolerance tests or fasting plasma glucose values as more suitable diagnostic tests than A1C in the pediatric population, especially among certain ethnicities (186), while fasting glucose alone may overdiagnose diabetes in children (187,188). In addition, many of these studies do not recognize that diabetes diagnostic criteria are based on long-term health outcomes, and validations are not currently available in the pediatric population (189). An analysis of National Health and Nutrition Examination Survey (NHANES) data suggests using A1C for screening of high-risk youth (190). The ADA acknowledges the limited data supporting A1C for diagnosing type 2 diabetes in children and adolescents. Although A1C is not recommended for diagnosis of diabetes in children with cystic fibrosis or symptoms suggestive of acute onset of type 1 diabetes, and only A1C assays without interference are appropriate for children with hemoglobinopathies, the ADA continues to recommend A1C for diagnosis of type 2 diabetes in this population (186).

Diagnostic Challenges

Given the current obesity epidemic, distinguishing between type 1 and type 2 diabetes in children can be difficult. Overweight and obesity are common in children with type 1 diabetes (34), and diabetes-associated autoantibodies and ketosis may be present in pediatric individuals with clinical features of type 2 diabetes (including obesity and acanthosis nigricans) (187). The presence of islet autoantibodies has been associated with faster progression to insulin deficiency (187). At the onset of diabetes, DKA occurs in ∼11% of youth aged 10–19 years with type 2 diabetes (191). Although uncommon, type 2 diabetes has been observed in prepubertal children under the age of 10 years, thus it should be part of the differential in children with suggestive symptoms (192). Finally, obesity contributes to the development of type 1 diabetes in some individuals (193), which further

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blurs the lines between diabetes types. We must acknowledge that people with type 1 diabetes can also experience weight gain and insulin resistance. However, accurate diagnosis is critical, as treatment plans, educational approaches, nutrition advice, and outcomes differ markedly between individuals with predominantly insulin resistance and absolute insulinopenia phenotypes. The significant diagnostic difficulties posed by maturity-onset diabetes of the young are discussed in Section 2, "Diagnosis and Classification of Diabetes." In addition, there are rare and atypical diabetes cases that represent a challenge for clinicians and researchers.

Management

Lifestyle Management

Recommendations

14.53 All youth with type 2 diabetes and their families should receive comprehensive DSMES that is specific to youth with type 2 diabetes and is culturally appropriate. **B**

14.54 Youth with overweight or obesity and type 2 diabetes and their families should be provided with developmentally and culturally appropriate comprehensive lifestyle programs that are integrated with diabetes management to achieve at least a 7–10% decrease in excess weight. **B**

14.55 Given the necessity of long-term weight management for youth with type 2 diabetes, lifestyle intervention should be based on a chronic care model and offered in the context of diabetes care. **E**

14.56 Youth with prediabetes and type 2 diabetes, like all children and adolescents, should be encouraged to participate in at least 60 min of moderate to vigorous physical activity daily (with muscle and bone strength training at least 3 days/week) **B** and to decrease sedentary recreational screen time. **C**

14.57 Nutrition for youth with prediabetes and type 2 diabetes, like for all children and adolescents, should focus on key nutrition principles (i.e., eat more nonstarchy vegetables, whole fruits, legumes, whole grains, nuts and seeds, and low-fat dairy products and eat less meat, sugar-sweetened beverages, sweets, refined grains, and processed or ultraprocessed foods). **B**

Glycemic Goals

Recommendations

14.58 Real-time CGM or intermittently scanned CGM should be offered for diabetes management in youth with type 2 diabetes on multiple daily injections or insulin pumps who are capable of using the device safely (either by themselves or with a caregiver). The choice of device should be made based on an individual's and family's circumstances, desires, and needs. **E**

14.59 Glycemic status should be assessed at least every 3 months. **E**

14.60 Consider setting an A1C goal of <6.5% (<48 mmol/mol) for most children and adolescents with type 2 diabetes who have a low risk of hypoglycemia. For those at higher risk of hypoglycemia, A1C goals should be individualized as clinically appropriate. **C**

Pharmacologic Management

Recommendations

14.61 Initiate pharmacologic therapy, in addition to behavioral counseling for healthful nutrition and physical activity changes, at diagnosis of type 2 diabetes. **A**

14.62 In individuals with incidentally diagnosed or metabolically stable diabetes (A1C <8.5% [<69 mmol/mol] and asymptomatic), metformin is the initial pharmacologic treatment of choice if kidney function is normal. **A**

14.63 Youth with marked hyperglycemia (blood glucose ≥250 mg/dL [≥13.9 mmol/L], A1C ≥8.5% [≥69 mmol/mol]) without acidosis at diagnosis who are symptomatic with polyuria, polydipsia, nocturia, and/or weight loss should be treated initially with long-acting insulin while metformin is initiated and titrated. **B**

14.64 Initiate subcutaneous or intravenous insulin treatment in individuals with ketoacidosis to rapidly correct the hyperglycemia and the metabolic derangement. Once acidosis is resolved, metformin should be initiated while subcutaneous insulin therapy is continued. **A**

14.65 In individuals presenting with severe hyperglycemia (blood glucose ≥600 mg/dL [≥33.3 mmol/L]), consider assessment for hyperglycemic hyperosmolar state. **A**

14.66 If glycemic goals are no longer met with metformin (with or without long-acting insulin), glucagon-like peptide 1 (GLP-1) receptor agonist therapy and/or empagliflozin should be considered in children 10 years of age or older. **A**

14.67 When choosing glucose-lowering or other medications for youth with overweight or obesity and type 2 diabetes, consider medication-taking behavior and the medications' effect on weight. **E**

14.68 For youth not meeting glycemic goals, consider maximizing noninsulin therapies (metformin, a GLP-1 receptor agonist, and empagliflozin) before initiating and/or the intensifying insulin therapy plan. **E**

14.69 In individuals initially treated with insulin and metformin and/or other glucose-lowering medications who are meeting glucose goals based on blood glucose monitoring or CGM, insulin can be tapered over 2–6 weeks by decreasing the insulin dose 10–30% every few days. **B**

Treatment of youth-onset type 2 diabetes should include lifestyle management, DSMES, and pharmacologic treatment. Initial treatment of youth with obesity and diabetes must consider that diabetes type is often uncertain in the first few weeks of treatment due to overlap in presentation and that a substantial percentage of youth with type 2 diabetes will present with clinically significant ketoacidosis (194). Therefore, initial therapy should address the hyperglycemia and associated metabolic derangements irrespective of ultimate diabetes type, with adjustment of therapy once metabolic compensation has been established and subsequent information, such as islet autoantibody results, becomes available. **Figure 14.1** provides an approach to the initial treatment of new-onset diabetes in youth with overweight or obesity with clinical suspicion of type 2 diabetes.

Glycemic goals should be individualized, taking into consideration the long-term health benefits of more stringent goals and risk for adverse effects, such as hypoglycemia. A lower A1C goal of <6.5% in youth with type 2 diabetes compared with <7% recommended in type 1 diabetes is justified by a lower risk of hypoglycemia and higher risk of

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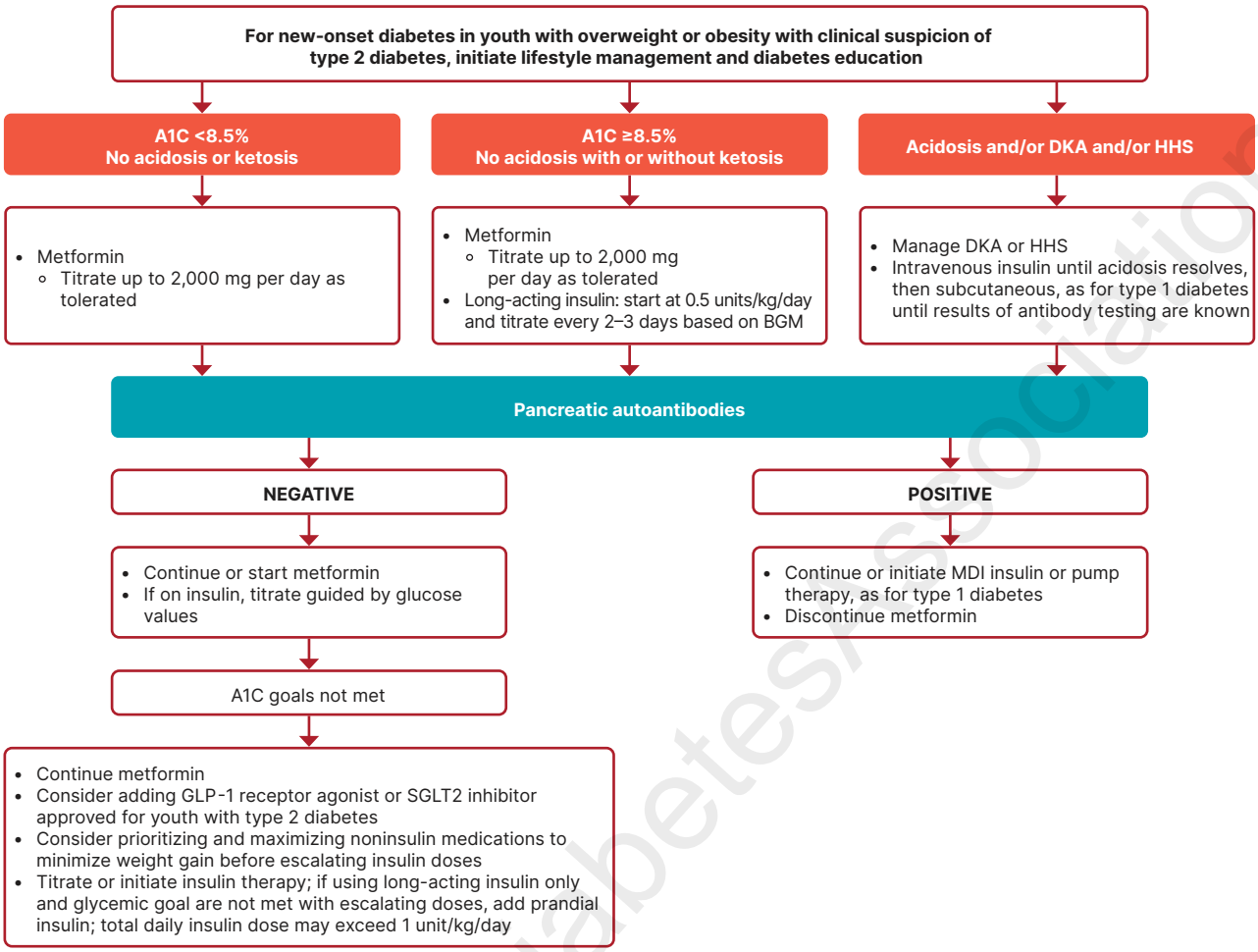

Figure 14.1—Management of new-onset diabetes in youth with overweight or obesity with clinical suspicion of type 2 diabetes. A1C 8.5% = 69 mmol/mol. BGM, blood glucose monitoring; CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; GLP-1, glucagon-like peptide 1; HHS, hyperosmolar hyperglycemic state; MDI, multiple daily injections; SGLT2, sodium–glucose cotransporter 2. Adapted from the ADA position statement "Evaluation and Management of Youth-Onset Type 2 Diabetes" (3).

complications in youth with type 2 diabetes (177,195–199).

Self-management in pediatric diabetes involves both the youth and their parents or adult caregivers. Individuals and their families should receive education and support for healthful nutrition and physical activity, such as a balanced meal plan, achieving and maintaining a healthy weight, and regular physical activity. Physical activity should include aerobic, muscle-strengthening, and bone-strengthening activities (24). A family-centered approach to nutrition and lifestyle modification is essential in children and adolescents with type 2 diabetes, and nutrition recommendations should be culturally appropriate and sensitive to family resources (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes"). Given the complex social and environmental context surrounding youth with type 2 diabetes, individual-level lifestyle interventions may not be sufficient to address the complex interplay of family dynamics, behavioral health, community readiness, and the broader environmental system (3).

An interprofessional diabetes team, including a physician, diabetes care and education specialist (CDCES), registered dietitian nutritionist, and behavioral health specialist or social worker, is essential. In addition to achieving glycemic goals and self-management education (200–202), initial treatment must include management of comorbidities such as obesity, dyslipidemia, hypertension, and microvascular complications.

Current pharmacologic treatment options for youth-onset type 2 diabetes are limited to four approved drug classes: insulin, metformin, glucagon-like peptide 1 (GLP-1) receptor agonists, and sodium–glucose cotransporter 2 inhibitors. Presentation with ketoacidosis or marked ketosis requires a period of insulin therapy until fasting and postprandial glycemia have been restored to normal or near-normal levels. Insulin pump therapy may be considered as an option for those on long-term multiple daily injections who are able to safely manage the device. Initial treatment should also be with insulin when the distinction between type 1 diabetes and type 2 diabetes is unclear and in individuals who have random blood glucose concentrations ≥250 mg/dL (≥13.9 mmol/L) and/or A1C ≥8.5% (≥69 mmol/mol) (203). Metformin therapy should be added after resolution of ketosis or ketoacidosis.

When initial insulin treatment is not required, initiation of metformin is recommended as first-line therapy. The TODAY study found that metformin alone provided durable glycemic management (A1C

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≤8% [≤64 mmol/mol] for 6 months) in approximately half of the subjects (204). The Restoring Insulin Secretion (RISE) Consortium study did not demonstrate differences in measures of glucose or β-cell function preservation between metformin and insulin, but there was more weight gain with insulin (205).

To date, the TODAY study is the only trial combining lifestyle and metformin therapy in youth with type 2 diabetes; the combination did not perform better than metformin alone in achieving durable glycemic levels (204).

Randomized controlled trials in youth have shown that GLP-1 receptor agonists are safe and effective for decreasing A1C (206–210) and promoting weight loss at higher doses approved for obesity (211). Use of GLP-1 receptor agonists can increase the frequency of gastrointestinal side effects and should not be used in individuals with a family history of medullary thyroid cancer.

In addition to GLP-1 receptor agonists, sodium–glucose cotransporter-2 inhibitors are well-studied drugs in adults with type 2 diabetes, and empagliflozin is now approved for use in youth with type 2 diabetes. In a recent multicenter double-blind, placebo-controlled trial, 158 children with type 2 diabetes aged between 10 and 17 years were randomized to 10 mg empagliflozin, 5 mg linagliptin, or placebo. Participants in the empagliflozin group who did not have A1C below 7.0% by week 12 underwent a second double-blinded randomization at week 14 to either remain on 10 mg of empagliflozin or increase their dose to 25 mg. In the empagliflozin pooled group compared with the placebo group, there was a significant reduction in A1C of 0.84% ($P = 0.012$). There were no episodes of severe hypoglycemia during the study (212).

Blood glucose monitoring plans should be individualized, taking into consideration the pharmacologic treatment of the person. Although data on CGM in youth with type 2 diabetes are sparse (213,214), CGM could be considered in individuals requiring frequent blood glucose monitoring for diabetes management.

Metabolic Surgery

Recommendations

14.70 Metabolic surgery may be considered for the treatment of adolescents with type 2 diabetes who have class 2 obesity or higher (BMI >35 kg/m^2 or >120% of 95th percentile for age and sex, whichever is lower) and who have elevated A1C and/or serious comorbidities despite lifestyle and pharmacologic intervention. **A**

14.71 Metabolic surgery should be performed only by an experienced surgeon working as part of a well-organized and engaged interprofessional team, including a surgeon, endocrinologist, registered dietitian nutritionist, behavioral health specialist, and nurse. **A**

The results of weight loss and lifestyle interventions for obesity in children and adolescents have been disappointing, and treatment options as adjuncts to lifestyle therapy are limited. Recent U.S. Food and Drug Administration–approved medications for youth ages 12 years and older include phentermine and topiramate extended-release capsules and GLP-1 receptor agonists (211,215–217). Over the last decade, weight loss surgery has been increasingly performed in adolescents with obesity. Small retrospective analyses and a prospective multicenter, nonrandomized study suggest that bariatric or metabolic surgery have benefits in adolescents with obesity and type 2 diabetes like those observed in adults. Early follow-up studies indicate that adolescents experience similar degrees of weight loss compared with adults and even higher rates of type 2 diabetes and hypertension remission (218). A secondary data analysis from the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) and TODAY studies suggests surgical treatment of adolescents with severe obesity and type 2 diabetes is associated with improved glycemia compared with the agents used in the TODAY study (219); however, no randomized trials have compared the effectiveness and safety of surgery with those of conventional treatment options in adolescents and particularly with the vertical sleeve gastrectomy, which is the most widely performed metabolic surgery in adolescents (220). The guidelines used as an indication for metabolic surgery in adolescents generally include class 2 obesity or higher (BMI >35 kg/m^2 or >120% of 95th percentile for age and sex, whichever is lower, with comorbidities) or BMI >40 kg/m^2 with or without comorbidities (221–227). A number of groups, including the Pediatric Bariatric Study Group and Teen-LABS study, have demonstrated the effectiveness of metabolic surgery in adolescents (221–225). However, long-term data on the rates of complications, reoperations, nutritional deficiencies, and diabetes recurrence are still needed.

Prevention and Management of Diabetes Complications

Hypertension

Recommendations

14.72 Blood pressure should be measured at every clinic visit. In youth with high blood pressure (blood pressure ≥ 90th percentile for age, sex, and height or, in adolescents aged ≥13 years, ≥120/80 mmHg) on three separate measurements, ambulatory blood pressure monitoring should be strongly considered. **B**

14.73 After excluding secondary hypertension, treatment of elevated blood pressure (defined as 90th to <95th percentile for age, sex, and height or, in adolescents aged ≥13 years, 120–129/<80 mmHg) is lifestyle modification focused on healthy nutrition, physical activity, sleep, and, if appropriate, weight management. **C**

14.74 In addition to lifestyle modification, ACE inhibitors or angiotensin receptor blockers should be started for treatment of confirmed hypertension (defined as blood pressure consistently ≥95th percentile for age, sex, and height or, in adolescents aged ≥13 years, ≥130/80 mmHg). Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception. **B**

14.75 The goal of treatment is blood pressure <90th percentile for age, sex, and height or, in adolescents aged ≥13 years, <130/80 mmHg. **C**

Nephropathy

Recommendations

14.76 Urine albumin-to-creatinine ratio should be obtained at the time of diagnosis and annually thereafter. An elevated urine albumin-to-creatinine ratio (>30 mg/g creatinine) should be confirmed on two of three samples. **B**

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14.77 Estimated glomerular filtration rate (GFR) should be determined at the time of diagnosis and annually thereafter. E

14.78 In youth with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin-to-creatinine ratio (30–299 mg/g creatinine) and should be considered for those with urinary albumin-to-creatinine ratio >300 mg/g creatinine and/or estimated GFR <60 mL/min/1.73 m^2. E Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and ACE inhibitors and angiotensin receptor blockers should be avoided in individuals of childbearing age who are not using reliable contraception. B

14.79 For youth with nephropathy, continue monitoring (yearly and/or as indicated by urinary albumin-to-creatinine ratio and estimated GFR) to detect disease progression. E

14.80 Referral to nephrology is recommended in case of uncertainty of etiology, worsening urinary albumin-to-creatinine ratio, or decrease in estimated GFR. E

Neuropathy

Recommendations

14.81 Youth with type 2 diabetes should be screened for the presence of neuropathy by foot examination at diagnosis and annually. The examination should include inspection, assessment of foot pulses, pinprick and 10-g monofilament sensation tests, testing of vibration sensation using a 128-Hz tuning fork, and ankle reflex tests. C

14.82 Prevention of neuropathy should focus on achieving glycemic goals. C

Retinopathy

Recommendations

14.83 Screening for retinopathy should be performed by dilated fundoscopy at or soon after diagnosis and annually thereafter. C

14.84 Optimizing glycemia is recommended to decrease the risk or slow the progression of retinopathy. B

14.85 Less frequent examination (every 2 years) may be considered if achieving glycemic goals and a normal eye exam. C

14.86 Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. E

Metabolic Dysfunction–Associated Steatotic Liver Disease Recommendations

Recommendations

14.87 Evaluation of youth with type 2 diabetes for metabolic dysfunction–associated steatotic liver disease (by measuring AST and ALT) should be done at diagnosis and annually thereafter. B

14.88 Referral to gastroenterology should be considered for persistently elevated or worsening transaminases. B

Obstructive Sleep Apnea

Recommendation

14.89 Screening for symptoms of sleep apnea should be done at each visit, and referral to a pediatric sleep specialist for evaluation and a polysomnogram, if indicated, is recommended. Obstructive sleep apnea should be treated when documented. B

Polycystic Ovary Syndrome

Recommendations

14.90 Evaluate for polycystic ovary syndrome in female adolescents with type 2 diabetes, including laboratory studies, when indicated. B

14.91 Metformin, in addition to lifestyle modification, is likely to improve the menstrual cyclicity and hyperandrogenism in female individuals with type 2 diabetes. E

Cardiovascular Disease

Recommendation

14.92 Intensive lifestyle interventions focusing on weight loss, dyslipidemia, hypertension, and dysglycemia are important to prevent overt macrovascular disease in early adulthood. E

Dyslipidemia

Recommendations

14.93 Lipid screening should be performed initially after optimizing glycemia and annually thereafter. B

14.94 Optimal goals are LDL cholesterol <100 mg/dL (<2.6 mmol/L), HDL cholesterol >35 mg/dL (>0.91 mmol/L), and triglycerides <150 mg/dL (<1.7 mmol/L). E

14.95 If lipids are abnormal, initial therapy should consist of optimizing glycemia and medical nutritional therapy to limit the amount of calories from fat to 25–30% and saturated fat to <7%, limit cholesterol to <200 mg/day, avoid *trans* fats, and aim for ~10% calories from monounsaturated fats for elevated LDL. For elevated triglycerides, MNT should also focus on decreasing carbohydrate intake and increasing dietary n-3 fatty acids in addition to the above changes. A

14.96 If LDL cholesterol remains >130 mg/dL (>3.4 mmol/L) after 6 months of dietary intervention, initiate therapy with statin, with a goal of LDL <100 mg/dL (<2.6 mmol/L). Due to the potential teratogenic effects, individuals of childbearing age should receive reproductive counseling, and statins should be avoided in individuals of childbearing age who are not using reliable contraception. B

14.97 If triglycerides are >400 mg/dL (>4.7 mmol/L) fasting or >1,000 mg/dL (>11.6 mmol/L) nonfasting, optimize glycemia and begin fibrate, with a goal of <400 mg/dL (<4.7 mmol/L) fasting to reduce risk for pancreatitis. C

Cardiac Function Testing

Recommendation

14.98 Routine screening for heart disease with electrocardiogram, echocardiogram, or stress testing is not recommended in asymptomatic youth with type 2 diabetes. B

Comorbidities may already be present at the time of diagnosis of type 2 diabetes in youth (176,228). Therefore, blood pressure measurement, a fasting lipid

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panel, assessment of random urine albumin-to-creatinine ratio, foot examination for neuropathy, and a dilated eye examination should be performed at diagnosis. Additional medical conditions that may need to be addressed include polycystic ovary disease and other comorbidities associated with pediatric obesity, such as sleep apnea, hepatic steatosis, orthopedic complications, and psychosocial concerns. The ADA position statement "Evaluation and Management of Youth-Onset Type 2 Diabetes" (3) provides guidance on the prevention, screening, and treatment of type 2 diabetes and its comorbidities in children and adolescents.

Youth-onset type 2 diabetes is associated with significant microvascular and macrovascular risk burden and a substantial increase in the risk of cardiovascular morbidity and mortality at an earlier age than in those diagnosed later in life (177, 229). The higher complication risk in earlier-onset type 2 diabetes is likely related to prolonged lifetime exposure to hyperglycemia and other atherogenic risk factors, including insulin resistance, dyslipidemia, hypertension, and chronic inflammation. There is a low risk of hypoglycemia in youth with type 2 diabetes, even if they are being treated with insulin (230), and there are high rates of complications (196–198,230). These diabetes comorbidities also appear to be higher than those in youth with type 1 diabetes despite shorter diabetes duration and lower A1C (228). In addition, the progression of vascular abnormalities appears to be more pronounced in youth-onset type 2 diabetes than with type 1 diabetes of similar duration, including ischemic heart disease and stroke (229).

In youth with type 2 diabetes and polycystic ovary syndrome, oral contraceptives are appropriate agents.

Psychosocial Factors

Recommendations

14.99 Health care professionals should screen for food insecurity, housing stability, health literacy, financial barriers, and social or community support and apply that information to treatment decisions. **E**

14.100 Use age-appropriate standardized and validated tools to screen for diabetes distress, depressive symptoms, and behavioral health concerns in youth with type 2 diabetes, with attention to symptoms of depression and disordered eating, and refer to a qualified behavioral health professional when indicated. **B**

14.101 Starting at puberty, preconception counseling should be incorporated into routine diabetes clinic visits for all individuals of childbearing potential because of the adverse pregnancy outcomes in this population. **A**

Most youth with type 2 diabetes come from historically marginalized communities, have low socioeconomic status, and often experience multiple psychosocial stressors (9,40,42,231). Consideration of the sociocultural context and efforts to personalize diabetes management are of critical importance to minimize barriers to care, enhance participation, and maximize response to treatment. Screening for food insecurity, housing stability, and other barriers related to the social determinants of health should be part of routine pediatric diabetes care (232). Please see Section 1, "Improving Care and Promoting Health in Populations," for further information on how to screen and address social determinants of health–related barriers.

Evidence about psychosocial concerns in youth with type 2 diabetes is limited (233–236), but given the sociocultural context for many youth, combined with the medical burden and obesity associated with type 2 diabetes, continuous monitoring of behavioral health is recommended. Symptoms of depression and disordered eating are common and associated with higher A1C (41,233,237,238). Early detection of psychological and behavioral concerns can facilitate effective treatment options to improve psychosocial well-being and support diabetes (42). When psychological symptoms are identified, referral to a behavioral health professional, ideally with experience in pediatric diabetes, may be warranted. Although far less research has been done on psychological and behavioral interventions for youth with type 2 diabetes than for youth with type 1 diabetes, behavioral professionals can provide behavioral health care services to support youth with type 2 diabetes (50–52). Many of the medications prescribed for diabetes and psychiatric disorders are associated with weight gain and can increase concerns about eating, body shape, and weight (239,240).

The TODAY study documented high rates of maternal complications during pregnancy and low rates of preconception counseling and contraception use in youth with type 2 diabetes (241). Preconception counseling tailored for adolescents with diabetes (including type 2 diabetes) has sustained behavioral benefits (65).

SUBSTANCE USE IN PEDIATRIC DIABETES

Tobacco, Electronic Cigarettes, Alcohol, and Cannabis

Recommendations

14.102 Adolescents and young adults should be screened for tobacco or nicotine, electronic cigarettes, substance use, and alcohol use at diagnosis and regularly thereafter. **C**

14.103 Elicit a smoking history at initial and follow-up diabetes visits; discourage smoking in youth who do not smoke and encourage smoking cessation in those who do smoke. **A**

14.104 Electronic cigarette use or vaping should be discouraged. **A**

14.105 Advise all youth with diabetes not to use cannabis recreationally in any form. **E**

The adverse health effects of smoking and use of tobacco products are well recognized with respect to future cancer and CVD risk. Despite this, smoking rates are significantly higher among youth with diabetes than among youth without diabetes (242). In youth with diabetes, it is important to avoid additional CVD risk factors. Smoking increases the risk of the onset of albuminuria; therefore, smoking avoidance is important to prevent both microvascular and macrovascular complications (150). Discouraging use of tobacco products, including electronic cigarettes (243, 244), is an important part of routine diabetes care. Individuals with diabetes should be advised to avoid vaping and using electronic cigarettes, either as a way to stop smoking tobacco or as a recreational drug. In younger children, it is important to assess exposure to cigarette smoke in the home because of the adverse effects of secondhand smoke and to discourage youth from ever smoking.

As alcohol use has implications for glycemic management and safety in youth and young adults with diabetes, efforts are warranted to reduce alcohol use and

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increase education about the risks of alcohol use and strategies to minimize risks. A psychoeducational intervention for adolescents with chronic medical conditions, including type 1 diabetes, has demonstrated benefits for knowledge, perceived benefits, and reduced use (245). See also Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes."

Finally, increased legalization and multiple formulations of cannabis products have resulted in increased use of these products among youth and young adults. In 2022, 30.7% of 12th graders reported using cannabis in the past year and 6.3% reported using it daily over the past 30 days (246). Cannabis users with type 1 diabetes are at increased risk for hyperglycemic ketosis due to cannabis hyperemesis syndrome (severe nausea, abdominal pain, and vomiting) (247). For youth with type 1 diabetes presenting with a hyperglycemic emergency, health care professionals should consider cannabis hyperemesis syndrome in individuals with pH $\geq$7.4 and bicarbonate $>$15 mmol/L in the presence of ketosis (247). Routine diabetes care should discourage the use of recreational cannabis in all forms. See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for more information about smoking cessation, tobacco, electronic cigarettes, and cannabis in people with diabetes.

TRANSITION FROM PEDIATRIC TO ADULT CARE

Recommendations

14.106 Diabetes care teams should implement transition preparation programs for youth beginning in early adolescence and, at the latest, at least 1 year before the anticipated transfer from pediatric to adult health care. **E**

14.107 Interprofessional adult and pediatric health care teams should provide support and resources for adolescents, young adults, and their families prior to and during the transfer process from pediatric to adult health care. **C**

14.108 Pediatric diabetes specialists should partner with youth with diabetes and their caregivers to engage in shared decision-making for the timing of transfer to an adult diabetes specialist. There is no age-specific cutoff for youth with diabetes to transfer to an adult diabetes specialist. **E**

Care and close supervision of diabetes management are increasingly shifted from parents and other adults to the youth with type 1 or type 2 diabetes throughout childhood and adolescence. The shift from pediatric to adult health care professionals, however, often occurs abruptly as the older teen enters the next developmental stage, referred to as emerging adulthood (248), which is a critical period for young people who have diabetes. During this period of major life transitions, youth may begin to move out of their parents' or caregivers' homes and become increasingly responsible for their diabetes care. Their new responsibilities include self-management of their diabetes, making medical appointments, and financing health care once they are no longer covered by their parents' health insurance plans (ongoing coverage until age 26 years is currently available under provisions of the U.S. Affordable Care Act). In addition to lapses in health care, this is also a period associated with deterioration in glycemic stability; increased occurrence of acute complications; psychosocial, emotional, and behavioral challenges; and the emergence of chronic complications (249,250). The transfer period from pediatric to adult care is prone to fragmentation in health care delivery, which may adversely impact health care quality, cost, and outcomes (251). Worsening diabetes health outcomes during the transition to adult care and early adulthood have been documented (252,253).

Comprehensive and coordinated planning that begins in early adolescence is necessary to facilitate a seamless transition from pediatric to adult health care (249, 254). Research on effective interventions to promote successful transition to adult care is limited, although there are promising developments that may improve attendance at follow-up appointments and lower hospitalizations (255,256). Use of transition coordinators, technology to support communication with young adults, and other interventions may be useful in addressing the identified needs and preferences of young adults for transition (257) and in supporting successful establishment in adult care settings (258–261). Given the behavioral, psychosocial, and developmental factors that relate to this transition, diabetes care teams addressing transition should include physicians, certified diabetes care and education specialists, nurses, behavioral health professionals, registered dietitian nutritionists, and social workers (50,262). Resources to enhance social and peer support during the transition process may also be valuable (263). A comprehensive discussion regarding the challenges faced during this period, including specific recommendations, is found in the ADA position statement "Diabetes Care for Emerging Adults: Recommendations for Transition From Pediatric to Adult Diabetes Care Systems" (249). Ultimately, there is no age cutoff for youth with diabetes to transfer to adult diabetes care. The decision to transfer should be a collaborative process in which the youth with diabetes, their caregivers, and pediatric diabetes specialists discuss their readiness, preferences, and concerns to ensure that the transfer aligns with their needs and circumstances (256).

The Endocrine Society, in collaboration with the ADA and other organizations, has developed transition tools for clinicians and youth and families (254).

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15. Management of Diabetes in Pregnancy: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

DIABETES IN PREGNANCY

The prevalence of diabetes in pregnancy has been increasing in the U.S. in parallel with the worldwide epidemic of obesity. Not only is the prevalence of type 1 diabetes and type 2 diabetes increasing in individuals of reproductive age but there is also a dramatic increase in the reported rates of gestational diabetes mellitus (GDM). Diabetes confers significantly greater maternal and fetal risk that is largely related to the degree of hyperglycemia but also is related to chronic complications and comorbidities of diabetes. In general, specific risks of diabetes in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, fetal demise, macrosomia, neonatal hypoglycemia, neonatal hyperbilirubinemia, and neonatal respiratory distress syndrome. In addition, exposure to hyperglycemia in utero increases the risks of obesity, hypertension, and type 2 diabetes in offspring later in life (1,2).

Preconception Counseling

Recommendations

15.1 Starting at puberty and continuing in all people with diabetes and childbearing potential, preconception counseling should be incorporated into routine diabetes care. **A**

15.2 Family planning should be discussed, and effective contraception (with consideration of long-acting, reversible contraception) should be prescribed and used until an individual's treatment plan and A1C are optimized for pregnancy. **A**

15.3 Preconception counseling should address the importance of achieving glucose levels as close to normal as is safely possible, ideally A1C $<6.5\%$ (<48 mmol/mol), to reduce the risk of congenital anomalies, preeclampsia, macrosomia, preterm birth, and other complications. **A**

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.*

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15.4 Individuals with a history of gestational diabetes mellitus (GDM) should seek preconception screening for diabetes and preconception care to identify and treat hyperglycemia and prevent congenital malformations. **E**

Preconception counseling for pregnant people with preexisting type 1 or type 2 diabetes is highly effective in reducing the risk of congenital malformations and decreasing the risk of preterm delivery and admission to neonatal intensive care units. Preconception counseling is also associated with reductions in perinatal mortality and small-for-gestational-age birth weight (3). A key point is the need to incorporate a question about plans for pregnancy into the routine primary and gynecologic care of people with diabetes.

There are opportunities at any health care visit to educate all adults and adolescents with diabetes and childbearing potential about the risks of unplanned pregnancies and about improved maternal and fetal outcomes with pregnancy planning (4). Education and counseling should be offered, even when individuals already use contraception or do not intend to conceive (5). Effective preconception counseling could avert substantial health and associated cost burdens related to the offspring (6). Family planning should be discussed, including the benefits of long-acting, reversible contraception, and effective contraception should be prescribed and used until the individual is prepared and ready to become pregnant (7–11).

All individuals with diabetes and childbearing potential should be informed about the importance of achieving and maintaining as near euglycemia as safely possible prior to conception and throughout pregnancy. Observational studies show an increased risk of diabetic embryopathy, especially anencephaly, microcephaly, congenital heart disease, kidney anomalies, and caudal regression, directly proportional to elevations in A1C during the first 10 weeks of pregnancy (12). Although observational studies are confounded by the association between elevated periconceptional A1C and other engagement in self-care behaviors, the quantity and consistency of data are convincing and support the recommendation to optimize glycemia prior to conception with an A1C <6.5% (<48 mmol/mol), as this is associated with the lowest risk of congenital anomalies (given that organogenesis occurs primarily at 5–8 weeks of gestation), preeclampsia, and preterm birth (12–16). In a systematic review and meta-analysis of observational studies, preconception care for pregnant individuals with preexisting diabetes was associated with lower A1C and reduced risks of birth defects, preterm delivery, perinatal mortality, small-for-gestational-age births, and neonatal intensive care unit admissions (17).

To minimize the occurrence of complications, beginning at the onset of puberty or at diagnosis, all adults and adolescents with diabetes of childbearing potential should receive education about *1*) the risks of malformations associated with unplanned pregnancies, even with mild hyperglycemia, and *2*) the use of effective contraception at all times when trying to prevent a pregnancy. Preconception counseling using developmentally appropriate educational tools enables adolescents with childbearing potential to make well-informed decisions (4). Preconception counseling resources tailored to adolescents are available at no cost through the American Diabetes Association (ADA) (18).

Individuals with prediabetes or a history of GDM will need preconception evaluation for as long as they have childbearing potential. Individuals with a history of GDM who are planning pregnancy should undergo screening for prediabetes or type 2 diabetes prior to conception, as outlined in Section 2, "Diagnosis and Classification of Diabetes." In the nonpregnant state, evaluation may be performed with any glycemic test recommended in Section 2. If the evaluation reveals euglycemia without prediabetes or type 2 diabetes, then with a subsequent pregnancy the individual with GDM should be screened for abnormal glucose metabolism (<15 weeks) or GDM at 24–28 weeks (if abnormal glucose metabolism testing was not previously performed or was not present) as outlined in Section 2. Should prediabetes or type 2 diabetes be diagnosed, the individual should initiate treatment with a goal to achieve and maintain an A1C of <6.5% (<48 mmol/mol) prior to conception using therapies approved for use in pregnancy. Preconception evaluation should assess maternal weight. In a randomized trial of individuals with overweight or obesity and a history of GDM, weight loss prior to a subsequent pregnancy was associated with a lower risk of GDM recurrence, especially when weight loss was ≥5% (odds ratio [OR] 0.18, 95% CI 0.04–0.88) (19). Counseling on weight management should include the known benefits and risks of different strategies for achieving and maintaining weight loss. For strategies that include pharmacotherapy, recommendations should be given for when changes in medications should occur prior to pregnancy.

Preconception Care

Recommendations

15.5 Individuals with preexisting diabetes who are planning a pregnancy should ideally begin receiving interprofessional care for preconception, which includes an endocrinology health care professional, maternal-fetal medicine specialist, registered dietitian nutritionist, and diabetes care and education specialist, when available. **B**

15.6 In addition to focused attention on achieving glycemic goals, **A** standard preconception care should be augmented with extra focus on nutrition, physical activity, diabetes self-care education, and screening for diabetes comorbidities and complications. **B**

15.7 Individuals with preexisting diabetes who are planning a pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Dilated eye examinations should occur ideally before pregnancy as well as in the first trimester, and then pregnant individuals should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy and as recommended by the eye care health care professional. **B**

The importance of preconception care for all pregnant people is highlighted by American College of Obstetricians and Gynecologists (ACOG) Committee Opinion 762, "Prepregnancy Counseling" (5). Preconception care for people with prediabetes and diabetes should include the standard screening and care recommended for any person planning pregnancy (5). Prescription of prenatal vitamins with at least 400–800 μg of folic acid (20) and 150 mg of potassium iodide (21) is recommended prior to conception. Review and counseling on abstaining from nicotine products, alcohol, and recreational drugs, including marijuana, is important. Standard

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care includes screening for sexually transmitted infections and thyroid disease, recommended vaccinations, routine genetic screening, a careful review of all prescription and nonprescription medications, herbal supplements, and nonherbal supplements used and a review of travel history and plans with special attention on areas known to have relevant endemic viruses, as outlined by ACOG. See **Table 15.1** for additional details on elements of preconception care (5,20,22).

Due to the complexity of insulin management in pregnancy, referral to a specialized center offering team-based care (with team members including a maternal-fetal medicine specialist, endocrinologist or other health care professional experienced in managing pregnancy and preexisting diabetes, registered dietitian nutritionist (RDN), diabetes care and education specialist, and social worker, as needed) is recommended if this resource is available. When a single specialized center is not available, providing an interprofessional team approach through interprofessional team members at different centers may still be beneficial.

The most important diabetes-specific component of preconception care is the attainment of glycemic goals prior to conception. Diabetes-specific counseling should include an explanation of the risks to mother and fetus related to pregnancies associated with diabetes and the ways to reduce risks, including glycemic goal setting, lifestyle and behavioral management, and medical nutrition therapy (3). Risks for GDM are characterized by an increased risk of large-for-gestational-age birth weight and neonatal and pregnancy complications and an increased risk of long-term maternal type 2 diabetes and abnormal glucose metabolism of offspring in childhood. These associations with maternal oral glucose tolerance test (OGTT) results are continuous with no clear inflection points (23,24). Offspring with exposure to untreated GDM have reduced insulin sensitivity and β-cell compensation and are more likely to have impaired glucose tolerance in childhood (25). In other words, short-term and long-term risks increase with progressive maternal hyperglycemia.

Counseling on the specific risks of obesity in pregnancy and lifestyle interventions to prevent and treat obesity, including referral to an RDN, is recommended regardless of diabetes status (26). The risk for associated hypertension and other comorbidities may be as high or higher with type 2 diabetes as it is with type 1 diabetes, even if diabetes is better managed and of shorter apparent duration, with pregnancy loss appearing to be more prevalent in the third trimester in those with type 2 diabetes compared with the

Table 15.1—Checklist for preconception care for people with prediabetes, diabetes, or a history of gestational diabetes mellitus

Preconception education should include:

- ☐ Comprehensive nutrition assessment and recommendations for:
  - Overweight and obesity or underweight
  - Meal planning
  - Correction of dietary nutritional deficiencies
  - Caffeine intake
  - Safe food preparation technique
- ☐ Lifestyle recommendations for:
  - Regular moderate exercise
  - Avoidance of hyperthermia (hot tubs)
  - Adequate sleep
- ☐ Comprehensive diabetes self-management education
- ☐ Counseling on diabetes in pregnancy per current standards, including natural history of insulin resistance in pregnancy and postpartum; preconception glycemic goals; avoidance of DKA and severe hyperglycemia; avoidance of severe hypoglycemia; progression of retinopathy in individuals with preexisting diabetes; PCOS (if applicable); fertility in people with diabetes; genetics of diabetes; risks to pregnancy including miscarriage, stillbirth, congenital malformations, macrosomia, preterm labor and delivery, hypertensive disorders in pregnancy
- ☐ Supplementation
  - Folic acid supplement (400–800 μg/day routine)
  - Appropriate use of over-the-counter medications and supplements

Health assessment and plan should include:

- ☐ General evaluation of overall health
- ☐ Evaluation of diabetes and its comorbidities and complications, including DKA and severe hyperglycemia; severe hypoglycemia/hypoglycemia unawareness; barriers to care; comorbidities such as hyperlipidemia, hypertension, MASLD, PCOS, and thyroid dysfunction; complications such as macrovascular disease in individuals with preexisting diabetes, nephropathy, neuropathy (including autonomic bowel and bladder dysfunction), and retinopathy
- ☐ Evaluation of obstetric or gynecologic history, including a history of cesarean section, congenital malformations or fetal loss, current methods of contraception, hypertensive disorders of pregnancy, postpartum hemorrhage, preterm delivery, previous macrosomia, Rh incompatibility, and thrombotic events (DVT/PE)
- ☐ Review of current medications and appropriateness during pregnancy

Screening should include:

- ☐ Diabetes complications and comorbidities in individuals with preexisting diabetes, including comprehensive foot exam; comprehensive ophthalmologic exam; ECG in individuals starting at age 35 years who have cardiac signs or symptoms or risk factors and, if abnormal, further evaluation; lipid panel; serum creatinine; TSH; and urine albumin-to-creatinine ratio
- ☐ Anemia
- ☐ Genetic carrier status (based on history):
  - Cystic fibrosis
  - Sickle cell anemia
  - Tay-Sachs disease
  - Thalassemia
  - Others if indicated
- ☐ Infectious disease (per ACOG guidelines)

Preconception plan should include:

- ☐ Immunizations (per ACOG guidelines) (165–167)
- ☐ Nutrition and medication plan to achieve glycemic goals prior to conception, including appropriate implementation of blood glucose monitoring, continuous glucose monitoring (if indicated and appropriate), and pump technology (if indicated and appropriate)
- ☐ Contraceptive plan to prevent pregnancy until glycemic goals are achieved
- ☐ Management plan for general health, gynecologic concerns, comorbid conditions, or complications, if present, including hypertension, nephropathy, retinopathy; Rh incompatibility; and thyroid dysfunction

Created using information from American College of Obstetricians and Gynecologists (ACOG) (5) and others (20,22). DKA, diabetic ketoacidosis; DVT/PE, deep vein thrombosis/pulmonary embolism; ECG, electrocardiogram; MASLD, metabolic dysfunction-associated steatotic liver disease; PCOS, polycystic ovary syndrome; TSH, thyroid-stimulating hormone.

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first trimester in those with type 1 diabetes (27,28).

For individuals with preexisting diabetes, the presence of microvascular complications is associated with higher risk of disease progression and adverse pregnancy outcomes (29). Diabetes-specific testing should include A1C, creatinine, and urinary albumin-to-creatinine ratio. Special attention should be paid to the review of the medication list for potentially harmful drugs, e.g., ACE inhibitors (30), angiotensin receptor blockers (30), and statins in some cases (31). For individuals using medications that are not approved for use in pregnancy (such as some glucose-lowering, lipid-lowering, and antihypertensive agents), preconception care should include recommendations for when changes in medications should occur to stabilize the conditions and risk factors managed by these medications (such as glucose levels, weight, lipids, and blood pressure) on alternate therapies prior to pregnancy. A referral for a comprehensive eye exam is recommended. Individuals with preexisting diabetic retinopathy will need close monitoring during pregnancy to assess stability or progression of retinopathy and provide treatment if indicated (32).

GLYCEMIC GOALS IN PREGNANCY

Recommendations

15.8 Fasting, preprandial, and postprandial blood glucose monitoring are recommended in individuals with diabetes in pregnancy to achieve optimal glucose levels. Glucose goals are fasting plasma glucose <95 mg/dL (<5.3 mmol/L) and either 1-h postprandial glucose <140 mg/dL (<7.8 mmol/L) or 2-h postprandial glucose <120 mg/dL (<6.7 mmol/L). **B**

15.9 Due to increased red blood cell turnover, A1C is slightly lower during pregnancy in people with and without diabetes. Ideally, the A1C goal in pregnancy is <6% (<42 mmol/mol) if this can be achieved without significant hypoglycemia, but the goal may be relaxed to <7% (<53 mmol/mol) if necessary to prevent hypoglycemia. **B**

15.10 Continuous glucose monitoring (CGM) can help to achieve glycemic goals (e.g., time in range, time above range) **A** and A1C goal **B** in type 1 diabetes and pregnancy and may be beneficial for other types of diabetes in pregnancy. **E**

15.11 Recommend CGM to pregnant individuals with type 1 diabetes. **A** In conjunction with aims to achieve traditional pre- and postprandial glycemic goals, real-time CGM can reduce the risk for large-for-gestational-age infants and neonatal hypoglycemia in pregnancy complicated by type 1 diabetes. **A**

15.12 CGM metrics may be used in combination with blood glucose monitoring to achieve optimal pre- and postprandial glycemic goals. **E**

15.13 Commonly used estimated A1C and glucose management indicator calculations should not be used in pregnancy as estimates of A1C. **C**

Insulin Physiology

Pregnancy in people with normal glucose metabolism is characterized by fasting levels of blood glucose that are lower than those in the nonpregnant state due to insulin-independent glucose uptake by the fetus and placenta and by mild postprandial hyperglycemia and carbohydrate intolerance as a result of diabetogenic placental factors. Early pregnancy may be a time of enhanced insulin sensitivity and lower glucose levels and is followed by progressive insulin resistance in the second and third trimesters (33–35). Insulin resistance drops rapidly with the delivery of the placenta. In people with normal pancreatic function, insulin production is sufficient to meet the challenge of this physiological insulin resistance and to maintain normal glucose levels. However, in people with diabetes, hyperglycemia occurs if treatment is not adjusted appropriately.

Glucose Monitoring

Reflecting this physiology, fasting and postprandial blood glucose monitoring is recommended to achieve glycemic goals in pregnant people with diabetes. Preprandial testing is also recommended when using insulin pumps or basal-bolus therapy so that the premeal rapid-acting insulin dosage can be adjusted. Postprandial monitoring is associated with better glycemic outcomes and a lower risk of preeclampsia (36–38). There are no adequately powered randomized trials comparing different fasting and postmeal glycemic goals for preexisting diabetes in pregnancy.

Similar to the glycemic goals recommended by ACOG (39), the ADA-recommended goals for pregnant people with type 1 or type 2 diabetes are shown in **Table 15.2**. Lower limits are based on the mean of normal blood glucose in pregnancy (40) but do not apply to individuals with type 2 diabetes treated with nutrition alone. Hypoglycemia in pregnancy is as defined and discussed in Recommendations 6.10–6.18 (see Section 6, "Glycemic Goals and Hypoglycemia"). The most appropriate hypoglycemia threshold level in pregnancy has not been validated but has ranged from <60 to <70 mg/dL (<3.3 to <3.9 mmol/L) in the past. Current recommendations for hypoglycemia thresholds include blood glucose <70 mg/dL (<3.9 mmol/L) and sensor glucose <63 mg/dL (<3.5 mmol/L) (40,41). These fasting or premeal and postprandial glucose values represent optimal levels if they can be achieved safely. In practice, it may be challenging for a person with type 1 diabetes to achieve these goals without hypoglycemia, particularly those with a history of recurrent hypoglycemia or impaired awareness of hypoglycemia. If an individual cannot achieve these goals without significant hypoglycemia, aim for less stringent goals based on clinical experience and individualization of care.

For individuals with GDM, glucose monitoring should aim for the goals recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (42) (**Table 15.2**).

A1C in Pregnancy

In studies of individuals without preexisting diabetes, increasing A1C levels within the normal range are associated with adverse outcomes (43). In the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, increasing levels of glycemia were also associated with worsening outcomes (23). Observational studies in preexisting diabetes and pregnancy show the lowest rates of adverse fetal outcomes in association with A1C <6–6.5% (<42–48 mmol/mol) early in gestation (13,14,16,44). Clinical trials have not evaluated the risks and benefits of achieving these goals, and treatment goals should account for the risk of maternal hypoglycemia in setting an individualized goal of <6% (<42 mmol/mol) to

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Table 15.2—Blood glucose goals in pregnancies associated with diabetes

	Blood glucose goal		
Glucose measurement	Type 1 diabetes or type 2 diabetes^	GDM treated with insulin	GDM not treated with insulin
Fasting glucose	70–95 mg/dL (3.9–5.3 mmol/L)	70–95 mg/dL (3.9–5.3 mmol/L)	<95 mg/dL (<5.3 mmol/L)
1-h postprandial glucose	110–140 mg/dL* (6.1–7.8 mmol/L)	110–140 mg/dL* (6.1–7.8 mmol/L)	<140 mg/dL* (<7.8 mmol/L)
2-h postprandial glucose	100–120 mg/dL (5.6–6.7 mmol/L)	100–120 mg/dL (5.6–6.7 mmol/L)	<120 mg/dL (<6.7 mmol/L)

Gestational diabetes mellitus (GDM) blood glucose goals shown are recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (42). ^Lower glucose limits do not apply to individuals with type 2 diabetes treated with nutrition alone. Aim for less stringent goals if these cannot be achieved without significant hypoglycemia, based on clinical experience and individualization of care. *Optimal goal includes either a 1-h postprandial glucose level or 2-h postprandial glucose level within column of type of diabetes.

<7% (<53 mmol/mol). Due to physiological increases in red blood cell turnover, A1C levels fall during normal pregnancy (45,46). Additionally, as A1C represents an integrated measure of glucose, it may not fully capture postprandial hyperglycemia, which drives macrosomia. Thus, although A1C may be useful, it should be used as a secondary measure of glycemic outcomes in pregnancy, after blood glucose monitoring.

In the second and third trimesters, A1C <6% (<42 mmol/mol) has the lowest risk of large-for-gestational-age infants (44,47,48), preterm delivery (49), and preeclampsia (1,50). Taking all of this into account, a goal of <6% (<42 mmol/mol) is optimal during pregnancy if it can be achieved without significant hypoglycemia, which, in addition to the usual adverse sequelae, may increase the risk of low birth weight (51,52). Given the alteration in red blood cell kinetics during pregnancy and physiological changes in glycemic parameters, A1C levels may need to be monitored more frequently than usual (e.g., monthly).

Continuous Glucose Monitoring in Pregnancy

The Continuous Glucose Monitoring in Pregnant Women With Type 1 Diabetes Trial (CONCEPTT) was a randomized controlled trial (RCT) of real-time continuous glucose monitoring (CGM) in addition to standard care, including optimization of pre- and postprandial glucose goals versus standard care for pregnant people with type 1 diabetes. It demonstrated the value of using real-time CGM in pregnant individuals with type 1 diabetes by showing a mild improvement in A1C and significant improvements in the maternal glucose time in range (TIR) and time above range (TAR), without an increase in hypoglycemia, and reductions in large-for-gestational-age births, length of infant hospital stays, and severe neonatal hypoglycemia (53). An observational cohort study that evaluated the glycemic variables reported using CGM systems found that lower mean glucose, lower SD, and higher percentage of TIR were associated with lower risks of large-for-gestational-age births and other adverse neonatal outcomes (54). Data from one study suggest that the use of the CGM-reported mean glucose is superior to the use of estimated A1C, glucose management indicator, and other calculations to estimate A1C, given the changes to A1C that occur in pregnancy (55). One RCT and two observational studies have found that a 5% increase in CGM TIR was associated with improvements in neonatal morbidity, including large-for-gestational-age births and neonatal intensive care unit admissions (53,54,56). CGM TIR can be used for assessment of glycemic outcomes in people with type 1 diabetes, but it does not provide actionable data to address fasting and postprandial hypoglycemia or hyperglycemia. The cost of CGM use by pregnant individuals with type 1 diabetes is offset by improved maternal and neonatal outcomes (57).

There are insufficient data to support the use of CGM in all people with type 2 diabetes or GDM (58,59). The decision of whether to use CGM in pregnant individuals with type 2 diabetes or GDM should be individualized based on treatment plan, circumstances, preferences, and needs.

The international consensus on TIR (41) endorses pregnancy glucose goal ranges and goals for TIR for people with type 1 diabetes using CGM as reported on the ambulatory glucose profile. The international consensus on TIR (41) endorses the same sensor glucose goal ranges for individuals with type 2 diabetes in pregnancy and GDM but could not quantify the goal of amount of time spent within each category because of insufficient data. However, the consensus does not specify the type or accuracy of the CGM device or need for alarms and alerts. A small prospective, observational study of pregnant people with type 1 diabetes simultaneously monitored with intermittently scanning CGM (isCGM) and real-time CGM for 7 days in early pregnancy demonstrated a higher percentage of time below range (TBR) in the isCGM group. Asymptomatic hypoglycemia measured by isCGM should therefore not necessarily lead to a reduction of insulin dose and/or increased carbohydrate intake at bedtime unless these episodes are confirmed by blood glucose meter measurements (60). Selection of CGM device should be based on an individual's circumstances, preferences, and needs.

Goals for sensor glucose ranges in pregnancy:

- Goal sensor glucose range 63–140 mg/dL (3.5–7.8 mmol/L): TIR, goal >70%
- TBR (<63 mg/dL [<3.5 mmol/L]): level 1 TBR, goal <4%
- TBR (<54 mg/dL [<3.0 mmol/L]): level 2 TBR, goal <1%
- TAR (>140 mg/dL [>7.8 mmol/L]): TAR, goal <25%

Goals for time spent in each range are specific for pregnant individuals with type 1 diabetes.

MANAGEMENT OF DIABETES IN PREGNANCY

Recommendations

15.14 Nutrition counseling before and during pregnancy should promote an

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eating pattern including fruits, vegetables, legumes, whole grains, nuts, seeds, fish, and other lean protein, which will provide a balance of macronutrients and healthy n-3 fatty acids. C

15.15 Lifestyle behavior change is an essential component of management of GDM and may suffice as treatment for many individuals. Insulin should be added if needed to achieve glycemic goals. A

15.16 Telehealth visits used in combination with in-person visits for pregnant people with GDM can improve outcomes compared with standard in-person care alone. A

15.17 Insulin should be used to manage type 1 diabetes in pregnancy A and is the preferred agent for the management of GDM A and type 2 diabetes in pregnancy. B

15.18 Either multiple daily injections or insulin pump technology can be used in pregnancy complicated by type 1 diabetes. C

15.19 Automated insulin delivery (AID) systems with pregnancy-specific glucose targets are recommended for pregnant individuals with type 1 diabetes. A

15.20 AID systems without pregnancy-specific glucose targets or a pregnancy-specific algorithm may be considered for select pregnant individuals with type 1 diabetes when used with assistive techniques and working with experienced health care teams. B

15.21 Metformin and glyburide, individually or in combination, should not be used as first-line agents for management of diabetes in pregnancy, as both cross the placenta to the fetus A and may not be sufficient to achieve glycemic goals. B Other oral and noninsulin injectable glucose-lowering medications lack long-term safety data and are not recommended. E

15.22 Metformin, when used to treat polycystic ovary syndrome and induce ovulation, should be discontinued by the end of the first trimester. A

The management of pregnancies associated with diabetes includes appropriate nutrition, lifestyle and behavior management, physical activity goals, and pharmacotherapy to support the maternal, fetal, and placental needs and reach glycemic goals regardless of the diabetes type.

Medical Nutrition Therapy

In people with preexisting diabetes, glycemic goals are usually achieved through a combination of insulin administration and medical nutrition therapy. Because glycemic goals in pregnant individuals are stricter than in nonpregnant individuals, it is important that pregnant people with diabetes eat consistent amounts of carbohydrates to match their insulin dosage and to avoid hyperglycemia or hypoglycemia. Referral to an RDN is important to establish a food plan and insulin-to-carbohydrate ratio and determine weight gain goals. The quality of the carbohydrates should be evaluated. A subgroup analysis of the CONCEPTT study demonstrated that the diets of individuals planning pregnancy and currently pregnant assessed during the run-in phase prior to randomization were characterized by high-fat, low-fiber, and poor-quality carbohydrate intakes. Fruit and vegetable consumption was inadequate, with one in four participants at risk for micronutrient deficiencies, highlighting the importance of medical nutrition therapy (61).

An expert panel on nutrition in pregnancy and the U.S. Department of Health and Human Services recommend a balance of macronutrients. An eating pattern that severely restricts any macronutrient class should be avoided, specifically the ketogenic diet that lacks carbohydrates, the paleo diet because of dairy restriction, and any eating pattern characterized by excess saturated fats (62). Pregnant individuals with diabetes are recommended to consume whole foods, including fruits, vegetables, legumes, whole grains, lean protein, and healthy fats with n-3 fatty acids, which includes nuts and seeds and fish, which are less likely to promote excessive weight gain (63). Processed foods, fatty red meat, and sweetened foods and beverages should be limited (62,63).

The recommended dietary reference intake for all pregnant people is a minimum of 175 g of carbohydrate (~35% of a 2,000-calorie diet), a minimum of 71 g of protein, and 28 g of fiber (64). The nutrition plan should emphasize monounsaturated and polyunsaturated fats while limiting saturated fats and avoiding *trans* fats. As is true for all nutrition therapy in people with diabetes, the amount and type of carbohydrate will impact glucose levels. Promoting higher-quality, nutrient-dense carbohydrates results in ability to meet fasting or postprandial glucose goals, lower free fatty acids, improved insulin action, and vascular benefits and may reduce excess infant adiposity. Individuals who substitute fat for carbohydrates may unintentionally enhance lipolysis, promote elevated free fatty acids, and worsen maternal insulin resistance (65,66). Fasting urine ketone testing may be useful to identify those who are severely restricting carbohydrates to manage blood glucose. Carbohydrate restriction can increase the risk of higher dietary fat consumption, which may lead to fetal overgrowth (62). Simple carbohydrates will result in higher postmeal excursions.

Medical nutrition therapy for GDM is an individualized nutrition plan developed between the pregnant person and an RDN familiar with the management of GDM (67,68). The food plan should provide adequate calorie intake to promote fetal, neonatal, and maternal health, achieve glycemic goals, and promote appropriate weight gain, according to the 2009 National Academy of Medicine recommendations (69). There is no definitive research that identifies a specific optimal calorie intake for people with GDM or suggests that their calorie needs are different from those of pregnant individuals without GDM. The food plan should be based on a nutrition assessment with dietary reference intake guidance from the National Academy of Medicine.

Lifestyle and Behavioral Management

Although there is some heterogeneity, many RCTs and a Cochrane review suggest that the risk of GDM may be reduced by diet, exercise, and lifestyle counseling, particularly when interventions are started during the first trimester or early in the second trimester (70–72).

After diagnosis of GDM, treatment starts with medical nutrition therapy, physical activity, and weight management, depending on pregestational weight, as outlined in this section. Depending on the population, studies suggest that 70–85% of people diagnosed with GDM under Carpenter-Coustan criteria can manage GDM with lifestyle modification alone; it is anticipated that this proportion will be even higher if the lower International Association of the Diabetes and Pregnancy Study Groups (73) diagnostic thresholds are used.

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Physical Activity

It is recommended that generally healthy people do at least 150 min of moderate-intensity aerobic activity each week during pregnancy and postpartum, preferably spread throughout the week (74). Adjustments to a physical activity routine or plan should be done in consultation with a health care professional, especially if someone is considering a big change in physical activity intensity (74). Such activity improves cardiorespiratory fitness and reduces the risk for excessive gestational weight gain or postpartum weight retention (74).

With respect to GDM, a systematic review demonstrated improvements in glucose outcomes and reductions in need to start insulin or insulin dose requirements with an exercise intervention. However, there was heterogeneity in the types of effective exercise (aerobic, resistance, or both) and duration of exercise (20–50 min/day, 2–7 days/week of moderate intensity) (75), so there is insufficient evidence about which specific type of exercise program has the biggest impact on these diabetes-related outcomes in pregnancy.

Health Care Delivery for People With Diabetes in Pregnancy

As discussed in the preconception care subsection above, team-based care is recommended either through a single specialized center (when available) or multiple centers with interprofessional team members as part of the care plan during pregnancy. A meta-analysis of 32 RCTs evaluating the effectiveness of telemedicine interventions, which ranged from telemedicine visits to the use of health apps, used in combination with in-person visits for GDM demonstrated reduced incidences of cesarean delivery, premature rupture of membranes, pregnancy-induced hypertension or preeclampsia, preterm birth, neonatal asphyxia, and polyhydramnios compared with standard in-person care alone (76).

Pharmacologic Therapy

Insulin

Insulin should be used to manage type 1 diabetes in pregnancy and is preferred for the management of type 2 diabetes in pregnancy and GDM. The physiology of pregnancy necessitates frequent titration of insulin to match changing requirements and underscores the importance of daily and frequent blood glucose monitoring. In early pregnancy, many people with type 1 diabetes will have lower insulin requirements and an increased risk for hypoglycemia (33). At around 16 weeks, insulin resistance begins to increase, and total daily insulin doses increase linearly by ∼5% per week through week 36. This usually results in a doubling of daily insulin dose compared with the prepregnancy requirement. While there is an increase in both basal and bolus insulin requirements, bolus insulin requirements take up a larger proportion of overall total daily insulin needs in individuals with preexisting diabetes as pregnancy progresses (34,35). The insulin requirement levels off toward the end of the third trimester. A rapid and significant reduction in insulin requirements may indicate the development of placental insufficiency (36), although data are conflicting (77).

Optimal glycemic goals are often easier to achieve during pregnancy with type 2 diabetes than with type 1 diabetes but can require much higher doses of insulin, sometimes necessitating concentrated insulin formulations. It is recommended that insulin management be performed with interprofessional team members with relevant expertise.

None of the currently available human insulin preparations have been demonstrated to cross the placenta (78–83). Insulins studied in RCTs are preferred (84–86) over those studied in cohort studies (87), which are preferred over those studied in case reports only.

Both multiple daily insulin injections and continuous subcutaneous insulin infusion are reasonable delivery strategies in pregnancy, with neither showing superiority over the other (82,88). Partial closed-loop therapy, such as predictive low-glucose suspend (PLGS) technology, has been shown in nonpregnant people to be better than sensor-augmented insulin pumps (SAP) for reducing low glucose values (89). It may be suited for pregnancy because predictive low-glucose thresholds for suspending insulin are in the pregnancy ranges of premeal and overnight glucose goals and may allow for more aggressive prandial dosing.

Automated insulin delivery (AID) systems have been studied in pregnancy and postpartum. In one study, 124 pregnant individuals with type 1 diabetes used either an AID system with glucose targets that could be set near or in the pregnancy-specific fasting glucose range or standard of care (CGM use with another insulin delivery strategy). Investigators recommended pump glucose targets of 100 mg/dL in early pregnancy and 81–90 mg/dL from 16 to 20 weeks onward. The AID group had a higher CGM TIR (10.5% difference between groups, $P < 0.001$), lower TAR (−10.2% [95% CI −13.8 to −6.6]), and lower A1C (−0.31% [−0.50 to −0.12]), and a subset of participants who were interviewed reported benefits with AID use during pregnancy (e.g., more enjoyment of pregnancy, better sleep, less worry) (90,91).

There have been RCTs examining AID systems that do not have either pregnancy-specific pump glucose targets in the algorithms or algorithms that adapt specifically to pregnancy but were used with assistive techniques. In a study with 95 pregnant individuals with type 1 diabetes, participants used an AID system set to a pump glucose target of 100 mg/dL or to standard of care. The 24-h TIR was similar between groups, but the nocturnal TIR was higher (6.58%, $P = 0.003$), the 24-h TBR was lower (−1.34%, $P = 0.002$), and the nocturnal TBR was lower (−1.86%, $P = 0.0005$) in the AID group (92). AID users reported higher diabetes treatment satisfaction and had less hypoglycemia unawareness (per Gold scores) (92). In a pilot study ($n = 23$) where participants were randomized in the second trimester to AID with a system whose glucose target is 120 mg/dL or SAP with the same system, time spent in TBR decreased significantly in the AID group from baseline to third trimester (7.5% first trimester vs. 2.8% third trimester, $P < 0.05$), but the average sensor glucose was higher in the AID group in the third trimester (mean [SE] 119 [4] SAP vs. 132 [4] AID, $P = 0.0475$) without significant differences between groups in other CGM metrics (93). These two studies used assistive techniques, such as administration of fake carbohydrate insulin boluses for carbohydrates that were not consumed, and pump management was determined by expert guidance from an experienced interprofessional team (92–94). Thus, it may be appropriate to continue or initiate AID therapy with systems that do not have pregnancy-specific glucose targets or algorithms in carefully selected pregnant individuals with type 1 diabetes in the setting

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of using assistive techniques with expert guidance (92–94). Assessments of potential candidates for AID wear in pregnancy should include relevant parameters such as glycemic levels, presence or absence of severe hypoglycemic or hyperglycemic events, ability or comfort in engaging with diabetes technology, psychosocial determinants, cost, individual preference, and other factors as relevant.

Continuous subcutaneous insulin infusion was compared with intravenous insulin infusion in an RCT of 70 participants during labor and delivery. There was no difference between groups in the primary outcome of neonatal hypoglycemia or in secondary outcomes (e.g., mean neonatal glucose in first 24 h of life, severe neonatal hypoglycemia) (95). In an RCT of 18 participants using AID or sensor-augmented pump therapy for 12 weeks postpartum (96), those in the AID group had fewer hypoglycemia episodes (96). See sensor-augmented pumps and automated insulin delivery systems in Section 7, "Diabetes Technology," for more information on these systems.

Treatment of GDM with lifestyle and insulin has been demonstrated to improve perinatal outcomes in two large RCTs, as summarized in a U.S. Preventive Services Task Force review (97). Insulin is the first-line agent recommended for the treatment of GDM in the U.S. While individual studies support limited efficacy of metformin (98,99) and glyburide (100) in reducing glucose levels for the treatment of GDM, these agents are not recommended as the first-line treatment of GDM because they are known to cross the placenta and data on long-term safety for offspring is of some concern (39). Furthermore, in separate RCTs, glyburide and metformin failed to achieve adequate glycemic outcomes in 23% and 25–28% of participants with GDM, respectively (101,102).

Sulfonylureas

Sulfonylureas are known to cross the placenta and have been associated with increased neonatal hypoglycemia. Concentrations of glyburide in umbilical cord plasma are approximately 50–70% of maternal levels (101,102). In systematic reviews and meta-analyses, compared with insulin or metformin, glyburide was associated with a higher rate of neonatal hypoglycemia and macrosomia and an increased neonatal abdominal circumference (103,104).

Glyburide was not found to be noninferior to insulin based on a composite outcome of neonatal hypoglycemia, macrosomia, and hyperbilirubinemia (105). Long-term safety data for offspring exposed to glyburide are not available (105).

Metformin

Metformin was associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin in systematic reviews and RCTs for GDM treatment, but treatment monotherapy failure occurred in 14–46% of individuals (103,106–109). A meta-analysis of 11 RCTs demonstrated that metformin treatment in pregnancy does not reduce the risk of GDM in high-risk individuals with obesity, polycystic ovary syndrome, or preexisting insulin resistance (110). RCTs of individuals with preexisting type 2 diabetes treated either with insulin alone or insulin plus metformin did not show differences in composite neonatal health outcomes between groups (111,112), and one of these also included individuals diagnosed with diabetes early in gestation (112). Neonatal birth weights were smaller in the metformin groups of these studies, but the metformin group experienced more drug intolerance in one study and there was a doubling of small-for-gestational-age neonates in the other (111,112). RCTs comparing metformin with other therapies for ovulation induction in individuals with polycystic ovary syndrome have not demonstrated benefit in preventing spontaneous abortion or GDM (113), and there is no evidence-based need to continue metformin in these individuals (114–116).

Of note, metformin readily crosses the placenta, resulting in umbilical cord blood levels of metformin as high or higher than simultaneous maternal levels (117,118). In the Metformin in Gestational Diabetes: The Offspring Follow-Up (MiG TOFU) study's analyses of 7- to 9-year-old offspring, the 9-year-old offspring exposed to metformin for the treatment of GDM in the Auckland cohort (but not the Adelaide cohort) were heavier and had a higher waist-to-height ratio and waist circumference than those exposed to insulin (119). In one RCT of metformin use in pregnancy for polycystic ovary syndrome, follow-up of 4-year-old offspring demonstrated higher BMI and increased obesity in the offspring exposed to metformin (120). A follow-up study at 5–10 years showed that the offspring had higher BMI, weight-to-height ratios, and waist circumferences and a borderline increase in fat mass (121,122). A meta-analysis demonstrated that metformin exposure resulted in smaller neonates with an acceleration of postnatal growth, resulting in higher BMI in childhood (121). Follow-up of offspring from the Metformin in Women with Type 2 Diabetes in Pregnancy (MiTy Kids) trial showed no differences in anthropometrics of children at 24 months (123).

There are some people with GDM requiring medical therapy who may not be able to use insulin safely or effectively during pregnancy due to cost, comprehension, or cultural influences. Oral agents may be an alternative for these individuals after discussing the known risks and the need for more long-term safety data in offspring. However, due to the potential for growth restriction or acidosis in the setting of placental insufficiency, metformin should not be used in pregnant people with hypertension or preeclampsia or those at risk for intrauterine growth restriction (123–125).

Special Considerations for Management of Pregnancies With Diabetes

Pregnant individuals with type 1 diabetes have an increased risk of hypoglycemia in the first trimester and after delivery, and like all pregnant people, they have altered counterregulatory response in pregnancy that may decrease hypoglycemia awareness. Education for people with diabetes and family members about the prevention, recognition, and treatment of hypoglycemia is important before, during, and after pregnancy to help prevent and manage hypoglycemia risk.

Pregnancy is a ketogenic state, and people with type 1 diabetes and, to a lesser extent, those with type 2 diabetes are at risk for diabetic ketoacidosis (DKA) at lower blood glucose levels than in the nonpregnant state. Pregnant people with type 1 diabetes should be advised to obtain ketone test strips and receive education on DKA prevention and detection. DKA carries a high risk of stillbirth. Those in DKA who are unable to eat often require 10% dextrose with an insulin drip to adequately meet the higher carbohydrate demands of the placenta and fetus in the third trimester to resolve their ketosis.

Retinopathy is a special concern in pregnancy. The necessary rapid implementation of euglycemia in the setting of retinopathy

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is associated with worsening of retinopathy (126). Meta-analyses have also demonstrated a high risk of new-onset retinopathy and progression of existing retinopathy in pregnant individuals with type 1 or type 2 diabetes (32,127). Therefore, it is recommended that individuals with preexisting diabetes have dilated eye examinations before pregnancy, in each trimester of pregnancy, and for 1 year postpartum as indicated by the degree of retinopathy and as recommended by the eye care health care professional.

Recommended weight gain during pregnancy for people with overweight status is 15–25 lbs (6.8–11.3 kg) and for those with obesity is 10–20 lbs (4.5–9.1 kg) (69). There are no adequate data on optimal weight gain versus weight maintenance in pregnant people with BMI >35 kg/m^2; however, losing weight is not recommended because of the increased risk of small-for-gestational-age infants (26).

PREECLAMPSIA AND ASPIRIN

Recommendation

15.23 Pregnant individuals with type 1 or type 2 diabetes should be prescribed low-dose aspirin 100–150 mg/day starting at 12–16 weeks of gestation to lower the risk of preeclampsia. **E** A dosage of 162 mg/day may be acceptable; **E** currently, in the U.S., low-dose aspirin is available in 81-mg tablets.

Diabetes in pregnancy is associated with an increased risk of preeclampsia (128). The U.S. Preventive Services Task Force recommends that blood pressure measurements be obtained throughout gestation to screen for hypertensive disorders of pregnancy (129). The Task Force also recommends using low-dose aspirin (81 mg/day) as a preventive medication at 12 weeks of gestation in individuals at high risk for preeclampsia, such as those with type 1 or type 2 diabetes (130). However, a meta-analysis and an additional trial demonstrate that low-dose aspirin <100 mg is not effective in reducing preeclampsia, so a dose of >100 mg is required (131–133). A cost-benefit analysis has concluded that this approach would reduce morbidity, save lives, and lower health care costs (134). There are insufficient data about whether the use of aspirin specifically in pregnant people with preexisting diabetes ultimately reduces the incidence of preeclampsia (135,136), although a meta-analysis showed that preeclampsia reductions occurred with aspirin administration in high-risk groups overall (128). Individuals with GDM may be candidates for aspirin therapy for preeclampsia prevention if they have a single high-risk factor, such as chronic hypertension or an autoimmune disease, or multiple moderate risk factors, such as being nulliparous, having obesity, being age ≥35 years, or other factors per the U.S. Preventive Services Task Force (130). More studies are needed to assess the long-term effects of prenatal aspirin exposure on offspring (135).

PREGNANCY AND DRUG CONSIDERATIONS

Recommendations

15.24 In pregnant individuals with diabetes and chronic hypertension, a blood pressure threshold of 140/90 mmHg for initiation or titration of therapy is associated with better pregnancy outcomes than reserving treatment for severe hypertension, with no increase in risk of small-for-gestational-age birth weight. **A** There are limited data on the optimal lower limit, but therapy should be deintensified for blood pressure <90/60 mmHg. **E** A blood pressure goal of 110–135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension. **A**

15.25a Potentially harmful medications in pregnancy (e.g., ACE inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists) should be stopped prior to conception and avoided in sexually active individuals of childbearing potential who are not using reliable contraception. **B**

15.25b In most circumstances, lipid-lowering medications should be stopped prior to conception and avoided in sexually active individuals of childbearing potential with diabetes who are not using reliable contraception. **B** In some circumstances (familial hypercholesterolemia, prior atherosclerotic cardiovascular disease event), statin therapy may be continued when the benefits outweigh risks. **E**

In normal pregnancy, blood pressure is lower than in the nonpregnant state. The Chronic Hypertension and Pregnancy (CHAP) Trial Consortium's RCT on treatment of mild chronic hypertension during pregnancy demonstrated that a blood pressure of 140/90 mmHg, as the threshold for initiation or titration of treatment, reduces the incidence of adverse pregnancy outcomes without compromising fetal growth (137). The CHAP Consortium's study mitigates concerns about small-for-gestational-age birth weight. Attained mean ± SD blood pressure measurements in the treated versus untreated groups were systolic 129.5 ± 10.0 vs. 132.6 ± 10.1 mmHg (between-group difference −3.11 [95% CI −3.95 to 2.28]) and diastolic 79.1 ± 7.4 vs. 81.5 ± 8.0 mmHg (−2.33 [95% CI −2.97 to 0.04]), respectively (137). Individuals with diabetes had an even better composite outcome score than those without diabetes (137).

As a result of the CHAP study, ACOG issued a Practice Advisory recommending a blood pressure of 140/90 mmHg as the threshold for initiation or titration of medical therapy for chronic hypertension in pregnancy (138) rather than their previously recommended threshold of 160/110 mmHg (139).

Data from the previously published Control of Hypertension in Pregnancy Study (CHIPS) supports a blood pressure goal of 110–135/85 mmHg to reduce the risk of unmanaged maternal hypertension and minimize impaired fetal growth (139–141). The 2015 study (140) excluded pregnancies complicated by preexisting diabetes, and only 6% of participants had GDM at enrollment. There was no difference in pregnancy loss, neonatal care, or other neonatal outcomes between the groups with tighter versus less tight management of hypertension (140).

During pregnancy, treatment with ACE inhibitors and angiotensin receptor blockers is contraindicated because they may cause fetal renal dysplasia, oligohydramnios, pulmonary hypoplasia, and intrauterine growth restriction (30). A large study found that after adjusting for confounders, first-trimester ACE inhibitor exposure does not appear to be associated with congenital malformations (142). ACE inhibitors and angiotensin receptor blockers should be stopped prior to pregnancy or as soon as possible in the first trimester to avoid second- and third-trimester fetopathy (142). Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, nifedipine,

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labetalol, and clonidine. Atenolol is not recommended, but other β-blockers may be used, if necessary. Diuretic use during pregnancy is generally not recommended, although it may be used safely when prescribed at lower doses for individuals in certain circumstances (e.g., chronic kidney disease and reduced glomerular filtration rate) (143).

For most individuals, lipid-lowering medications (e.g., bempedoic acid, PCSK9 therapies, fibrates) should be stopped prior to pregnancy or at the first pregnancy visit (31). Based on available evidence, statins should also be avoided in pregnancy in most circumstances (31). The risk of teratogenicity with statins appears to be low, but data are limited (31). Statins can be considered in a shared decision-making process between pregnant people with diabetes and their health care teams, including discussion of risks and benefits in pregnant individuals at high-risk, such as those with a history of atherosclerotic cardiovascular disease or familial hypercholesterolemia (homozygous or severe heterozygous) (31). Hydrophilic statins, such as pravastatin, may be associated with less fetal harm than lipophilic statins (144). Pravastatin has been studied in multiple pregnancy trials administering therapy at various time points in gestation with the aim to reduce preeclampsia risk, and although its ability to do so is inconclusive to date, there does not appear to be increased neonatal mortality or morbidity associated with its use during gestation (31). See pregnancy and antihypertensive medications in Section 10, "Cardiovascular Disease and Risk Management," for more information on managing blood pressure in pregnancy.

POSTPARTUM CARE

Recommendations

15.26 Insulin requirements need to be evaluated and adjusted for individuals requiring insulin after delivery because insulin resistance decreases dramatically immediately postpartum. **C**

15.27 A contraceptive plan should be discussed and implemented with all people with diabetes of childbearing potential. **A**

15.28 Breastfeeding efforts are recommended for all individuals with diabetes. **A** Breastfeeding is recommended for individuals with a history of GDM for multiple benefits, **A** including a reduced risk for type 2 diabetes later in life. **B**

15.29 Postpartum care should include psychosocial assessment and support for self-care. **E**

15.30 Screen individuals with a recent history of GDM at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. **B**

15.31 Individuals with a history of GDM should have lifelong screening for the development of type 2 diabetes or prediabetes every 1–3 years. **B**

15.32 Individuals with overweight or obesity and a history of GDM found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes. **A**

Diabetes Treatment Postpartum

For individuals requiring insulin after delivery, insulin sensitivity increases dramatically with the delivery of the placenta. In one study, insulin requirements in the immediate postpartum period are roughly 34% lower than prepregnancy insulin requirements (145). Insulin sensitivity then returns to prepregnancy levels over the following 1–2 weeks. For individuals taking insulin, particular attention should be directed to hypoglycemia prevention in the setting of breastfeeding and erratic sleep and eating schedules (146). Individuals with GDM usually do not require diabetes medications in the postpartum period.

Contraception

A major barrier to effective preconception care is the fact that the majority of pregnancies are unplanned. Planning pregnancy is critical in individuals with preexisting diabetes to achieve the optimal glycemic goals necessary to prevent congenital malformations and reduce the risk of other complications. Therefore, all individuals with diabetes of childbearing potential should have family planning options reviewed at regular intervals to make sure that effective contraception is implemented and maintained. This applies to individuals in the immediate postpartum period. Individuals with diabetes have the same contraception options and recommendations as those without diabetes, although the existence of diabetes complications or other vascular disease may modify recommended options. Long-acting, reversible contraception may be ideal for individuals with diabetes and childbearing potential. The risk of an unplanned pregnancy outweighs the risk of any currently available contraception option.

Lactation

Considering the immediate nutritional and immunological benefits of breastfeeding for the baby, all mothers, including those with diabetes, should be supported in attempts to breastfeed. An analysis of 28 systematic reviews and meta-analyses of associations between breastfeeding and outcomes in children found that breastfeeding was associated with numerous health benefits for children, such as reduced infant mortality due to infectious diseases at <6 months of age (OR 0.22–0.59 across studies), reduced respiratory infections in children aged <2 years, and reduced asthma or wheezing in children aged 5–18 years (OR 0.91, 0.85–0.98) (147). The same analysis found that breastfeeding was associated with improved maternal health outcomes, including reduced risks of breast cancer (OR 0.81 [95% CI 0.77–0.86]), ovarian cancer (OR 0.70 [95% CI 0.64–0.75]), and type 2 diabetes (OR 0.68 [95% CI 0.57–0.82]). Breastfeeding may also confer longer-term metabolic benefits to both mother (148) and offspring (149). Breastfeeding reduces the risk of developing type 2 diabetes in mothers with previous GDM (148). It may improve the metabolic risk factors of offspring, but more studies are needed (150). However, lactation can increase the risk of overnight hypoglycemia, and insulin dosing may need to be adjusted.

Special Postpartum Considerations for Individuals With Gestational Diabetes Mellitus

Because GDM often represents previously undiagnosed prediabetes, type 2 diabetes, maturity-onset diabetes of the young, or even developing type 1 diabetes, individuals with GDM should be tested for persistent diabetes or prediabetes at 4–12 weeks postpartum with a fasting 75-g OGTT using nonpregnancy criteria as outlined in Section 2, "Diagnosis and Classification of Diabetes," specifically **Tables 2.1** and **2.2**. The OGTT is recommended over A1C at 4–12 weeks postpartum, because A1C may be persistently impacted (lowered) by the increased

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red blood cell turnover related to pregnancy, by blood loss at delivery, or by the preceding 3-month glucose profile. The OGTT is more sensitive at detecting glucose intolerance, including both prediabetes and diabetes, and has been examined as a screening tool for these conditions in the first 12 weeks after delivery in individuals who had a recent pregnancy with GDM (151,152). In the absence of unequivocal hyperglycemia, a positive screen for diabetes requires two abnormal values. If both the fasting plasma glucose (≥126 mg/dL [≥7.0 mmol/L]) and 2-h plasma glucose (≥200 mg/dL [≥11.1 mmol/L]) are abnormal in a single screening test, then the diagnosis of diabetes is made. If only one abnormal value in the OGTT meets diabetes criteria, the test should be repeated to confirm that the abnormality persists. OGTT testing immediately postpartum, while still hospitalized, has demonstrated improved engagement in testing but also variably reduced sensitivity to the diagnosis of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes (153,154).

Individuals with a history of GDM should have ongoing screening for prediabetes or type 2 diabetes every 1–3 years, even if results of the initial 75-g OGTT at 4–12 weeks postpartum are normal. Ongoing evaluation may be performed with any recommended glycemic test (e.g., annual A1C, annual fasting plasma glucose, or triennial 75-g OGTT using thresholds for nonpregnant individuals).

Individuals with a history of GDM have an increased lifetime maternal risk for diabetes estimated at 50–60% (155,156), and those with GDM have a 10-fold increased risk of developing type 2 diabetes compared with those without GDM (155). Absolute risk of developing type 2 diabetes after GDM increases linearly through a person's lifetime, being ∼20% at 10 years, 30% at 20 years, 40% at 30 years, 50% at 40 years, and 60% at 50 years (156). Hazard ratios for incident diabetes were significantly elevated for a history of GDM in a single pregnancy but were even higher for a history of two GDM pregnancies in a large retrospective cohort study (hazard ratios ranged from 4.35- to 15.8-fold based on number of pregnancies with GDM and in which pregnancy the individual had GDM (first or second) (157). In the prospective Nurses' Health Study II (NHS II), subsequent diabetes risk after a history of GDM was significantly lower in those who followed healthy eating patterns (158). Adjusting for BMI moderately attenuated this association. Interpregnancy weight gain is associated with increased risk of adverse pregnancy outcomes (159) and higher risk of GDM, while in people with BMI >25 kg/m^2, weight loss is associated with lower risk of developing GDM in the subsequent pregnancy (160). Development of type 2 diabetes is 18% higher per unit of BMI increase from prepregnancy BMI at follow-up, highlighting the importance of effective weight management after GDM (161). In addition, postdelivery lifestyle interventions are effective in reducing risk of type 2 diabetes (162).

Both metformin and intensive lifestyle intervention prevent or delay progression to diabetes in individuals with prediabetes and a history of GDM. Only five to six individuals with prediabetes and a history of GDM need to be treated with either intervention to prevent one case of diabetes over 3 years (163). In these individuals, lifestyle intervention and metformin reduced progression to diabetes by 35% and 40%, respectively, over 10 years compared with placebo (164). If the pregnancy has motivated the adoption of healthy nutrition, building on these gains to support weight loss is recommended in the postpartum period (see Section 3, "Prevention or Delay of Diabetes and Associated Comorbidities").

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16. Diabetes Care in the Hospital: Standards of Care in Diabetes—2025

American Diabetes Association Professional Practice Committee*

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Among hospitalized individuals, hyperglycemia, hypoglycemia, and glucose variability are associated with adverse outcomes, including increased morbidity and mortality (1). Identification and careful management of people with diabetes and dysglycemia during hospitalization has direct and immediate benefits. Diabetes management in the inpatient setting is facilitated by identification and treatment of hyperglycemia prior to elective procedures, a dedicated inpatient diabetes management service applying validated standards of care, and a proactive transition plan for outpatient diabetes care with timely scheduled follow-up appointments. These steps can improve outcomes, shorten hospital stays, and reduce the need for readmission and emergency department visits. For older hospitalized individuals or for people with diabetes in long-term care facilities, please see Section 13, "Older Adults."

HOSPITAL CARE DELIVERY STANDARDS

Recommendations

16.1 Perform an A1C test on all people with diabetes or hyperglycemia (random blood glucose >140 mg/dL [>7.8 mmol/L]) admitted to the hospital if no A1C test result is available from the prior 3 months. **B**

16.2 Institutions should implement protocols using validated written or computerized provider order entry sets for management of dysglycemia in the hospital that allow for a personalized approach. **B**

Considerations on Admission

High-quality hospital care for diabetes requires clear and actionable standards for care delivery, which are best implemented using structured order sets and quality improvement strategies for process improvement. Unfortunately, "best practice" protocols,

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reviews, and guidelines are inconsistently implemented within hospitals (2). To correct this, medical centers striving for optimal inpatient diabetes treatment should establish protocols and structured order sets, which include computerized provider order entry (CPOE). Institutions are encouraged to perform audits regularly to monitor proper use and institute educational/training programs to update staff on an ongoing basis.

Initial evaluation should state the type of diabetes (i.e., type 1, type 2, gestational, pancreatogenic, stress hyperglycemia, drug related, or nutrition related [e.g., enteral or parenteral nutrition]) when it is known. Because inpatient treatment and discharge planning are more effective when preadmission glycemia is considered, A1C should be measured for all people with diabetes or dysglycemia admitted to the hospital if no A1C test result is available from the previous 3 months (3,4). In addition, diabetes self-management knowledge and behaviors should be assessed on admission, and diabetes self-management education should be provided throughout the hospital stay, especially if a new treatment plan is being considered. Diabetes self-management education should include the knowledge and skills needed after discharge, such as medication dosing and administration, glucose monitoring, and recognition and treatment of hypoglycemia (5). Evidence supports preadmission treatment of hyperglycemia in people scheduled for elective surgery as an effective means of reducing adverse outcomes (6,7).

The National Academy of Medicine recommends CPOE to prevent medication-related errors and to increase medication administration efficiency (8). Systematic reviews of randomized controlled trials using computerized assistance to improve glycemic outcomes in the hospital found significant improvement in the percentage of time individuals spent in the glycemic goal range, lower mean blood glucose levels, and no increase in hypoglycemia (9). Where feasible, there should be structured order sets that provide computerized guidance for glycemic management. Insulin dosing algorithms using machine learning and data in the electronic health record (EHR) currently in development show promise for predicting insulin requirements during hospitalization (10,11).

Diabetes Care Specialists in the Hospital

Recommendation

16.3 When caring for hospitalized people with diabetes (with an existing or new diagnosis) or stress hyperglycemia, consult with a specialized diabetes or glucose management team when available. **B**

Care provided by appropriately trained specialists or specialty teams may reduce the length of stay and improve glycemic and other clinical outcomes (12–14). In addition, the increased risk of 30-day readmission following hospitalization that has been attributed to diabetes can be reduced, and costs saved, when inpatient care is provided by a specialized diabetes management team (12,15,16). In a cross-sectional study comparing usual care to specialists reviewing diabetes cases and making recommendations virtually through the EHR, rates of both hyperglycemia and hypoglycemia were reduced by 30–40% (17). Providing diabetes self-management education and developing a diabetes discharge plan that includes continued access to diabetes medications and supplies and ongoing education and support are key strategies to improve long-term outcomes (18,19). Details of diabetes care team composition and other resources are available from the Joint Commission accreditation program for the hospital care of diabetes, the Society of Hospital Medicine workbook, and the Joint British Diabetes Societies (JBDS) for Inpatient Care Group (20–22).

GLYCEMIC GOALS IN HOSPITALIZED ADULTS

Recommendations

16.4a Insulin should be initiated or intensified for treatment of persistent hyperglycemia starting at a threshold of ≥180 mg/dL (≥10.0 mmol/L) (confirmed on two occasions within 24 h) for the majority of critically ill individuals (those in the intensive care unit [ICU]). **A**

16.4b Insulin and/or other glucose-lowering therapies should be initiated or intensified for treatment of persistent hyperglycemia starting at a threshold of ≥180 mg/dL (≥10.0 mmol/L) (confirmed on two occasions within 24 h) for the majority of noncritically ill individuals (those not in the ICU). **B**

16.5a Once therapy is initiated, a glycemic goal of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for most critically ill individuals (those in the ICU) with hyperglycemia. **A** More stringent individualized glycemic goals may be appropriate for selected critically ill individuals if they can be achieved without significant hypoglycemia. **B**

16.5b For noncritically ill individuals (those not in the ICU), a glycemic goal of 100–180 mg/dL (5.6-10.0 mmol/L) is recommended if it can be achieved without significant hypoglycemia. **B**

Standard Definitions of Glucose Abnormalities

Hyperglycemia in hospitalized individuals is defined as blood glucose levels >140 mg/dL (>7.8 mmol/L) (23). An admission A1C value ≥6.5% (≥48 mmol/mol) suggests that the onset of diabetes preceded hospitalization (see Section 2, "Diagnosis and Classification of Diabetes"). Level 1 hypoglycemia is defined as a glucose concentration of 54–69 mg/dL (3.0–3.8 mmol/L). Level 2 hypoglycemia is defined as a glucose concentration <54 mg/dL (<3.0 mmol/L), which is typically the threshold for neuroglycopenic symptoms. Level 3 hypoglycemia is defined as a clinical event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery (**Table 6.4**) (24,25). Levels 2 and 3 require immediate intervention and correction of low blood glucose. Prompt treatment of level 1 hypoglycemia is recommended for prevention of progression to more significant level 2 and level 3 hypoglycemia.

Glycemic Goals

In a landmark clinical trial conducted in a surgical intensive care unit (ICU), Van den Berghe et al. (26) demonstrated that an intensive intravenous insulin protocol with a glycemic goal of 80–110 mg/dL (4.4–6.1 mmol/L) reduced mortality by 40% compared with a standard approach of a glycemic goal of 180–215 mg/dL (10–12 mmol/L) in critically ill hospitalized individuals with diabetes and/or stress hyperglycemia and recent surgery. This study provided evidence that active treatment to lower blood glucose in hospitalized

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individuals could have immediate benefits. However, several multicenter studies, including the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, in critically ill hospitalized individuals in medical and surgical ICUs (27–29) led to a reconsideration of the optimal glucose lowering goal in critical illness. In these trials, critically ill individuals randomized to intensive glycemic management (80–110 mg/dL [4.4–6.1 mmol/L]) derived no significant treatment advantage compared with a group with more moderate glycemic goals (140–180 mg/dL [7.8–10.0 mmol/L]) and had slightly but significantly higher mortality (27.5% vs. 25%). The intensively treated group had 10- to 15-fold greater rates of hypoglycemia, which may have contributed to the adverse outcomes noted. The findings from the NICE-SUGAR trial, supported by several meta-analyses and a randomized controlled trial, showed higher rates of hypoglycemia and an increase in mortality with more aggressive glycemic management goals compared with moderate glycemic goals (27,30,31). Based on these results, insulin and/or other therapies should be initiated for the treatment of persistent hyperglycemia ≥180 mg/dL (≥10.0 mmol/L). Once therapy is initiated, a glycemic goal of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for most critically ill individuals with hyperglycemia. Although not as well supported by data from randomized controlled trials, these recommendations have been extended to hospitalized individuals without critical illness. More stringent glycemic goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected individuals (e.g., critically ill individuals undergoing cardiac surgery) if they can be achieved without significant hypoglycemia (32,33).

For inpatient management of hyperglycemia in noncritical care settings, a glycemic goal of 100–180 mg/dL (5.6–10.0 mmol/L) is recommended, whether it is hyperglycemia due to newly diagnosed diabetes or stress hyperglycemia or hyperglycemia related to diabetes prior to admission (34). It has been found that fasting glucose levels <100 mg/dL (<5.6 mmol/L) are predictors of hypoglycemia within the next 24 h (35). Glycemic levels up to 250 mg/dL (13.9 mmol/L) may be acceptable in selected populations (terminally ill individuals with short life expectancy, advanced kidney failure [and/or on dialysis], high risk for hypoglycemia, and/or labile glycemic excursions). In these individuals, less aggressive treatment goals that would help avoid symptomatic hypoglycemia and/or hyperglycemia are often appropriate. Clinical judgment combined with ongoing assessment of clinical status, including changes in the trajectory of glucose measures, illness severity, nutritional status, or concomitant medications that might affect glucose levels (e.g., glucocorticoids), may be incorporated into the day-to-day decisions regarding treatment goals.

GLUCOSE MONITORING

In hospitalized individuals with diabetes who are eating, point-of-care (POC) blood glucose monitoring should be performed before meals; in those not eating, glucose monitoring is advised every 4–6 h (34). More frequent POC blood glucose monitoring ranging from every 30 min to every 2 h is the required standard for safe use of intravenous insulin therapy.

Hospital blood glucose monitoring should be performed with U.S. Food and Drug Administration (FDA)-approved POC hospital-calibrated glucose monitoring systems (36). POC blood glucose meters are not as accurate or as precise as laboratory glucose analyzers, and capillary blood glucose readings are subject to artifacts due to perfusion, edema, anemia/erythrocytosis, and several medications commonly used in the hospital (36) (**Table 7.1**). The FDA has established standards for capillary (finger-stick) POC glucose monitoring in the hospital (36). The balance between analytic requirements (e.g., accuracy, precision, and interference) and clinical requirements (e.g., rapidity, simplicity, and POC) has not been uniformly resolved (36–39), and most hospitals have arrived at their own policies to balance these parameters. It is critically important that devices selected for in-hospital use, and the workflow through which they are applied, undergo careful analysis of performance and reliability and ongoing quality assessments (39). Recent studies indicate that POC measures provide adequate information for usual practice, with only rare instances where care has been compromised (37,38). Best practice dictates that any glucose result that does not correlate with the individual's clinical status should be confirmed by repeating the test first and measuring a sample in the clinical laboratory if the second result is similar, particularly for asymptomatic hypoglycemic events.

Continuous Glucose Monitoring

Recommendations

16.6 In people with diabetes using a personal continuous glucose monitoring (CGM) device, the use of CGM should be continued during hospitalization if clinically appropriate, with confirmatory point-of-care (POC) blood glucose measurements for insulin dosing decisions and hypoglycemia assessment, if resources and training are available, and according to an institutional protocol. **B**

16.7 Continue use of insulin pump or automated insulin delivery in people with diabetes who are hospitalized when clinically appropriate, with confirmatory POC blood glucose measurements for insulin dosing decisions and hypoglycemia assessment and treatment. This is contingent upon availability of necessary supplies, resources, and training, ongoing competency assessments, and implementation of institutional diabetes technology protocols. **C**

Several studies have demonstrated that inpatient use of continuous glucose monitoring (CGM) has advantages over POC glucose monitoring in detecting hypoglycemia, particularly nocturnal, prolonged and/or asymptomatic hypoglycemia (40–42), and in reducing recurrent hypoglycemia (43,44). However, at this time, initiating use of a new CGM device has not been approved by the FDA. During the coronavirus disease 2019 (COVID-19) pandemic, many institutions used CGM in ICU and non-ICU settings, with the aim of minimizing exposure time and saving personal protective equipment, under an FDA policy of enforcement discretion (45,46). Data on the safety and efficacy of real-time CGM use in the hospital, particularly with implementation of remote monitoring (e.g., a glucose telemetry system), is growing (44,46–49).

Continuation of personal CGM device use, particularly for people with type 1 or type 2 diabetes treated with intensive insulin therapy and at increased risk for hypoglycemia during hospitalization, is recommended. Confirmatory POC capillary

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glucose monitoring, using hospital-calibrated glucose meters, is recommended for insulin dosing and hypoglycemia assessment (e.g., hybrid testing protocols) (42,46,50). People with diabetes should be counseled about meaningful use of trend arrows and alarms and the importance of notifying nursing staff for confirmation of these events with POC capillary glucose monitoring. Similarly, continuation of automated insulin delivery systems should be supported during hospitalization, when clinically appropriate, and with proper staff training and supervision (42,46). Observational studies have demonstrated improvements in patient satisfaction and improved detection of glycemic excursions (41,48). Consultation with the endocrinology/diabetes care team or diabetes care and education specialists, if available, is recommended, especially if the reason for admission is suspected to be related to device malfunction or lack of adequate education/training or use. Hospitals are encouraged to develop institutional policies and have the availability of trained personnel with knowledge of diabetes technology. Recent review articles provide details on accuracy, interferences, precautions, and contraindications of diabetes technology devices in the hospital setting (49,51).

For more information on CGM, see Section 7, "Diabetes Technology."

GLUCOSE-LOWERING TREATMENT IN HOSPITALIZED INDIVDIUALS

An individualized approach for glycemic management is encouraged throughout the hospital stay and should take into consideration several predictive factors for achieving glycemic goals, such as prior home use and doses of insulin or noninsulin therapy, expected level of insulin resistance, prior A1C, current glucose levels, oral intake, and duration of diabetes.

Insulin Therapy

Recommendations

16.8a Continuous intravenous insulin infusion is recommended for achieving glycemic goals and avoiding hypoglycemia in critically ill individuals. **A**

16.8b Basal insulin or a basal plus bolus correction insulin plan is the preferred treatment for noncritically ill hospitalized individuals with poor or no oral intake. **A**

16.9 An insulin plan with basal, prandial, and correction components is the preferred treatment for most noncritically ill hospitalized individuals with adequate nutritional intake. **A**

16.10 For most individuals, sole use of a correction or supplemental insulin without basal insulin (formerly referred to as a sliding scale) in the inpatient setting is discouraged. **A**

Critical Care Setting

Continuous intravenous insulin infusion is the most effective method for achieving specific glycemic goals and avoiding hypoglycemia in the critical care setting. Intravenous insulin infusions should be administered using validated written or computerized protocols that allow for predefined adjustments in the insulin infusion rate based on glycemic fluctuations and immediate past and current insulin infusion rates (52). For diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) management, continuous intravenous insulin infusion is given for correction of hyperglycemia, hyperketonemia, and acid-base disorder following a fixed-rate intravenous insulin infusion (53) or nurse-driven protocol with a variable rate based on glucose values (54). Individuals with mild and uncomplicated DKA can be managed with subcutaneous rapid-acting insulin doses given every 1–2 h (55).

Noncritical Care Setting

In most instances, insulin is the preferred treatment for hyperglycemia in hospitalized individuals. In certain circumstances, it may be appropriate to continue home oral glucose-lowering medications or initiate use of agents such as dipeptidyl peptidase 4 inhibitors (DPP-4i) (2,50). Several reports indicate that inpatient use of insulin pens is safe and may improve nurse satisfaction when safety protocols, including nursing education, are in place to guarantee single-person use (56–58).

Outside of critical care units, scheduled subcutaneous insulin orders are recommended for the management of hyperglycemia in people with diabetes and hyperglycemia. Use of insulin analogs or human insulin results in similar glycemic outcomes in the hospital setting, but regular insulin may increase the risk of hypoglycemic events (59). The use of subcutaneous rapid- or short-acting insulin before meals, or every 4–6 h if no meals are given or if the individual is receiving continuous enteral or parenteral nutrition, is indicated to correct or prevent hyperglycemia. Basal insulin, or a basal plus bolus correction schedule, is the preferred treatment for noncritically ill hospitalized individuals with inadequate or restricted oral intake. An insulin schedule with basal, prandial, and correction components is the preferred treatment for most noncritically ill hospitalized people with diabetes with adequate nutritional intake.

A randomized controlled trial has shown that basal plus bolus treatment improved glycemic outcomes and reduced hospital complications compared with a correction or supplemental insulin without basal insulin (formerly known as sliding scale) for people with type 2 diabetes admitted for general surgery (60). Prolonged use of correction or supplemental insulin without basal insulin is strongly discouraged in the inpatient setting, with the exception of that for people with type 2 diabetes in noncritical care with mild hyperglycemia or stress hyperglycemia (61,62).

A prospective randomized inpatient study of 70/30 intermediate-acting (NPH)/regular insulin mixture versus basal-bolus therapy showed comparable glycemic outcomes but significantly increased hypoglycemia in the group receiving the insulin mixture (63). Therefore, insulin mixtures such as 75/25, 70/30, or 50/50 insulins are not routinely recommended for in-hospital use.

Data on the use of glargine U-300 and degludec U-100 or U-200 in the inpatient and perioperative settings are limited. A few studies have shown that they demonstrated similar efficacy and safety compared with glargine U-100 (64–66).

Type 1 Diabetes

For people with type 1 diabetes, dosing insulin based solely on premeal glucose levels does not account for basal insulin requirements or caloric intake and increases the risk of both hypoglycemia and hyperglycemia (67). Typically, basal insulin dosing is based on body weight and expected sensitivity to insulin, and there is some evidence that people with renal insufficiency should be treated with lower insulin doses (68,69). An insulin schedule with basal and correction components is necessary for all hospitalized individuals with type 1 diabetes, even for those

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taking nothing by mouth, with the addition of prandial insulin when individuals are eating. Policies and best practice alerts in the EHR should be put in place to ensure that basal insulin (given subcutaneously, via insulin pump or by insulin infusion) is not held for people with type 1 diabetes, especially during care transitions, and that ongoing prescriber and nursing education is provided (57).

Transitioning From Intravenous to Subcutaneous Insulin

When discontinuing intravenous insulin, a transition protocol is recommended, as it is associated with less morbidity and lower costs. Subcutaneous basal insulin should be given 2 h before intravenous infusion is discontinued, with the aim of minimizing rebound hyperglycemia while the subcutaneous insulin action rises (70,71).

Emerging data from studies in people with hyperglycemia with and without DKA show that the administration of a low dose (0.15–0.3 units/kg) of basal insulin analog in addition to intravenous insulin infusion may reduce the duration of insulin infusion and length of hospital stay and prevent rebound hyperglycemia without increased risk of hypoglycemia (72–74).

For transitioning, the total daily dose of subcutaneous insulin may be calculated based on the insulin infusion rate during the prior 6–8 h when stable glycemic goals were achieved, based on prior home insulin dose, or following a weight-based approach (70). For people being transitioned to concentrated insulin (U-200, U-300, or U-500) in the inpatient setting, it is important to ensure correct dosing by using a separate insulin pen or vial for each individual and by meticulous pharmacy and nursing supervision of the dose administered (64–66,75).

Noninsulin Therapies

Recommendation

16.11 For people with type 2 diabetes hospitalized with heart failure, it is recommended that use of a sodium–glucose cotransporter 2 inhibitor be initiated or continued during hospitalization and upon discharge, if there are no contraindications and after recovery from the acute illness. **A**

The safety and efficacy of noninsulin glucose-lowering therapies in the hospital setting has recently expanded (2,50, 76–78). A randomized trial and an observational study have demonstrated the safety and efficacy of DPP-4i in specific groups of hospitalized people with diabetes (79,80). The use of DPP-4i with or without basal insulin may be a safer and simpler plan for people with mild to moderate hyperglycemia on admission (e.g., admission glucose <180–200 mg/dL), with reduced risk of hypoglycemia (2,80,81). However, the FDA states that health care professionals should consider discontinuing saxagliptin and alogliptin in people who develop heart failure (82). Data on the inpatient use of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are still mostly limited to research studies and select populations that are medically stable (77,78).

For people with type 2 diabetes hospitalized with heart failure, it is recommended that use of a sodium–glucose cotransporter 2 (SGLT2) inhibitor be initiated or continued during hospitalization and upon discharge, if there are no contraindications and after recovery from the acute illness (83,84). SGLT2 inhibitors should be avoided in cases of severe illness, in people with ketonemia or ketonuria, and during prolonged fasting and surgical procedures (85–88). Proactive adjustment of diuretic dosing is recommended during hospitalization and/or discharge, especially in collaboration with a cardiology/heart failure consult team (85–88). It is recommended that SGLT2 inhibitors should be stopped 3 days before scheduled surgeries (4 days for ertugliflozin) (89).

HYPOGLYCEMIA

Recommendations

16.12 A hypoglycemia management surveillance protocol should be adopted by all health systems. A plan for identifying, treating, and preventing hypoglycemia should be established for each individual. Episodes of hypoglycemia in the hospital should be documented in the health record and tracked to inform quality improvements. **C**

16.13 Treatment plans should be reviewed and changed as necessary to prevent hypoglycemia and recurrent hypoglycemia when a blood glucose value of <70 mg/dL (<3.9 mmol/L) is documented. **C**

People with or without diabetes may experience hypoglycemia in the hospital setting. While hypoglycemia is associated with increased mortality (90,91), in many cases, it is a marker of an underlying disease rather than the cause of fatality. However, hypoglycemia is a severe consequence of dysregulated metabolism and/or diabetes treatment, and it is imperative that it be minimized during hospitalization. Many episodes of inpatient hypoglycemia are preventable. A hypoglycemia prevention and management protocol should be adopted and implemented by each hospital or hospital system. A standardized hospital-wide, nurse-initiated hypoglycemia treatment protocol should be in place to immediately address blood glucose levels <70 mg/dL (<3.9 mmol/L) (92,93). In addition, individualized plans for preventing and treating hypoglycemia for each person should also be developed. An American Diabetes Association (ADA) consensus statement recommends that an individual's treatment plan be reviewed any time a blood glucose value of <70 mg/dL (<3.9 mmol/L) occurs, as this level often predicts subsequent level 3 hypoglycemia (94). Episodes of hypoglycemia in the hospital should be documented in the EHR and tracked (1). A key strategy is embedding hypoglycemia treatment into all insulin and insulin infusion orders.

Inpatient Hypoglycemia: Risk Factors, Treatment, and Prevention

Insulin is one of the most common medications that causes adverse events in hospitalized individuals. Errors in insulin dosing, missed doses, and/or administration errors including incorrect insulin type and/or timing of dose occur relatively frequently (95–97) and include prescriber (ordering), pharmacy (dispensing), and nursing (administration) errors. Common preventable sources of iatrogenic hypoglycemia are improper prescribing of other glucose-lowering medications and inappropriate management and follow-up of the first episode of hypoglycemia (34). Kidney failure is an important risk factor for hypoglycemia in the hospital (98), possibly as a result of decreased insulin clearance. Studies of "bundled" preventive therapies, including proactive surveillance of glycemic outliers and an interprofessional data-driven approach to glycemic management, showed that hypoglycemic episodes in the hospital could be reduced

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or prevented. Compared with baseline, studies found that hypoglycemic events decreased by 56–80% (93,99,100). The Joint Commission, a global quality improvement and patient safety in health care organization, recommends that all hypoglycemic episodes be evaluated for a root cause and the episodes be aggregated and reviewed to address systemic issues and possible solutions (21).

In addition to errors with insulin treatment, iatrogenic hypoglycemia may occur after a sudden reduction of corticosteroid dose, reduced oral intake, emesis, inappropriate timing of short- or rapid-acting insulin doses in relation to meals, reduced infusion rate of intravenous dextrose, unexpected interruption of enteral or parenteral feedings, delayed or missed blood glucose checks, and altered ability of the individual to report symptoms (101).

Recent inpatient studies show promise for CGM to alert of impending hypoglycemia, offering an opportunity to mitigate it before it happens (42,46,48). The use of personal CGM and automated insulin delivery devices, such as insulin pumps that can automatically deliver correction doses and change basal delivery rates in real time, should be supported for ongoing use during hospitalization for individuals who are capable of operating their devices safely and independently when proper oversight supervision is available. Hospitals should be encouraged to develop policies and protocols to support inpatient use of individual- and hospital-owned diabetes technology and have expert staff available for safe implementation and evaluation of continued use during the hospital stay (51). Hospital information technology teams are beginning to integrate CGM data into the EHR. The ability to download and interpret diabetes device data during hospitalization can inform insulin dosing during hospitalization and care transitions (42).

For more information on CGM, see Section 7, "Diabetes Technology."

Predicting and Preventing Hypoglycemia

In people with diabetes, it is well established that an episode of severe hypoglycemia increases the risk for a subsequent event, partly because of impaired counterregulation (102). In a study of hospitalized individuals, 84% of people who had an episode of severe hypoglycemia (defined as <40 mg/dL [<2.2 mmol/L]) had a preceding episode of hypoglycemia (<70 mg/dL [<3.9 mmol/L]) during the same admission (103). In another study of hypoglycemic episodes (defined as <50 mg/dL [<2.8 mmol/L]), 78% of individuals were taking basal insulin, with the incidence of hypoglycemia peaking between midnight and 6:00 A.M. Despite recognition of hypoglycemia, 75% of individuals did not have their dose of basal insulin changed before the next basal insulin administration (104). Several groups have developed algorithms to predict episodes of hypoglycemia in the inpatient setting (105,106). Models such as these are potentially important and, once validated for general use, could provide a valuable tool to reduce rates of hypoglycemia in the hospital. In one retrospective cohort study, a fasting blood glucose of <100 mg/dL was shown to be a predictor of next-day hypoglycemia (35).

MEDICAL NUTRITION THERAPY IN THE HOSPITAL

The goals of medical nutrition therapy in the hospital are to provide adequate calories to meet metabolic demands, optimize glycemic outcomes, address personal food preferences, and facilitate the creation of a discharge plan. The ADA does not endorse any single meal plan or specified percentages of macronutrients. Current nutrition recommendations advise individualization based on treatment goals, physiological parameters, and medication use. Controlled carbohydrate meal plans, where the amount of carbohydrate on each meal tray is calculated, are preferred by many hospitals, as they facilitate matching the prandial insulin dose to the amount of carbohydrate given (107). Orders should also indicate that the meal delivery and nutritional insulin coverage should be coordinated, as their variability often creates the possibility of hyperglycemic and hypoglycemic events (18). Some hospitals offer "meals on demand," where individuals may order meals from the menu at any time during the day. This option improves patient satisfaction but complicates glucose monitoring–insulin–meal coordination and can lead to insulin stacking if meals are too close together. Finally, if the hospital food service supports carbohydrate counting, this option should be made available to people with diabetes counting carbohydrates at home, especially people wearing insulin pumps (108,109).

SELF-MANAGEMENT IN THE HOSPITAL

Diabetes self-management in the hospital may be appropriate for select individuals who wish to continue to perform self-care while acutely ill (110–112). Candidates include children with parental supervision, adolescents, and adults who successfully perform diabetes self-management at home and whose cognitive and physical skills needed to successfully self-administer insulin and perform glucose monitoring are not compromised (5,42). In addition, they should have adequate oral intake, be proficient in carbohydrate estimation, take multiple daily insulin injections or wear insulin pumps, have stable insulin requirements, and understand sick-day management. If self-management is supported, a policy should include a requirement that people with diabetes and the care team agree on a daily basis during hospitalization that self-management is appropriate. Hospital personal medication policies may include guidance for people with diabetes who wish to take their own or hospital-dispensed insulin and noninsulin injectable medications during their hospital stay. A hospital policy for personal medication may include a pharmacy exception on a case-by-case basis as determined in consultation with the care team. Pharmacy must verify any home medication and require a prescriber order for the individual to self-administer home or hospital-dispensed medication under the supervision of the registered nurse. If an insulin pump or CGM device is worn, hospital policy and procedures delineating guidelines for wearing an insulin pump and/or CGM device should be developed according to consensus guidelines, including the changing of insulin infusion sites and CGM glucose sensors (42,113). As outlined in Recommendations 7.31 and 7.32, people with diabetes wearing diabetes devices should be supported to continue them in an inpatient setting if they are assessed and deemed competent to perform self-care and proper supervision is available.

STANDARDS FOR SPECIAL SITUATIONS

Enteral and Parenteral Feedings

For individuals receiving enteral or parenteral nutrition who require insulin,

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the insulin orders should include coverage of basal, prandial, and correctional needs (108,114,115). It is essential that people with type 1 diabetes continue to receive basal insulin even if feedings are discontinued.

Most adults receiving basal insulin should continue with their basal dose, while the insulin dose for the total daily nutritional component may be calculated as 1 unit of insulin for every 10–15 g of carbohydrate in the enteral and parenteral formulas. Commercially available cans of enteral nutrition contain variable amounts of carbohydrates and may be infused at different rates (109).

All of this must be considered when calculating insulin doses to cover the nutritional component of enteral nutrition (109). Giving NPH insulin two or three times daily (every 8 or 12 h) or regular insulin every 6 h to cover individual requirements are reasonable options. Adjustments in insulin doses should be made frequently. Correctional insulin should also be administered subcutaneously every 6 h with regular human insulin or rapid-acting insulin every 4 h. If enteral nutrition is interrupted, a dextrose infusion should be started immediately to prevent hypoglycemia and to allow time to determine more appropriate insulin doses.

For adults receiving enteral bolus feedings, approximately 1 unit of regular human insulin or rapid-acting insulin per every 10–15 g of carbohydrate should be given subcutaneously before each feeding. To mitigate any hyperglycemia, correctional insulin should be added as needed before each feeding.

In individuals receiving nocturnal tube feeding, NPH insulin administered along with the initiation of the feeding to cover this nutritional load is a reasonable approach.

For individuals receiving continuous peripheral or central parenteral nutrition, human regular insulin may be added to the solution, particularly if >20 units of correctional insulin have been required in the past 24 h. A starting dose of 1 unit of regular human insulin for every 10 g of dextrose has been recommended (1,108) and should be adjusted daily in the solution. Adding insulin to the parenteral nutrition bag is the safest way to prevent hypoglycemia if the parenteral nutrition is stopped or interrupted. Correctional insulin should be administered subcutaneously to address any hyperglycemia.

Because continuous enteral or parenteral nutrition results in a continuous postprandial state, efforts to bring blood glucose levels to below 140 mg/dL (7.8 mmol/L) substantially increase the risk of hypoglycemia in these individuals. For full enteral and parenteral feeding guidance, please refer to randomized controlled trials detailing this topic (114,116,117).

Glucocorticoid Therapy

The prevalence of consistent use of glucocorticoid therapy in hospitalized individuals can approach 10–15%, and these medications can induce hyperglycemia in 56–86% of these individuals with and without preexisting diabetes (118,119). If left untreated, this hyperglycemia increases mortality and morbidity risk, e.g., infections and cardiovascular events. Glucocorticoid type and duration of action must be considered in determining appropriate insulin treatments. Daily-ingested intermediate-acting glucocorticoids such as prednisone reach peak plasma levels in 4–6 h (120) but have pharmacologic actions that can last throughout the day. When monitored by CGM, the typical glycemic pattern for individuals treated with daily prednisone or prednisolone, administered in the morning, is characterized by normal or mild fasting hyperglycemia, with trends of increasing hyperglycemia during the afternoon, and peaking in the evening. These hyperglycemic excursions are more pronounced in individuals with type 2 diabetes than in those without diabetes (121).

For individuals treated with once- or twice-daily steroids, administering NPH insulin with prednisone or prednisolone dosing is a standard approach, aimed at matching the NPH actions with the steroid-induced hyperglycemic response. NPH may be administered in addition to daily basal-bolus insulin or in addition to oral glucose-lowering medications, depending on the type of diabetes and recent diabetes medication prior to starting steroids (122). Because NPH action peaks about 4–6 h after administration, it is recommended that it be administered concomitantly with intermediate-acting steroids (123). For long-acting glucocorticoids such as dexamethasone and multidose or continuous glucocorticoid use, long-acting basal insulin may be required to manage fasting blood glucose levels (50). For higher doses of glucocorticoids, increasing doses of prandial (if eating) and correction insulin, sometimes as much as 40–60% or more, are often needed in addition to basal insulin (124,125). A retrospective study found that increasing the ratio of insulin to steroids was positively associated with improved time in range (70–180 mg/dL [3.9–10.0 mmol/L]); however, there was an increase in hypoglycemia (118). If insulin orders are initiated, daily adjustments based on levels of glycemia and anticipated changes in type, dosages, and duration of glucocorticoids, along with POC blood glucose monitoring, are critical to reducing hypoglycemia and hyperglycemia.

Perioperative Care

It is estimated that up to 20% of individuals undergoing general surgery have diabetes, and 23–60% have prediabetes or undiagnosed diabetes. Surgical stress and counterregulatory hormone release increase the risk of hyperglycemia as well as mortality, infection, and length of stay (109,126,127). There is little data available to guide care of people with diabetes through the perioperative period. To reduce surgical risk in these individuals, some institutions (126,128,129) have A1C cutoffs for elective surgeries, and some have developed optimization programs to lower A1C prior to surgery (126,128–130).

The following approaches (126,128,130) may be considered:

1. A preoperative risk assessment should be performed for people with diabetes who are at high risk for ischemic heart disease and those with autonomic neuropathy or renal failure.
2. The A1C goal for elective surgeries should be <8% (<64.0 mmol/L) whenever possible.
3. The blood glucose goal in the perioperative period should be 100–180 mg/dL (5.6–10.0 mmol/L) (126) within 4 h of the surgery. CGM should not be used alone for glucose monitoring during surgery (129).
4. Metformin should be held on the day of surgery.
5. SGLT2 inhibitors should be discontinued 3–4 days before surgery.
6. Other oral glucose-lowering agents should be held the morning of surgery or procedure.
7. Insulin dose reductions include NPH insulin to one-half of the dose or long-acting basal insulin analogs

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to 75–80% of the dose or adjustment of insulin pump (if not in automated mode) basal rates based on the type of diabetes and clinical judgment (see Section 7, "Diabetes Technology").

8. Monitor blood glucose at least every 2–4 h while the individual takes nothing by mouth and administer short- or rapid-acting insulin as needed.
9. Stricter peioperative glycemic goals are not advised, as perioperative glycemic goals stricter than 80–180 mg/dL (4.4–10.0 mmol/L) may not improve outcomes and are associated with increased hypoglycemia (128).
10. Compared with usual dosing, a reduction of 25% of basal insulin dose given the evening before surgery is more likely to achieve perioperative blood glucose goals with a lower risk for hypoglycemia (131).
11. In individuals undergoing noncardiac general surgery, basal insulin plus premeal short- or rapid-acting insulin (basal-bolus) coverage has been associated with improved glycemic outcomes and lower rates of perioperative complications compared with the reactive, correction-only short- or rapid-acting insulin coverage alone with no basal insulin dosing (60,126).
12. There is little data on the safe use and/or influence of GLP-1 RAs on glycemia and delayed gastric emptying in the perioperative period. With increasing use of GLP-1 RA and dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA medications for diabetes and/or weight loss, there are concerns about the safety of these drugs in the perioperative period. These drugs may be associated with nausea, vomiting, and delayed gastric emptying and have the potential to increase the risk of pulmonary aspiration during general anesthesia and deep sedation. The American Society of Anesthesiologists recommends holding GLP-1 RAs on the day of the procedure or surgery for daily dose agents and for at least 7 days prior to the procedures or surgery for once-weekly dose agents (132).

Despite the safety concerns around the use of GLP-1 RA and dual GIP and GLP-1 RA drugs in the perioperative setting, there is a need for guidance for individual risk assessment and mitigation strategies. While waiting for more definitive evidence, an interprofessional and personalized approach for perioperative management of individuals taking a GLP-1 RA or a dual GIP and GLP-1 RA is suggested. Factors such as the primary indication of these medications (e.g., diabetes or weight loss), current glycemic management, type of surgery or procedure and its urgency, type of anesthesia, consideration of preoperative gastric ultrasound to quantify gastric contents, and implementation of full stomach precautions will determine an individualized approach based on clinical judgement. If worsening of glycemic outcomes due to holding a GLP-1 RA or a dual GIP and GLP-1 RA is anticipated, an alternative strategy for perioperative glycemic management (e.g., insulin) should be considered.

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

Recommendations

16.14 Manage diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) by administering intravenous fluids, insulin, and electrolytes (**Fig. 16.1**) and by closely monitoring during treatment, ensuring timely and bridged transition to maintenance subcutaneous insulin administration, and identifying and treating the precipitating cause. **A**

16.15 The discharge planning process should include education on the recognition, prevention, and management of DKA and/or HHS for all individuals affected by or at high risk for these events to prevent recurrence and readmission. **B**

There is considerable variability in the presentation of DKA and HHS, including euglycemic DKA (defined as plasma glucose levels <200 mg/dL [<11.1 mmol/L] in the presence of ketosis and metabolic acidosis), mild to moderate hyperglycemia and acidosis, or severe hyperglycemia, dehydration, and coma; therefore, individualization of treatment based on a careful clinical and laboratory assessment is needed (70,73,133,134).

Management goals include restoration of circulatory volume and tissue perfusion, resolution of ketoacidosis, and correction of electrolyte imbalance and acidosis. It is also essential to treat any correctable underlying cause of DKA, such as sepsis, myocardial infarction, or stroke. In critically ill and mentally obtunded individuals with DKA or HHS, continuous intravenous insulin is the standard of care. Successful transition from intravenous to subcutaneous insulin requires administration of basal insulin 2–4 h before the intravenous insulin is stopped to prevent recurrence of ketoacidosis and rebound hyperglycemia while the subcutaneous insulin action rises (71,133,135). Studies have reported that the administration of a low dose of basal insulin analog in addition to intravenous insulin infusion may prevent rebound hyperglycemia without increased risk of hypoglycemia (72–74,133). There is no significant difference in outcomes for intravenous human regular insulin versus subcutaneous rapid-acting analogs when combined with aggressive fluid management for treating mild or moderate DKA (136). Individuals with uncomplicated DKA may sometimes be treated with subcutaneous rapid-acting insulin analogs in the emergency department or step-down units (137). This approach may be safer and more cost-effective than treatment with intravenous insulin. If subcutaneous insulin administration is used, it is important to provide an adequate fluid replacement, frequent POC blood glucose monitoring, treatment of any concurrent infections, and appropriate follow-up to avoid recurrent DKA. Several studies have shown that the use of bicarbonate in people with DKA made no difference in the resolution of acidosis or time to discharge, and its use is generally not recommended (138). For further treatment information and in-depth review, refer to the recently updated ADA consensus report (70).

TRANSITION FROM THE HOSPITAL TO THE AMBULATORY SETTING

Recommendation

16.16 A structured discharge plan should be tailored to the individual with diabetes. **B**

A structured discharge plan tailored to the individual may reduce the length of hospital stay and readmission rates and increase satisfaction with the hospital experience (139,140). Multiple strategies are key, including diabetes self-management education prior to discharge, diabetes medication reconciliation with attention to access, and scheduled virtual

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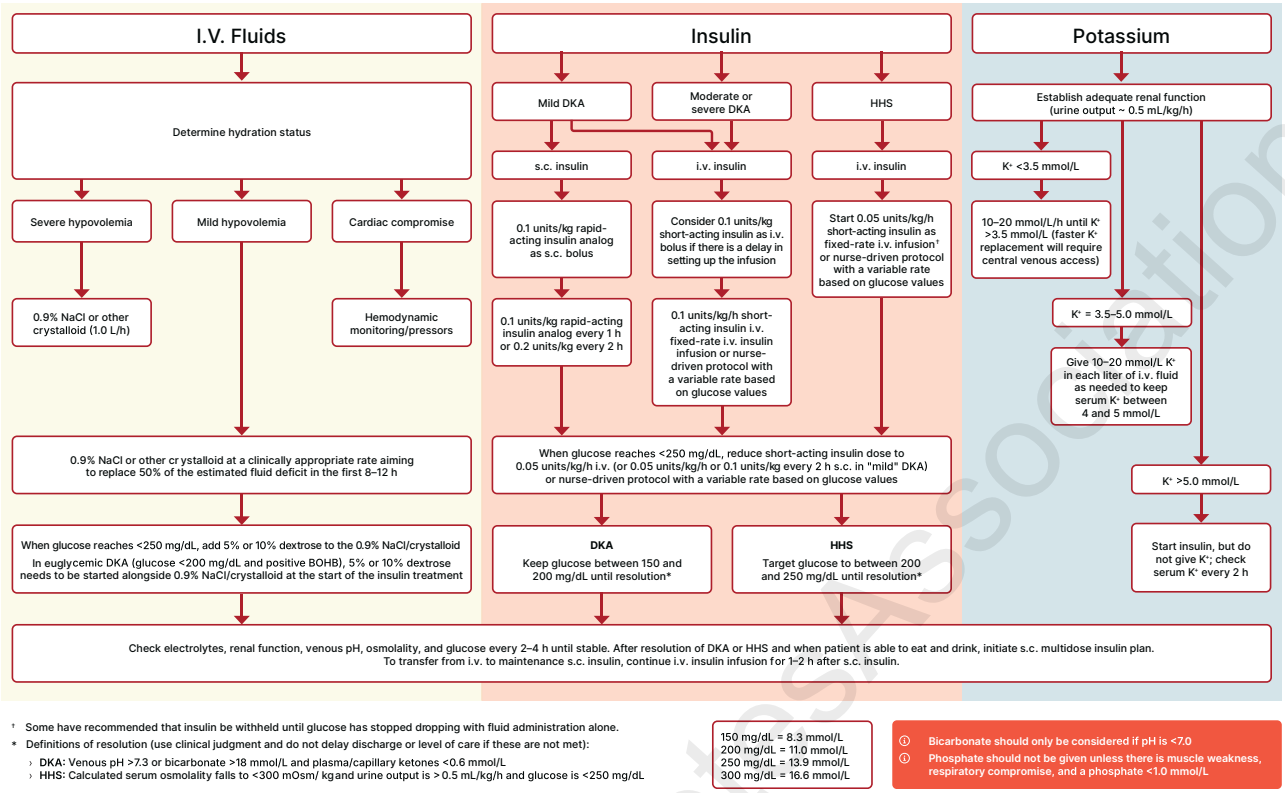

Figure 16.1—Treatment pathways for diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS). BOHB, β-hydroxybutyrate. Adapted from Umpierrez et al. (70).

and/or face-to-face follow-up visits after discharge. Discharge planning should begin at admission and be updated as individual needs change (141,142). Individualization and shared decision-making is key when creating a safe and effective discharge plan.

The transition from the acute care setting presents risks for all people with diabetes. Individuals may be discharged to varied settings, including home (with or without visiting nurse services), assisted living, rehabilitation, or skilled nursing facilities. For individuals discharged to home or assisted living, the optimal discharge plan will need to consider diabetes type and severity, effects of the illness on blood glucose levels, and the individual's circumstances, capabilities, and preferences (19,143,144). See Section 13, "Older Adults," for more information.

An outpatient follow-up visit with primary care, endocrinology, or a diabetes care and education specialist within 1 month of discharge is advised for all individuals experiencing hyperglycemia and/or hypoglycemia in the hospital. If glycemic management medications are changed or glucose management is not optimal at discharge, an earlier appointment (in 1–2 weeks) is preferred, and frequent contact to consider therapy adjustments may be needed to avoid hyperglycemia and hypoglycemia. A discharge algorithm for glycemic medication adjustment, based on admission A1C, diabetes medications before admission, and insulin usage during hospitalization was found useful to guide treatment decisions and significantly improve A1C after discharge (4).

Clear communication with outpatient health care professionals directly or via hospital discharge summaries facilitates safe transitions to outpatient care. Providing information regarding the root cause of hyperglycemia (or the plan for determining the cause), related complications and comorbidities, and recommended treatments can assist outpatient health care professionals as they assume ongoing care.

The Agency for Healthcare Research and Quality recommends that, at a minimum, discharge plans include the following (145):

Medication Reconciliation

- Home and hospital medications must be cross-checked to ensure that no chronic medications are stopped and to ensure the safety of new and old prescriptions.
- Prescriptions for new or changed medication should be filled and reviewed with the individual and care partners at or before discharge whenever possible.

Structured Discharge Communication

- Information on medication changes, pending tests and studies, and follow-up needs must be accurately and promptly communicated to outpatient health care professionals.
- Discharge summaries should be transmitted to the primary care health care professional as soon as possible after discharge.
- Scheduling follow-up appointments prior to discharge with people with diabetes agreeing to the time and place increases the likelihood that they will attend.

It is recommended that the following areas of knowledge be reviewed and addressed before hospital discharge:

- Identification of the health care professionals who will provide diabetes care after discharge.

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- Level of understanding related to the diabetes diagnosis, glucose monitoring, home glucose goals, and when to call a health care professional.
- Definition, recognition, treatment, and prevention of hyperglycemia and hypoglycemia.
- Information on choosing healthy food at home and referral to an outpatient registered dietitian nutritionist or diabetes care and education specialist to guide individualization of the meal plan, if needed.
- When and how to take blood glucose-lowering medications, including insulin administration and noninsulin injectables.
- Sick-day management (19,144).
- Proper use and disposal of diabetes supplies, e.g., insulin pens, pen needles, syringes, glucose meters, and lancets.

People with diabetes must be provided with appropriate durable medical equipment, medications, supplies (e.g., blood glucose test strips or CGM sensors), prescriptions, and appropriate education at the time of discharge to avoid a potentially dangerous hiatus in care.

PREVENTING ADMISSIONS AND READMISSIONS

In people with diabetes, the hospital readmission rate is between 14% and 20%, which is nearly twice that in people without diabetes (141,146). This may result in increased diabetes distress and has significant financial implications. Of people with diabetes who are hospitalized, 30% have two or more hospital stays, and these admissions account for over 50% of hospital costs for diabetes (147). Factors contributing to readmission include male sex, longer duration of prior hospitalization, number of previous hospitalizations, number and severity of comorbidities, and lower socioeconomic and/or educational status; factors that may reduce readmission rates include scheduled home health visits and timely ambulatory follow-up care (141,146). While there is no standardized protocol to prevent readmissions, several successful strategies have been reported that identify high-risk individuals and offer some possible solutions (141). To prevent readmissions, monitor insulin adjustments for individuals admitted with A1C >9% (>75 mmol/mol) (148) or DKA (149,150) and follow a transitional care model (151). For individuals hospitalized with severe hypoglycemia, impaired awareness of hypoglycemia, or high risk for hypoglycemia (end-stage kidney disease, intensive insulin management, frailty, etc.), consider prescribing glucagon to treat any future severe hypoglycemia events (152,153). For people with diabetes and chronic kidney disease, collaborative person-centered medical homes may decrease risk-adjusted readmission rates (154). Since recent studies have shown that use of CGM may prevent emergency department visits and hospital admission in people with type 1 and type 2 diabetes, it may be beneficial to initiate CGM just prior to discharge to facilitate follow-up and possibly prevent acute diabetes-related complications and readmission (155).

Age is also an important risk factor in hospitalization and readmission among people with diabetes (refer to Section 13, "Older Adults," for detailed criteria). Successful proactive care transitions from inpatient to outpatient is a key strategy for preventing readmission and emergency department visits.

THE FUTURE

Inpatient diabetes management is challenging for hospitals, health care professionals, and people with diabetes, as acute illness increases the risk of both hypoglycemia and hyperglycemia. The use of decision support tools and best practice advisories in the EHR has facilitated health care professionals following the recommendations in this standard of care. In addition, personal and hospital-owned diabetes devices and dosing algorithms are changing the way we provide care. Future enhancements will likely continue to improve the quality of care we deliver in hospitals and in transitions from inpatient to outpatient.

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17. Diabetes Advocacy: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, an interprofessional expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Managing the daily health demands of diabetes can be challenging. People living with diabetes should not have to face discrimination due to diabetes. By advocating for the rights of those with diabetes at all levels, the American Diabetes Association (ADA) can help to ensure that they live a healthy and productive life. A strategic goal of the ADA is for more children and adults with diabetes to live free from the burden of discrimination. The ADA is also focused on making sure cost is not a barrier to successful diabetes management.

One tactic for achieving these goals has been to implement the ADA Standards of Care through advocacy-oriented statements. The ADA publishes evidence-based, peer-reviewed statements on topics such as diabetes and employment, diabetes and driving, insulin access and affordability, and diabetes management in certain settings such as schools, childcare programs, and detention facilities. In addition to the ADA's clinical documents, these advocacy statements are important tools in educating schools, employers, licensing agencies, policymakers, and others about the intersection of diabetes management and the law and for providing scientifically supported policy recommendations.

ADVOCACY STATEMENTS

The following is a partial list of advocacy statements ordered by publication date, with the most recent statement appearing first. A comprehensive list of advocacy statements is available at professional.diabetes.org/content/key-statements-and-reports.

Diabetes Care in the School Setting

A sizable portion of a child's day is spent in school, so close communication with and training and cooperation of school personnel are essential to optimize diabetes management, safety, and access to all school-sponsored opportunities. Additionally, the updated statement further details optimal use of technologies, management of diabetes, behavioral health considerations, and guidance for diabetes care in special situations (e.g., emergency situations or clinical trial participation). Refer to the

**A complete list of members of the American Diabetes Association Professional Practice Committee can be found at https://doi.org/10.2337/dc25-SINT.*

Duality of interest information for each author is available at https://doi.org/10.2337/dc25-SDIS.

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published ADA statement for diabetes management information for students with diabetes in elementary and secondary school settings (1).

Diabetes and Driving

People with diabetes who wish to operate on-road motor vehicles are subject to various licensing requirements applied by both state and federal jurisdictions. For an overview of existing licensing rules for people with diabetes, factors that impact driving for this population, diabetes technology use, and general guidelines for assessing driver fitness and determining appropriate licensing restrictions, refer to the published ADA statement (2).

Diabetes Management in Detention Facilities

People with diabetes who are in detention facilities deserve equitable care that meets national standards. As many facilities differ and have unique challenges, written policies and procedures are essential to create a solid foundation and infrastructure for diabetes management and the training of medical and security staff. Policies should address considerations such as security needs, transfers, access to medical personnel, needed supplies and equipment, and empowering diabetes self-management. For a comprehensive discussion on these considerations, refer to the published ADA statement (3).

Care of Young Children With Diabetes in the Childcare and Community Setting

Very young children (aged <5 years) with diabetes have legal protections and can be safely cared for by childcare professionals with appropriate training, access to resources, and a communication system with parents or guardians and the child's diabetes health care professional. Refer to the published ADA advocacy statement for information on young children aged <5 years in settings such as childcare centers, preschools, camps, and other programs (4).

Insulin Access and Affordability

The ADA's Insulin Access and Affordability Working Group compiled public information and convened a series of meetings with stakeholders throughout the insulin supply chain to learn how each entity affects the cost of insulin for the consumer. Their conclusions and recommendations are published in an ADA statement (5).

Diabetes and Employment

Any person with diabetes, whether insulin treated or noninsulin treated, should be eligible for any employment for which they are otherwise qualified. Employment decisions should never be based on generalizations or stereotypes regarding the effects of diabetes. For a general set of guidelines for evaluating individuals with diabetes for employment, including how an assessment should be performed and what changes (accommodations) in the workplace may be needed for an individual with diabetes, refer to the published ADA statement (6).

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Committee members disclosed the following financial or other dualities of interest covering the period 12 months before December 2024

Member	Employment	Research grant	Other research support	Speakers bureau and honoraria	Ownership interest	Consultant and advisory board	Other
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*≥$10,000 per year from company to individual. #Grant or contract is to university or other employer. §Nuha A. ElSayed and Raveendhara R. Bannuru are also part of the American Diabetes Association Scientific Team. †Robert A. Gabbay is former American Diabetes Association staff. ‡Roeland J.W. Middelbeek is now employed by Novo Nordisk, and all of his work on the guidelines was completed prior to his position start date.

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