HHS Public Access

Author manuscript

Endocr Pract. Author manuscript; available in PMC 2023 May 21.

Published in final edited form as:

Endocr Pract. 2022 October ; 28(10): 923–1049. doi:10.1016/j.eprac.2022.08.002.

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Disclaimer: American Association of Clinical Endocrinology clinical practice guidelines include systematically developed recommendations to assist health care professionals in medical decision-making for specific clinical conditions. Most of the content herein is based on scientific evidence. In areas of uncertainty, or when clarification is required, expert opinion and professional judgment were applied.

This guideline is a working document that reflects the state of the field at the time of publication. Since rapid changes in this area are expected, periodic revisions are inevitable. We encourage health care professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision(s) by health care professionals to apply the recommendations provided in this guideline, including prescribing of any medications, must be made in consideration of the recommendations presented, the most recently published prescribing information for medications, local resources, and individual patient circumstances.

Disclosures and Conflicts of Interest Policy

The Task Force was empaneled in accordance with AACE's Conflict of Interest (COI) Policy and approved by the AACE COI Subcommittee. All members of the expert Task Force completed AACE's disclosure form regarding any multiplicities of interests related to commercial and direct financial relationships within the preceding 12 months with companies that develop products connected with endocrine disorders. Categories for disclosure include employment, stock or other ownership, direct financial relationships (eg, speaker or consultant), research funding, authorship or panel involvement on a guideline related to an overlapping topic, or other situations related to a perceived COI. The AACE COI Subcommittee reviewed these disclosures against an AACE-approved list of affected companies for this guideline and reached consensus regarding members who could serve on the Task Force in the nonconflicted majority, those who could serve in the conflicted minority with management strategy, and those who were disqualified from serving on the Task Force. The AACE CPG Oversight Committee reviewed and approved the AACE COI Subcommittee's decisions regarding manageable COI and empanelment. Members of this Task Force were reminded to update potential disclosures if new potential conflicts arose during their appointments and to verifycurrency of disclosures. AACE made every effort to minimize the potential for conflicts of interest that could influence the recommendations of this CPG.

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Panel Composition

The Task Force was empaneled in accordance with AACE's COI Policy. This evidence-based CPG was developed by a group of credentialed medical professionals in the fields of endocrinology, cardiology, neurology, nephrology, obstetrics and gynecology, ophthalmology, and pediatrics, and a methodologic specialist.

Guideline: Developing a Diabetes Mellitus Comprehensive Care Pland—2022 Update

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Review Process

Drafts of this guideline were reviewed and approved by all task force members, the AACE CPG Oversight Committee, the AACE Board of Directors, and peer reviewers for *Endocrine Practice*.

Updating Policy

AACE reviews and updates or retires its evidence-based guidelines every 3 to 5 years or after significant scientific developments or change in public policy as determined by the AACE executive leadership, AACE CPG Oversight Committee, and relevant AACE Disease-State Network.

Document Expiration Date: October 2025

References are followed by an evidence level [EL] rating of 1, 2, 3, or 4. See Supplementary Table 1 for additional information about evidence level ratings. References with an “a” suffix denote late-breaking or supplementary references.

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Abstract

Objective: The objective of this clinical practice guideline is to provide updated and new evidence-based recommendations for the comprehensive care of persons with diabetes mellitus to clinicians, diabetes-care teams, other health care professionals and stakeholders, and individuals with diabetes and their caregivers.

Methods: The American Association of Clinical Endocrinology selected a task force of medical experts and staff who updated and assessed clinical questions and recommendations from the prior 2015 version of this guideline and conducted literature searches for relevant scientific papers published from January 1, 2015, through May 15, 2022. Selected studies from results of literature searches composed the evidence base to update 2015 recommendations as well as to develop new recommendations based on review of clinical evidence, current practice, expertise, and consensus, according to established American Association of Clinical Endocrinology protocol for guideline development.

Results: This guideline includes 170 updated and new evidence-based clinical practice recommendations for the comprehensive care of persons with diabetes. Recommendations are divided into four sections: (1) screening, diagnosis, glycemic targets, and glycemic monitoring; (2) comorbidities and complications, including obesity and management with lifestyle, nutrition, and bariatric surgery, hypertension, dyslipidemia, retinopathy, neuropathy, diabetic kidney disease, and cardiovascular disease; (3) management of prediabetes, type 2 diabetes with antihyperglycemic pharmacotherapy and glycemic targets, type 1 diabetes with insulin therapy, hypoglycemia, hospitalized persons, and women with diabetes in pregnancy; (4) education and new topics regarding diabetes and infertility, nutritional supplements, secondary diabetes, social determinants of health, and virtual care, as well as updated recommendations on cancer risk, nonpharmacologic components of pediatric care plans, depression, education and team approach, occupational risk, role of sleep medicine, and vaccinations in persons with diabetes.

Conclusions: This updated clinical practice guideline provides evidence-based recommendations to assist with person-centered, team-based clinical decision-making to improve the care of persons with diabetes mellitus.

Lay Abstract

Advances in medications and tools to monitor blood sugar are helping persons with diabetes greatly improve control of their blood sugar levels, excess weight, high blood pressure, and quality of life. This American Association of Clinical Endocrinology guideline provides recommendations for the diagnosis and treatment of persons with prediabetes and diabetes and its prevention.

Care of persons with prediabetes and diabetes includes change in lifestyle with a focus on sleep, healthy eating, and exercise. Reaching goals for blood sugar, blood pressure, fats like cholesterol, and weight can prevent harm from diabetes to eyes, kidneys, heart, and nervous system. Many newer, safer drugs control blood sugar and reduce risk of heart and kidney disease. Some drugs also lower cholesterol and weight. Ways to check blood sugar levels with fingersticks or sensors placed under the skin (continuous glucose monitors) have improved, making it easier and safer for persons with diabetes to avoid both low and high blood sugars.

A team approach helps people best manage diabetes. The individual with diabetes is the center of the team and should help make decisions together with their doctors. In addition to doctors, the team may include educators, nurses, dietitians, pharmacists, foot doctors, psychologists, and other specialists.

This guideline addresses other topics of interest to those living with or at risk for diabetes such as health care visits by computer or phone, access to care, management of diabetes at work, sleep disorders, depression, infertility, risk of cancer, safety of nutritional supplements, and benefits of vaccines. Also included are specific care and treatment needs of pregnant women and those who are hospitalized.

The American Association of Clinical Endocrinology hopes that this guideline will improve the management of diabetes and benefit all who live with prediabetes or diabetes and their caregivers.

Keywords

antihyperglycemic medications; atherosclerotic cardiovascular disease; cardiovascular diseases; diabetes; gestational; diabetes mellitus; diabetes mellitus, type 1; diabetes mellitus, type 2; diabetic nephropathies; diabetic neuropathies; diabetic retinopathy; dyslipidemias; guideline; hospitalization; hypertension; hypoglycemia; infertility; interdisciplinary communication; metabolic syndrome; obesity; occupations; prediabetic state; pregnancy; secondary diabetes; sleep apnea syndromes; telemedicine; vaccination

Introduction

This 2022 update of the American Association of Clinical Endocrinology (AACE) Clinical Practice Guideline: Developing a Comprehensive Diabetes Mellitus Care Plan includes revised and new recommendations for clinical practice based on evidence published since the previous edition of this clinical practice guideline (CPG) in 2015.[1] This updated CPG provides evidence-based guidance to assist clinicians, diabetes-care teams, investigators,

educators, and other health care professionals and stakeholders with decision-making in practice to improve prevention, diagnosis, and treatment of persons with diabetes mellitus (DM). Unless otherwise specified, persons with DM applies to adults.

The task force evaluated a vast pool of literature to revise, update, and create recommendations based on relevant new evidence of the highest quality that reflects advances in the diagnosis and management of DM with available new monitoring methods and therapies. Evidence from recent cardiovascular (CV) outcome trials (CVOTs); diabetic kidney disease (DKD), chronic kidney disease (CKD), and heart failure (HF) trials; and studies of antihyperglycemic therapy, diabetes technology, management of hypertension, neuropathy, hypoglycemia, obesity, obesity medications, and antihyperglycemic medications that also can produce significant weight reduction for the majority of those with DM who also are overweight have informed this guideline. Goals for treatment emphasize individualized targets for weight loss, glucose, lipids, and blood pressure (BP). In addition, this guideline promotes personalized management of DM with a focus on safety and advocates for a comprehensive approach to management of DM based on current evidence. Although glycemic control parameters such as hemoglobin A1c (A1C), postprandial glucose (PPG) excursions, fasting plasma glucose (FPG), continuous glucose monitoring (CGM) readings of time in/below/above range, and glycemic variability have an impact on risk of microvascular complications and CV disease (CVD), mortality, quality of life (QoL), and other factors also affect clinical outcomes in persons with DM. Therefore, in addition to glycemic control, recommendations consider micro- and macrovascular risk, including CV risk factors such as dyslipidemia, hypertension, and obesity.

Methods

The AACE CPG Oversight Committee confirmed the extent of new literature and the AACE Board of Directors approved development of this update of the 2015 AACE CPG to develop a comprehensive plan for the care of persons with DM in adherence to the 2017 AACE Protocol for Standardized Production of Clinical Practice Guidelines (Supplementary Tables 1–4).[1,2] AACE followed a rigorous developmental process based on strict methodology to systematically collect, objectively evaluate, and clearly summarize available scientific literature to develop trustworthy recommendations for clinical practice regarding care of persons with DM.

A methodologist conducted comprehensive literature searches in PubMed using medical subject headings, field descriptions, and free-text terms to identify all possible studies that included human participants and were published in English between January 1, 2015, and May 15, 2022. Bibliographies of select articles were also reviewed to ensure inclusion of all possibly relevant studies. The literature searches, examination of reference lists from primary and review articles, and identification of online sources yielded an evidence pool of 11,606 discrete potential references, of which 1871 citations—1840 articles (including late-breaking/supplementary articles) and 31 web links—were included to support this guideline's recommendations and background information.

At least 2 task force authors screened titles and abstracts of broad pools of evidence found in literature searches for each topic and submitted decisions to include or exclude each article along with rationale for exclusion. Disagreements about inclusion among reviewers were resolved by consensus with task force chairs and team leaders. Through this process, authors conducted a thorough appraisal of evidence based on the full scope of available literature to determine studies that best support each recommendation.

AACE methodologist and staff assigned evidence levels (ELs) 1 to 4 and study types to included studies according to established AACE evidence ratings (Supplementary Table 1). The task force considered the quality of each article in addition to ELs and study types to inform assigned grades for recommendations, which reflect the confidence and strength of evidence in aggregate (Supplementary Table 2 and 3). Recommendation qualifiers and subjective factors also informed the overall grade assigned to each recommendation (Supplementary Table 4). For some issues related to clinical practice and the care of persons with DM, there is little evidence of high quality available. Where the task force determined guidance to be necessary despite a lack of available supporting literature, a recommendation was developed based on expert opinion and consensus of task force authors' collective experience, knowledge, and judgment. Therefore, although randomized controlled trials (RCTs) and meta-analyses of these trials (rated the highest EL 1) support many recommendations, derivative EL 4 publications that include other primary evidence (rated EL 1, EL 2, and EL 3) are sometimes also cited. This CPG is intended to complement other previously published AACE DM-related guidelines and consensus statements as well as other organizations' DM-related guidance.

Questions related to clinical practice provide the framework for this guideline with answers in the form of recommendations. Task force authors revised prior questions where necessary and submitted contributions for new questions, which were integrated into the final document. This CPG includes 31 questions that cover the spectrum of DM management and 170 actionable clinical practice recommendations that provide brief, evidence-based answers to each question. Evidence bases summarize clinical context with a brief discussion of the best available scientific literature to support recommendations that answer corresponding questions. Although recommendations are concise and actionable, the evidence base for each specific topic provides additional information that explains the guidance for best clinical practice.

Table 1 lists all revised and new questions. Table 2 provides a summary of all questions and recommendations. Table 3 lists all tables, figures, and supplementary tables.

Task force authors discussed each recommendation in this updated CPG to achieve consensus regarding actionable language and grades of recommendations. Task force chairs and team leaders provided oversight throughout the entire development process. Semantic descriptors of "must," "should," and "may" generally but not strictly correlate with Grade A (strong), Grade B (intermediate), and Grade C (weak) recommendations, respectively; each semantic descriptor can be used with Grade D (no conclusive evidence and/or expert opinion) recommendations.[2] Deviations from this mapping take into consideration further decision-making based on clinical expertise. Thus, the process leading to a final

recommendation and grade was not rigid and incorporated expert discussion of objective and subjective factors that reflect optimal real-life clinical decision-making to enhance care of persons with DM whose individual circumstances and presentations differ. Ultimate clinical management is based on a combination of the best interest and input of each person with DM and reasonable clinical judgment of clinicians and diabetes care teams.

Limitations of the Literature

In the continually expanding and rapidly evolving literature on DM, there is significant heterogeneity among studies, including but not limited to differences in study design, comparators, and outcomes, as well as age, duration of DM, and other characteristics of participants. Many RCTs have employed an open-label design with potential bias or implemented a crossover design with an inherent limitation because the order of treatments may affect outcomes. Many well-designed studies are sponsored to some degree by industry, posing another challenge to interpretation, even though coordinating academic centers may have collected and analyzed data independently of sponsors. Recognizing these limitations, grading of the evidence base was informed by trial design, potential generalizability, risks, harms, and benefits.

Key Updates

- **Section 1, Screening, diagnosis, glycemic targets, and glycemic monitoring:** Screening criteria for the diagnosis of DM along with glycemic targets have been refreshed for 2022. Incorporation of advances in CGM has been strongly recommended in insulin-treated persons with type 1 diabetes (T1D) and type 2 diabetes (T2D).
- **Section 2, Management of comorbidities, including obesity and its management with lifestyle, nutrition, and bariatric surgery; hypertension; dyslipidemia; and complications: retinopathy, neuropathy, DKD or CKD in DM, and CVD:** Recognizing the importance of an individualized approach, person-centric recommendations for management of hypertension and dyslipidemia in those with DM have been updated. The importance of weight management throughout the natural history of DM has been stressed throughout the document. Recommendations on the prevention and management of retinopathy, neuropathy, and DKD or CKD in DM have been refreshed with consideration of the most recent advances. For those with DM and comorbidity of CVD or at high risk for CVD, the focus has shifted to the utility of antihyperglycemic agents and their impact on improving CV outcomes in those with atherosclerotic CV disease (ASCVD), HF, and/or with cerebrovascular disease.
- **Section 3, Management of prediabetes, T2D, and T1D with selection of glycemic targets, lifestyle interventions, antihyperglycemic pharmacotherapy (insulin therapy for all with T1D and select individuals with T2D); prevention, identification, and treatment of hypoglycemia; treatment of hospitalized persons with DM or those with hyperglycemia**

without diagnosis of DM; and women with GDM: Recommendations on identifying persons with prediabetes and incorporating validated approaches to prevention of DM and CV complications are included. In addition to a person's social and medical scenarios, other factors suchas hypoglycemia, weight gain/loss, CVoutcomes, kidney outcomes, and adverse events have been considered in the most appropriate therapeutic choices. When appropriate and safe, emphasis on early combination therapy and early titration to combination of complementary pharmacotherapies is encouraged.

- **Section 4, Education and new topics regarding DM and infertility, nutritional supplements, posttransplantation, secondary diabetes, social determinants of health (SDOH), and virtual care, as well as updated recommendations on cancer risk, nonpharmacologic components of pediatric plans, depression, education and team approach, occupational risk, role of sleep medicine, and vaccinations in persons with DM:** Common questions confronting clinicians in caring for those with DM are addressed in this section. Educational approaches and delivery of telehealth/virtual care, with recent studies of new platforms, are reviewed. Akin to pharmacologic therapies, no one approach is ideal for every individual with DM. Evidence-based recommendations are provided to approach male and female infertility, posttransplant diabetes, and secondary diabetes. Recommendations on topics that impact QoL such as sleep hygiene, depression, SDOH, and type of occupation are also included. During their care, persons with DM often ask about nutritional supplements and risk of cancer due to their condition or to their antihyperglycemic medications, which led to inclusion of several pragmatic safety-oriented recommendations. Finally, the use of vaccinations is recommended to maintain public health as well as to mitigate specific higher risks among those with DM.

Recommendations and Evidence Bases

Section 1: Screening, Diagnosis, Glycemic Targets, and Glycemic Monitoring

Question 1. How is the diagnosis of DM made and what is the current screening protocol for prediabetes and diabetes?

Recommendation 1.1: The diagnosis of DM is based on the following criteria (Table 4):

- FPG concentration 126 mg/dL (after 8 hours of an overnight fast), *or*
- Plasma glucose (PG) concentration 200 mg/dL 2 hours after ingesting a 75-g oral glucose load after an overnight fast of at least 8 hours, *or*
- Symptoms of hyperglycemia (eg, polyuria, polydipsia, polyphagia) and a random (nonfasting) PG concentration ≥200 mg/dL, *or*
- A1C level ≥6.5%

Diagnosis of DM requires 2 abnormal test results, either from the same sample or 2 abnormal results on samples drawn on different days. However, a glucose level ≥200 mg/dL in the presence of symptoms for DM confirms the diagnosis of DM.

Grade A; BEL 2 and expert opinion of task force

Recommendation 1.2: Prediabetes is identified by the presence of impaired fasting glucose (IFG) (100 to 125 mg/dL), impaired glucose tolerance (IGT), which is a PG value of 140 to 199 mg/dL 2 hours after ingesting 75 g of glucose, and/or A1C value between 5.7% and 6.4% (Table 4). A1C should be used only for screening for prediabetes. The diagnosis of prediabetes, which may manifest as either IFG or IGT, should be confirmed with glucose testing.

Grade B; BEL 2

Recommendation 1.3: T1D is characterized by marked insulin deficiency in the presence of hyperglycemia and positive autoantibody tests to glutamic acid decarboxylase (GAD65), pancreatic islet b cells (tyrosine phosphatase IA-2), and IA-2b zinc transporter (ZnT8), and/or insulin. The presence of immune markers and clinical presentation are needed to establish the correct diagnosis and to distinguish between T1D and T2D in children or adults, as well as to determine appropriate treatment.

Grade A; BEL 2

Recommendation 1.4: T2D is characterized by progressive loss of b-cell insulin secretion and variable defects in insulin sensitivity. T2D is often asymptomatic and can remain undiagnosed for many years; therefore, all adults 35 years of age with risk factors should be screened for DM (Table 5).

Grade A; BEL 1

Recommendation 1.5: GDM is defined as carbohydrate intolerance that begins or is first recognized during pregnancy and resolves postpartum. Pregnant women with risk factors for DM should be screened at the first prenatal visit for undiagnosed T2D using standard criteria (Table 4).

Grade B; BEL 1

Recommendation 1.6: Screen all pregnant women for GDM at 24 to 28 weeks' gestation. Diagnose GDM with either the one-step or the two-step approach.

- The one-step approach uses a 2-hour 75-g oral glucose tolerance test (OGTT) after ≥8 hours of fasting with diagnostic cutoffs of one or more FPG ≥92 mg/dL, 1-hour PG ≥180 mg/dL, or 2-hour PG ≥153 mg/dL.
- The two-step approach uses a nonfasting 1-hour 50-g glucose challenge test with 1-hour PG screening threshold of 130 or 140 mg/dL. For women with a positive screening test, the 3-hour 100-g OGTT is used for diagnosis with 2 or more PG

tests that meet the following thresholds: FPG ≥95 mg/dL, 1-hour ≥180 mg/dL, 2-hour ≥155 mg/dL, 3-hour ≥140 mg/dL.

Grade A; BEL 1

Recommendation 1.7: Clinicians should consider evaluation for monogenic DM in any child or young adult with an atypical presentation, clinical course, or response to therapy. Monogenic DM includes neonatal diabetes and nonautoimmune diabetes of multiple genetic causes, also known as maturity-onset diabetes of the young (MODY). Most children with DM occurring under age 6 months of age have a monogenic cause as autoimmune T1D rarely occurs before 6 months of age. Other monogenic forms of diabetes are characterized by mutation of genes of transcription factors, genes regulating pancreatic development or atrophy, abnormal insulin genes, genes related to endoplasmic reticulum stress that impair insulin secretion, or abnormal glucokinase genes that cause impaired insulin signaling.

Grade B; BEL 2

Evidence Base 1: How is the diagnosis of DM made and what is the current screening protocol for prediabetes and DM?

Diagnosis of DM—DM refers to a group of metabolic disorders that result in hyperglycemia, regardless of the underlying etiology. DM is diagnosed by using any of 3 established criteria for elevated blood glucose (BG) concentrations (Table 4). FPG ≥126 mg/dL, 2-hour PG ≥ 200 mg/dL during 75-g OGTT, and A1C ≥ 6.5% are equally appropriate for diagnostic screening (Table 4). The concordance between FPG, 2-hour PG, and A1C is not perfect; thus, the diagnosis of DM requires 2 different (fasting glucose and A1C) abnormal test results, either from the same sample or 2 abnormal results on samples drawn on different days.[3-5] A glucose level ≥200 mg/dL in the presence of hyperglycemia symptoms such as polyuria and polydipsia confirm the diagnosis of DM.[6] In individuals with discordant results from 2 different tests, the test result that is above the diagnostic cut point should be repeated on a different day.[4]

The A1C captures chronic hyperglycemia and is the gold standard for assessment of long-term glycemic control and risk of chronic micro- and macrovascular complications; however, analyses of the fidelity of DM diagnosis using A1C have reported a lower sensitivity than FPG or 2-hour OGTT.[4,5,7-10] A1C is known to be affected by nonglycemic factors such as changes in red blood cell maturity and survival and impaired renal function. A1C levels may be 0.4% to 0.6% higher in Blacks and Hispanics compared with Whites, despite equivalent levels of hyperglycemia in those with T2D.[11-17] In view of physiological changes in pregnancy that could affect glycated hemoglobin levels, A1C should not be used for GDM screening or diagnosis of DM.[18,19]

Classification of DM—DM is classified as T1D, T2D, GDM, monogenic DM, and other less common conditions, such as diabetes related to pancreatic disease, drug-induced, or rare insulin resistance and mitochondrial syndromes.[9,20,21] T1D accounts for 5% to 10% of all DM cases and occurs more commonly in children and young adults but can occur at any age. It is also more common in persons of European ancestry and is caused by

absolute insulin deficiency that usually results from an immune-mediated destruction of the pancreatic b cells. The presence or absence of autoimmune markers (autoantibodies to glutamic acid decarboxylase [GAD65], pancreatic islet b cells [tyrosine phosphatase IA-2], and IA-2b zinc transporter [ZnT8], and/or insulin) in addition to the clinical presentation may help establish the correct diagnosis to distinguish between T1D and T2D in children or adults.[22–27] Over 90% of newly diagnosed persons with T1D have 1 or more antibodies. The presence of >2 antibodies in a relative without diabetes of a person with T1D is highly predictive of developing T1D within 5 years. However, some forms of T1D have no evidence of autoimmunity and have been termed idiopathic. The clinical presentation and rate of b-cell destruction progression is variable, with higher rates of ketosis in children and slower progression in older adults. In some individuals with T1D in adulthood, the clinical presentation may follow a more indolent course (termed latent autoimmune diabetes in adults) with slower decline in b-cell insulin secretion. Many of these individuals are initially misdiagnosed as having T2D until the progression of insulin deficiency leads to insulin dependence.

Severe insulinopenia in T1D predisposes persons to diabetic ketoacidosis (DKA). However, DKA can also occur in persons with T2D.[28–31] Worldwide epidemiological studies have reported that between 13% and 80% of individuals with T1D present with DKA. The percentage of adults with T2D who present with DKA at diagnosis is unknown; however, the number of people with ketosis-prone or atypical T2D has increased. Ketosis-prone T2D most frequently occurs among Blacks of African ancestry or persons who identify as Afro-Caribbean or Hispanic. In contrast to the long-term insulin requirement of autoimmune T1D, many persons with ketosis-prone T2D can discontinue insulin after a few months of therapy and maintain acceptable glycemic control for many years on either diet or noninsulin therapies. At presentation, persons with ketosis-prone T2D have significant impairment of both insulin secretion and insulin action; however, at the time of near-normoglycemia remission, insulin secretion and action improve to levels similar to hyperglycemic persons with ketosis-resistant T2D.

T2D is considered a polygenic condition with considerable heterogeneity in degrees of insulin deficiency and resistance and accounts for >90% of all cases of DM.[32] Most persons with T2D are overweight or obese and have multiple risk factors for DM (Table 5). Insulin resistance and concurrent relative insulin deficiency and glucagon dysregulation underlie T2D pathophysiology.[33–35] The Centers for Disease Control and Prevention (CDC) has reported a higher prevalence of diagnosed DM in African Americans, Hispanic Americans, and other persons of non-European origin compared with European Americans.[36,37] T2D remains undiagnosed for years in many affected persons because they are frequently asymptomatic; therefore, screening individuals with multiple risk factors is needed to reduce the risk of long-term complications.[38,39] Up to 25% of persons with T2D have already developed at least 1 microvascular complication by the time of diagnosis.[40,41]

Monogenic diabetes accounts for 1% to 3% of DM diagnosed under 30 years of age (~0.4% of all DM) and frequently occurs in pubertal children or young adults <35 years of age. Many, but not all, will have a family history over 3 generations.[42–47] Monogenic diabetes includes neonatal diabetes, MODY, and diabetes associated with a variety of syndromes,

including mitochondrial disorders, lipodystrophy syndromes, Wolfram syndrome, and many others. Because most types of MODY are autosomal dominant disorders, affected people have a 50% chance of passing along the gene mutation to their children. There are 14 genes that have been implicated as causes of MODY accounting for 11 different types of MODY.[48,49] Establishing the correct diagnosis is important as appropriate treatment varies with the type of gene defect. MODY 2 can usually be managed with diet alone, while sulfonylurea (SU) therapy may be effective in MODY 1, 3, and 4.

Other causes of DM include diseases of the exocrine pancreas including (but not limited to) pancreatitis, trauma, cystic fibrosis, neoplastic disease, posttransplant diabetes, and iron deposition in hemochromatosis. Endocrine disorders including Cushing syndrome, acromegaly, glucagonoma, and pheochromocytoma can induce insulin resistance and T2D. Hyperglycemia may also be associated with the use of certain medications. Beyond the well-known agents (glucocorticoids, nicotinic acid, thiazides, interferon gamma, high-dose statins), agents such as atypical antipsychotics, immune checkpoint inhibitors, PI3 kinase inhibitors, tacrolimus, and octreotide have been shown to induce DM. Pathogenesis can be multifactorial with management depending on the severity of hyperglycemia. Careful follow-up for progression or regression of DM is necessary.

Screening and Diagnosis of GDM—All pregnant women should be screened for GDM at 24 to 28 weeks' gestation. Universal screening is recommended, as selective screening (only in women with risk factors) would miss a significant number of women with GDM and universal screening has been shown to be cost-effective compared with selective screening.[9,50–55] Children born to women with GDM have increased incidence of childhood adiposity and development of IGT in children aged 10 to 14 years compared with children born to mothers without GDM.[56,57]

GDM can be diagnosed with either the one-step or the two-step approach using the OGTT.[58] The one-step approach consists of the 2-hour 75-g load oral glucose load after an overnight fast to diagnose GDM as recommended by the International Association for Diabetes and Pregnancy Study Groups criteria.[9,52,54,55,59–63] The criteria for GDM are fasting glucose level ≥92 mg/dL, 1-hour postglucose challenge value ≥180 mg/dL, or 2-hour value ≥153 mg/dL. These criteria are based on trials such as the Hyperglycemia and Pregnancy Outcomes (HAPO) study.[59,64] The International Association for Diabetes and Pregnancy Study Groups criteria result in overall higher percentages of women diagnosed with GDM. Until recently, there were no large RCTs comparing the effect of one-step and two-step approaches on maternal and neonatal outcomes. An RCT performed at the Kaiser Permanente health systems in California and Hawaii examined the one-step (75 g) and the two-step (50 g) sequential approach on neonatal and gestational outcomes.[65] The study randomized 23,792 women to either the one-step or two-step approach. The diagnosis of GDM was twice as high in the one-step group compared with the two-step group (16.5% vs 8.5%). However, there were no differences in neonatal or maternal outcomes between the 2 approaches.[65] The higher diagnosis of GDM in the one-step approach can lead to more resource utilization for subsequent maternal treatment and fetal monitoring.[55,59,66] It should be noted that only 66% of the women randomized to the one-step approach adhered to the screening, whereas 92% of the women randomized to the two-step approach

adhered to the assigned screening process. With the two-step sequential screening approach using a nonfasting 1-hour 50-g glucose challenge test between 24- and 28-weeks' gestation, screening cutoffs are 130 mg/dL (90% sensitivity) or 140 mg/dL (80% sensitivity).[67] For women with a positive screening test, the 3-hour 100-g OGTT following 8 or more hours of no caloric intake, GDM is diagnosed if 2 or more PG values meet or exceed the following thresholds: fasting level of 95 mg/dL, 1-hour level of ≥180 mg/dL, 2-hour level of ≥155 mg/dL, or 3-hour level of ≥140 mg/dL.[68]

Question 2. What are the glycemic treatment goals for persons with DM?

2.1 Outpatient Glucose Targets for Nonpregnant Adults

Recommendation 2.1.1: An A1C level of ≤6.5% is recommended for most nonpregnant adults, if it can be achieved safely. To achieve this target A1C level, FPG may need to be <110 mg/dL, and the 2-hour PPG may need to be <140 mg/dL (Table 6). Glucose targets should be individualized with consideration for life expectancy, disease duration, presence or absence of micro- and macrovascular complications, CVD risk factors, comorbid conditions, and risk for hypoglycemia, as well as a person's cognitive and psychological status.

Grade A; BEL 1

Recommendation 2.1.2: Adopt less stringent glycemic goals (A1C 7% to 8%) in persons with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced renal disease, extensive comorbid conditions, or long-standing DM in which the A1C goal has been difficult to attain despite intensive efforts, so long as the person remains free of hyperglycemia-associated symptoms.

Grade A; BEL 1

2.2 Inpatient Glucose Targets for Nonpregnant Adults

Recommendation 2.2: For most hospitalized persons with hyperglycemia in both the intensive care unit (ICU) and non-ICU settings, a glucose range of 140 to 180 mg/dL is recommended, provided this target can be safely achieved (Table 6).

Grade A; BEL 1

2.3 Outpatient Glucose Targets for Pregnant Women

Recommendation 2.3: In women with GDM, the following glucose goals are recommended: fasting and PPG concentration ≤95 mg/dL and either a 1-hour postmeal glucose value ≤140 mg/dL or a 2-hour postmeal glucose value ≤120 mg/dL.

In women with preexisting T1D or T2D who become pregnant, it is recommended that glucose be controlled to meet the following goals, but only if the goals can be safely achieved: premeal, bedtime, and overnight glucose values between 60 and 95 mg/dL; a 1-hour PPG value between 110 and 140 mg/dL; a 2-hour glucose 100 to 120 mg/dL. A secondary target would be an A1C level of <6% if it can be accomplished without significant hypoglycemia.

Grade A; BEL 1

Evidence Base 2.1: Outpatient Glucose Targets for Nonpregnant Adults

There is no dispute that elevated glucose levels are associated with micro- and macrovascular complications of DM. Similarly, it has been accepted that strategies aimed at lowering glucose concentrations can lead to lower rates of microvascular and perhaps macroangiopathic complications.[69] Significant reductions in the risk or progression of nephropathy were seen in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, which targeted an A1C <6.5% in the intensive therapy group vs standard approaches.[70] Landmark trials near the turn of the 21st century confirmed that intensive approach to control was not necessarily associated with reduced CVD complication rates.[71] Duration of DM and preexisting ASCVD appeared to negate the benefit of improved glycemic control. This data derived from older clinical trials, relying on therapies associated with hypoglycemia, must be interpreted in the context of recent positive CVOTs with 3 new classes of medications not associated with hypoglycemia. The newer classes of antihyperglycemic agents appear to be either neutral (dipeptidyl peptidase 4 [DPP-4] inhibitors) or successful (glucagon-like peptide-1 receptor agonist [GLP-1 RA] or a sodium glucose cotransporter 2 inhibitor [SGLT2i]) in lowering the risk of CVD complications in those with T2D.

Epidemiologic evidence shows a continuous relationship between A1C and CVD and all-cause mortality.[72]

No RCTs have yet established optimal glycemic targets in persons with T2D. Professional organizations have relied on results from existing intervention trials achieving improved A1C levels and epidemiologic analyses of various studies to arrive at consensus statements or expert opinions regarding targets. Thus, some have recommended a general target A1C level 6.5%, while others have recommended a general target of <7%.[73–75] The potential risks of intensive glycemic control may be obviated by incorporating agents that are not associated with hypoglycemia, especially in persons with frequent severe hypoglycemia, hypoglycemia unawareness, or a very long duration of DM, and particularly in the presence of established and advanced atherosclerosis, advanced age, and terminal illness.[69,70,76–81]

Moreover, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, mortality increased with increasing A1C among intensively treated persons, with excess mortality only affecting persons whose A1C remained >7%.[82] Similar U-shaped curves were found in a 7-year observational study of persons with T1D and a 22-year observational study of >20,000 persons with T2D.[83,84] A corollary of this issue is the safety of those therapies in view of the demonstrated increase of frequency of severe hypoglycemia during attempts at intensive glycemic control.[70,76,80,85,86] As discussed in **Q14. How should hypoglycemia be managed?,** much of the mortality in the ACCORD trial may have been related to hypoglycemia, and the hazard ratio (HR) for hypoglycemia-associated deaths was actually higher in the standard treatment than the intensive therapy groups.[87]

As discussed in **Q12. How can glycemic targets be achieved in persons with T2D?** as well as in the AACE Comprehensive Type 2 Diabetes Management Algorithm,[73] some

newer therapies carry a lower risk of hypoglycemia, which may enable more persons to safely achieve individualized target A1C levels.[69,88–90] In addition, for persons with established ASCVD or multiple ASCVD risk factors, HF, or CKD, a GLP-1 RA or an SGLT2i with demonstrated CVD benefit is recommended as part of a glucose-lowering regimen independent of A1C. In such persons, GLP-1 RA and SGLT2is have been shown to have beneficial CVD benefits as well as benefits on indices of CKD (see **Q12. How can glycemic targets be achieved in persons with T2D?**).

Evidence Base 2.2: Inpatient Glucose Targets for Nonpregnant Adults

Inpatient hyperglycemia is associated with increased complications including surgical site infections, mortality, and increased length of hospital stay.[91–93] The level of hyperglycemia at which complications occur is debated. In the surgical ICU, earlier studies have indicated that intensive glucose control (80 to 110 mg/dL) inconsistently resulted in decreased length of stay.[94–96] The Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation study showed that more aggressive glucose targets of 81 to 108 mg/dL compared with a conventional glucose target (<180 mg/dL) in the ICU did not change length of stay, number of days needing mechanical ventilation, or need for renal replacement therapy.[95] However, the intensively controlled group had increased mortality and higher rates of hypoglycemia.[95,97] Lower levels of glycosylated hemoglobin in patients undergoing cardiac surgery are associated with a lower risk of early and late mortality, as well as in the incidence of postoperative acute kidney injury (AKI), neurologic complications, and wound infections.[98,99]

Further, the history of DM makes a difference as to whether postoperative complications occur. Those without preexisting DM or stress hyperglycemia have a higher incidence of more postheart surgery complications.[91,100–103] Intensive glycemic control post-operatively, compared to less intensive targets, has resulted in equivocal or mixed results; however, other studies have shown no benefits.[94,100,101,104] Intensive targets result in hypoglycemia, which, in turn, results in higher complications.[105,106] Therefore, we recommend a glucose target of 140 to 180 mg/dL in the ICU setting. More intensive targets can be used (110 to 140 mg/dL) if they can be achieved without hypoglycemia.

It is unclear whether the targets for the ICU should be the same in the non-ICU setting. Overall, studies have shown that treatment including a basal insulin regimen resulted in better glycemic control compared with sliding-scale insulin alone.[92,107–109] The better glycemic control resulted in improvements in rates of postsurgical complications.[92] Most studies of inpatient DM have treated to goal glucose levels 110 to 140 or 140 to 180 mg/dL. Large multicenter studies are needed to assess which glycemic targets predict complications while avoiding hypoglycemia. With CGM being used more frequently in the inpatient setting, lower targets may be achieved while avoiding hypoglycemia.

Evidence Base 2.3: Outpatient Glucose Targets for Pregnant Women

Elevated BG levels at conception and during the early first trimester are associated with increased rates of congenital malformations, spontaneous abortion, intrauterine fetal demise, pre-eclampsia, preterm delivery, and perinatal mortality.[110–114] Therefore, preconception

counseling is essential for women with T1D and T2D to minimize pregnancy risks. The goals of preconception care should be tight glycemic control with an A1C <6.5%, without significant hypoglycemia, which will lower risks of congenital malformations, preeclampsia, and perinatal mortality.[113]

The HAPO study showed that increasing glycemia is associated with increased neonatal adverse outcomes such as macrosomia, neonatal hypoglycemia, and cesarean delivery.[64,115–119]

The targets for glycemic control during pregnancy for women with preexisting DM and GDM are based on the physiology of nondiabetic pregnancies. The A1C target of <6% is recommended as A1C ≥6% in the second and third trimesters was associated with macrosomia in persons with T1D in the Diabetes and Pre-Eclampsia Intervention Trial.[120] Further, during pregnancy, A1C is reduced in women without GDM compared with nonpregnant women.[121] One observational study in Australia in women with GDM examined the impact of reference glucose control (fasting glucose <98 mg/dL [5.5 mmol/L], 2-hour postprandial <126 mg/dL [7 mmol/L]) or tight glucose control (fasting <90 mg/dL [5 mmol/L], 2-hour PPG <120 mg/dL [6.7 mmol/L]) on neonatal outcomes.[115] The study showed no difference in birthweights with the different glycemic targets. However, women with tighter glycemic control had higher adverse maternal outcomes such as increased cesarean section rates. There is an ongoing RCT (TARGET) that will assess the effect of tight glycemic control on both perinatal and maternal outcomes.[116] In women with preexisting DM and GDM, postprandial rather than preprandial glucose levels were associated with better neonatal and maternal outcomes.[117,122] Therefore, we suggest checking PPG levels in addition to fasting glucose and to target 2-hour BG of <120 mg/dL and a 1-hour BG <140 mg/dL, as there are no RCTs at the moment to inform us as to the best glycemic target.

CGM may help women achieve glucose goals and reduce hypoglycemia during pregnancy. Use of CGM can accurately identify glycemic patterns among pregnant women with DM. Data from RCTs on the effects of CGM use on maternal and fetal outcomes are limited and results are inconsistent. The CONCEPTT study's participants were randomly assigned to either CGM in addition to capillary glucose monitoring or capillary glucose monitoring alone and showed a modest reduction in A1C levels, increased time in target, reduced hyperglycemia, and less glycemic variability.[123] There was also lower incidence of large for gestational age (odds ratio [OR], 0.51; 95% CI, 0$28–0.90; $P = .0210$), fewer neonatal intensive care admissions lasting more than 24 hours (0.48; 95% CI, 0.26–0.86; $P = .0157$), fewer incidences of neonatal hypoglycemia (0.45; 95% CI, 0.22–0.89; $P = .0250$), and 1-day shorter length of hospital stay ($P = .0091$) in women with T1D on multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII). Improved glycemic control may result in improved neonatal health outcomes attributed to reduced exposure to maternal hyperglycemia. Some studies of CGM have included women with T1D and T2D and were performed with intermittently scanned CGM (isCGM) or blinded CGM, which did not show differences in neonatal outcomes.[124,125]

The use of CGM in women with GDM is limited. Some observational cohort studies that reported that the use of CGM resulted in lower mean glucose, lower standard deviation, and a higher percentage of time in target range were associated with lower risk of large-for-gestational-age births and other adverse neonatal outcomes.[126,127] Although the available evidence is not strong to support use of CGM in pregnant women with T2D and GDM for maternal or neonatal benefits, it may be used in select persons who are at risk for hypoglycemia, especially those treated with insulin. With improving CGM technology, increased acceptability by pregnant women with DM is anticipated.

Question 3: When and how should glucose monitoring be used?

Recommendation 3.1—A1C should be measured at least semiannually in all persons with DM and at least quarterly in persons not at their glycemic target.

Grade B; BEL 2

Recommendation 3.2—All persons who use insulin should use CGM or perform BG monitoring (BGM) a minimum of twice daily and ideally before any insulin injection. More frequent BGM may be needed by persons who are taking multiple insulin injections, persons not at A1C targets, or those with history of hypoglycemia. Persons who do not require insulin or insulin secretagogue therapy may often benefit from BGM, especially to provide feedback about the effects of their lifestyle choices (diet and physical activity), and to assess response to pharmacologic therapy.

Grade A; BEL 1

Recommendation 3.3—Real-time CGM (rtCGM) or isCGM is recommended for all persons with T1D, regardless of insulin delivery system, to improve A1C levels and to reduce the risk for hypoglycemia and DKA.

Grade A; BEL 1

Recommendation 3.4—rtCGM or isCGM is recommended for persons with T2D who are treated with insulin therapy or who have high risk for hypoglycemia and/or with hypoglycemia unawareness.

Grade A; BEL 1

Evidence Base 3: When and how should glucose monitoring be used?

Current glucose monitoring strategies can be classified into 2 categories: patient self-monitoring, which would allow individuals to change behavior (diet and/or exercise) or medication dose (most often insulin), and long-term assessment, which allows both the person with DM and the clinician to evaluate overall glucose control and risk for complications over weeks or months. Current forms of self-monitoring include BGM and CGM, whereas long-term assessment is most often by A1C. A1C is considered the current gold standard for monitoring chronic hyperglycemia and provides an indication of the average of BG levels over the previous 3 months. It is associated with the risk for the

development of long-term complications. However, A1C does not inform individuals about BG values on a daily basis; therefore, frequent measurements of BG levels are necessary for the day-to-day management of DM.

Glycated hemoglobin is quantified most commonly with methods that distinguish it from nonglycated hemoglobin on the basis of either charge (cation-exchange chromatography, electrophoresis, isoelectric focusing) or structural characteristics (affinity chromatography, immunoassays). A1C reflects average glycemia over the lifespan of the red blood cell (100 to 120 days), but 50% of A1C is determined by glycemia during the month preceding measurement. A1C is the metric used in clinical trials to assess the benefits of improved glycemic control.[128] The frequency of A1C testing should depend on the clinical situation and treatment regimen. A1C should be measured at least twice yearly in all persons with DM and at least quarterly in persons not at target.[129]

Currently, 99% of laboratories in the United States use a standardized and certified assay traced to the Diabetes Control and Complications Trial.[4,130] More recently, using CGM, each level of A1C was measured as “estimated average glucose.”[131] There are numerous populations in which A1C may not reflect average glucose.[132,133] These reasons can include changes in erythrocyte survival time (eg, hemolysis, splenomegaly, or use of epoetin alfa), alterations in the hemoglobin molecule (hemoglobinopathies), iron status, or recent blood transfusion.[4,14,134] Renal failure also results in a different A1C level than would be seen in those with normal kidney function.[135] In numerous cohorts and in national data, it has been shown that Blacks have higher A1C values than Whites in both the presence and absence of DM.[12,13,133,136] Hispanic Americans have values of A1C that are intermediate between Blacks and Whites.[136]

Current glucose meters perform rapid tests with small blood volumes and are easily operated by laypersons with DM in the outpatient setting.[137] They are equipped with a variety of features, ranging from storing results of glucose tests performed to simple pattern analysis, audible reporting of results, and wireless connectivity to smartphones. The Institutional Organization for Standardization specifies requirements for in vitro glucose monitoring systems that measure capillary BG for specific design verification procedures and for the validation of self-measurement performance by laypersons with DM.[138–140] The 2013 Institutional Organization for Standardization 15 197 standard for glucose meter accuracy is stricter than the 2003 version. The standard requires that 95% of values fall within ±15 mg/dL for glucose <100 mg/dL and within ±15% at ≥100 mg/dL.[140,141] In addition, at least 99% of pooled results shall fall within zones A and B of the consensus error grid.[140,141]

Frequency of BGM (in a retrospective analysis) has been shown to be predictive of A1C levels.[142–146] In persons who are not using insulin, regular BGM did not result in significant differences in glycemic control.[147–150] Use of structured BGM data to adjust medications is associated with greater A1C decreases than unstructured BGM.[151,152]

CGM has emerged as a standard of care for persons with DM who are treated with intensive insulin therapy. The indication for using new technologies and CGM for the management of DM was reported in the 2021 AACE Clinical Practice Guideline: The Use of Advanced

Technology in the Management of Persons with Diabetes Mellitus.[153] Based on the results of multiple studies reporting a strong linear relationship between percent time in range (TIR) (70–180 mg/dL) and A1C in persons with T1D and T2D, AACE recommends 2 metrics, percent TIR (>70%) and percent time below range (<70 mg/dL [<4%] and <54 mg/dL [<1%]), to be used as a starting point for the assessment of quality of glycemic control and as the basis for therapy adjustment.[154,155] The primary goal for effective and safe glucose management is to reduce the percent time below range while increasing the percent TIR. These recommendations align with recent reports from other national and international organizations.[129]

The clinical efficacy of CGM has been demonstrated in numerous retrospective studies and RCTs of individuals with T1D regardless of insulin delivery method.[156–161] Benefits of CGM in this population include reductions in A1C, fewer severe hypoglycemia events in children and adults, increased TIR, as well as significant reductions in hospitalizations for severe hypoglycemia and DKA.[156,162–168] There is emerging evidence that CGM is efficacious in reducing hyperglycemia and A1C levels in insulin-treated persons with T2D, including those taking 1 or 2 doses of basal insulin.[169–172]

CGM has also been shown to be effective in reducing incidence of severe hypoglycemia in individuals with T1D and T2D who are treated with intensive insulin therapy.[173] In addition, CGM use has been reported to reduce fear of hypoglycemia and increase confidence in avoiding/treating hypoglycemia.[156,174,175] Adherence to monitoring and treatment is the greatest predictor of glycemic control in persons with DM.[159,176–178]

Recent recommendations in CGM technology that provide guidance for clinicians, researchers, and individuals with DM to utilize are shown in Table 6.[179]

Section 2: Comorbidities and Complications

Question 4: How should hypertension be managed in persons with DM?

Recommendation 4.1—The recommended BP goal for most persons with T1D, T2D, or prediabetes is <130/80 mm Hg (Table 7).

Grade A; BEL 1

Recommendation 4.2—Therapeutic lifestyle interventions in persons with hypertension are recommended to include consultation with a registered dietitian for education about an overall healthy diet (such as the Mediterranean diet), weight management, reduced sodium intake (such as the Dietary Approaches to Stop Hypertension [DASH] diet), daily physical activity and regular exercise (several times a week), and as-needed consultation with a psychologist or certified diabetes care and education specialist (CDCES) to support long-term behavior change. (See also **R 11.2 to 11.4** and **R 12.1.1 to 12.1.5** on nutrition and lifestyle.)

Grade A; BEL 1

Recommendation 4.3—If BP goals are unattained with therapeutic lifestyle changes, use antihypertensive pharmacotherapy to achieve individual BP treatment goals.

Grade A; BEL 1

Recommendation 4.4—Select antihypertensive agents based on their ability to reduce BP to goal and prevent or slow the progression of micro- and macrovascular disease. Use either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) for BP control and to delay the progression of DKD or CKD in DM (see also **R 6.1 to R 6.6** on DKD or CKD in DM).

Grade A; BEL 1

Recommendation 4.5—Intensify pharmacotherapy as needed to achieve BP goals. Antihypertensive therapy may include combinations of either an ACE inhibitor or an ARB plus any of the following agents: diuretics, calcium channel antagonists, combined alpha-beta blockers, and newer-generation beta blockers. Consider a mineralocorticoid receptor antagonist for resistant hypertension.

Grade A; BEL 1

Evidence Base 4: How should hypertension be managed in persons with DM?

The majority of individuals with DM either have elevated BP or are receiving treatment for hypertension.[180] Hypertension is not only more prevalent in persons with T2D than in the general population, but hypertension also predicts progression to T2D. Once diagnosed with hypertension, an individual is 2.5 times more likely to be diagnosed with T2D within the next 5 years.[181,182] The combination of hypertension and T2D magnifies the risk of DM-related complications.[183,184] The UK Prospective Diabetes Study (UKPDS) demonstrated that hypertension treatment decreased both micro- and macrovascular complications of T2D.[185] This study showed that each 10 mm Hg decrease in systolic BP (achieved with either an ACE inhibitor [captopril] or a beta blocker [atenolol]) was associated with a 15% reduction in DM-related mortality, an 11% reduction in myocardial infarction (MI), and a 13% reduction in the microvascular complications of retinopathy or DKD.[186]

Subsequent trials that included large numbers of persons with T2D, including the Hypertension Optimal Treatment study, the Heart Outcomes Prevention Evaluation study, the Losartan Intervention for Endpoint Reduction in Hypertension study, the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, and the ADVANCE trial, have demonstrated that BP control improves CV outcomes when more intensive BP targets are set.[187–191] Numerous other studies have also demonstrated decreased DKD/CKD and retinopathy progression.[192–194] Based on these data, the Eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, AACE, American Diabetes Association (ADA), National Kidney Foundation-Kidney Disease Outcomes Quality Initiative, and American Heart Association (AHA) have recommended that BP in persons with T2D be controlled to <130/80 mm Hg.[195–199] However, the preferred goal for BP lowering remains controversial as clinical

trial data to support the level of <130/80 mm Hg are limited. Epidemiologic data suggest no evidence of a threshold for adverse outcomes with a BP level <115/75 mm Hg.[200] Clinical trial data show that intensifying therapy with BP-lowering medications slows the progression of DKD and retinopathy, though vigilance in monitoring renal function during intensive BP therapy is recommended.[185,186,201–203] Neither the ACCORD BP trial nor subanalyses of other large BP trials have shown that targeting a systolic BP <120 mm Hg (compared with <140 mm Hg) reduces risk of the composite outcome of fatal and nonfatal major CV events in persons with T2D, although stroke was significantly reduced (HR, 0.59; 95% CI, 0.39–0.89; $P = .01$).[204–206] Thus, data from prospective RCTs have not found an overall positive effect of BP targets <120/70 mm Hg on CV or renal outcomes in persons with T2D.[207,208] Various guidelines from different professional organizations have generally recommended a BP goal for persons with T2D of <130/80 mm Hg, with an option to individualize to the lower target of <120/70 mm Hg based on extrapolation from the Systolic Blood Pressure Intervention Trial in persons with hypertension without T2D.[199,209–213]

Once the diagnosis of hypertension is established, lowering BP decreases the risk of both micro- and macrovascular complications associated with T2D. Therapeutic lifestyle goals in persons with hypertension and T2D should include education about a healthy diet (such as the Mediterranean diet) with emphasis on weight management and reduced salt intake (such as the DASH diet), daily physical activity and regular exercise (several times a week) (also see the section on weight-loss therapy and lifestyle in Evidence Base 10).[214–220] Individuals should be referred to a registered dietitian for diet education and as needed to a psychologist or CDCES to support long-term behavior change. Cognitive behavioral therapy can be used to support adherence to medications.[221–225]

Analysis of the UKPDS data suggests that BP lowering should be a priority in managing a person presenting with newly diagnosed hypertension and DM. Although glucose and lipid management remain important, BP lowering may have an additive and significant impact on morbidity and mortality, particularly in persons with standard vs intensive glycemic control.[185,201,202,226,227]

Accurate measurement of BP is fundamental to diagnosis and effective management of hypertension.[210,211,228] The equipment, which can be aneroid, mercury, or electronic, should be inspected and validated on a regular maintenance schedule. Initial training and regularly scheduled retraining in the standardized technique for BP measurement provides consistency and reliability of BP readings. Individuals must be properly prepared and positioned to obtain an accurate BP; serial BP readings are recommended to be measured after being seated quietly for at least 5 minutes in a chair (rather than on an exam table) with feet on the floor and arm supported at heart level. Caffeine, exercise, and smoking should be avoided for at least 30 minutes prior to measurement. Measurement of BP in the standing position is also indicated in persons suspected to have postural hypotension. An appropriately sized cuff (ie, cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. At least 2, and preferably 3, serial measurements should be obtained, and the average BP recorded.

The use of 24-hour ambulatory BP monitoring (ABPM) is not currently included as part of the diagnostic criteria for hypertension, though it is an important tool for guiding management.[211,228] Persons whose 24-hour ABPM mean BP exceeds 135/85 mm Hg are nearly twice as likely to have a CV event as those with values that remain <135/85 mm Hg, irrespective of the level of the office BP.[229] Routine use of ABPM may be considered for the evaluation of white-coat hypertension, masked hypertension, and nighttime nondipping status, all of which are associated with increased long-term morbidity and mortality.[230] ABPM provides a longer assessment of a person's BP variability and may be utilized to guide BP management to facilitate medication adjustments and to avoid overtreatment.

BP goals are based upon evidence from clinical trials and should be individualized for persons with consideration of their anticipated lifespan and risk factors for heart disease, stroke, and DKD. The recommended BP goal for persons with T2D is <130/80 mm Hg based upon best available evidence-based data.[183,226,227,231–235] In the presence of multiple CVD risk factors, consideration may be given for a more intensive BP goal of <120/70 mm Hg, provided it can be attained safely. A less intense individualized goal >130/80 mm Hg may be considered in persons who are older and frail, or who have complicated comorbidities of T2D to include autonomic neuropathy and orthostatic hypotension, acute coronary syndromes (acute MI or hospitalization with unstable angina), or medication intolerance.[236,237] Frequent reassessment is needed to ensure that the BP goal is maintained without adverse effects of pharmacotherapy. If unacceptable side effects develop, consideration should be given to reducing dosage and/or changing the class of medication while intensifying therapeutic lifestyle changes.[215,216,219] If such changes do not alleviate symptoms, then consideration should be given to relaxing the target to a higher BP goal based upon individual characteristics, preferences, and priorities (Table 7).

The UKPDS group performed a 10-year posttrial monitoring observational study that demonstrated a loss of benefit within 2 years if tight BP control was not maintained.[201] These data reinforce the imperative to initiate BP-lowering therapy at diagnosis, to intensify treatment as needed to reach and maintain BP goal, and to monitor treatment safety and tolerance for enhanced compliance. The introduction of fixed-dose combination tablets combining 2 or 3 agents in 1 pill can facilitate compliance and adherence. The use of multiple fixed-dose combination pills can provide multiple-drug regimens with a reduced number of tablets and may help optimize adherence to reach BP goal.[238]

The selection of medications to lower BP in persons with T2D should be guided by individual-specific considerations and may include nontraditional BP-lowering agents such as SGLT2is and GLP-1 RAs, though these drugs alone may be inadequate to control BP.[239–244] Clinical trials with diuretics, ACE inhibitors, ARBs, alpha-adrenergic blockers, and calcium channel antagonists have a demonstrated benefit in the treatment of hypertension in both T1D and T2D.[187–189,210,245,246] The choice of pharmacologic agents is guided by additional considerations such as the presence of CKD, CVD, HF, or post-MI status; possible metabolic side effects; number of pills per day; and cost. During the course of T2D, an early primary goal is BP control to reduce risk of onset and progression of micro- and macrovascular disease, to include DKD and retinopathy.[191]

There appears to be inertia to treat residual hypertension in persons with T2D, and pharmacotherapy should be intensified when needed to achieve BP goals.[247–251] ACE inhibitors or ARBs are indicated as pharmacotherapy for BP control and to delay the progression of CKD.[252–254] They also have reported advantage over other treatments in reducing the risk of new-onset T2D in elderly persons.[255] Thiazide diuretics can effectively lower BP in persons aged 65 years and older, though low-dose hydrochlorothiazide can negatively impact fasting BG, A1C, and high-density lipoprotein cholesterol (HDL-C).[250,256,257] ACE inhibitors and ARBs should not be used together and should be used with caution with spironolactone to avoid hyperkalemia or AKI.[258,259]

BP control reduces the risk of stroke and major CVD events in persons with T2D.[208,227] As heart disease develops, consideration of CV benefits factor into the choice of agents to lower BP. Given that diastolic heart disease develops early in T2D and the renin-angiotensin-aldosterone system (RAAS) plays a critical role in the pathophysiology of HF, the use of an ACE inhibitor or ARBs could be considered early in the treatment of hypertension, before the diagnosis of HF.[260,261] However, the combination of multiple RAAS blockers (ie, ACE inhibitor, ARB, and/or renin inhibitor) should be avoided due to risk of hyperkalemia and AKI.[262,263]

Resistant hypertension is defined as BP ≥140/90 mm Hg in the presence of ≥3 antihypertensive agents at maximum tolerated doses, one of which is a diuretic.[264] The initial assessment should include adherence to lifestyle recommendations, the antihypertensive drug regimen, and assessment for white-coat hypertension. Secondary causes of hypertension should be ruled out when suspected. The addition of a mineralocorticoid receptor antagonist should be considered for management of resistant hypertension in persons with T2D; however, monitoring for hyperkalemia and kidney function is necessary in those taking an ACE inhibitor or ARB.[265]

Question 5: How should dyslipidemia be managed in persons with DM?

Recommendation 5.1—All persons with prediabetes, T1D over the age of 40, or T2D should have a lipid panel (fasting or nonfasting) checked at diagnosis and annually to assess CV and metabolic disease risks and at additional intervals as needed to monitor treatment to achieve lipid goals.

Grade B; BEL 2

Recommendation 5.2—Therapeutic lifestyle interventions for dyslipidemia are recommended for all persons with prediabetes, T1D over the age of 40, or T2D, to include education with a registered dietitian about a healthy diet with emphasis on weight management, daily physical activity, and regular exercise (several times a week). Consultation with a psychologist or CDCES is recommended to support long-term behavior change.

Grade A; BEL 1

Recommendation 5.3—Persons with prediabetes or T2D without ASCVD and with less than 2 traditional risk factors should be assessed with the aid of ASCVD risk calculators to determine initiation and intensity of lipid-lowering therapy (Fig. 1 and Table 8).

Grade A; BEL 1

Recommendation 5.4—Assess nontraditional ASCVD risk factors (Fig. 1) beyond a lipid panel to guide management when the initial shared decision is not self-evident.

Grade B; BEL 2

Recommendation 5.5—Manage persons with prediabetes and persons with T1D over the age of 40 in the same manner as those with T2D.

Grade A; BEL 1

Recommendation 5.6—In persons with high ASCVD risk, use a moderate-intensity statin regardless of DM type or status. In persons with very high ASCVD risk (T2D with 2 or more additional traditional ASCVD risk factors such as advancing age, hypertension, CKD stage 3a, cigarette smoking, family history of premature ASCVD in men <55 years and women <65 years, low HDL-C, or high non-HDL-C), use a high-intensity statin regardless of baseline low-density lipoprotein cholesterol (LDL-C) level. For persons at extreme risk of ASCVD event (current ASCVD or target organ damage), use a high-intensity statin plus other therapies as needed to achieve lipid targets (Fig. 1 and Table 10).

Grade A; BEL 1

Recommendation 5.7—Treatment targets for persons in a high ASCVD risk category are LDL-C <100 mg/dL, apolipoprotein B (apo B) <90 mg/dL, and non-HDL-C <130 mg/dL. Treatment targets for persons in a very high risk ASCVD category are LDL-C <70 mg/dL, apo B <80 mg/dL, and non-HDL-C <100 mg/dL. Treatment targets for persons with extreme risk of ASCVD include LDL-C <55 mg/dL, apo B <70 mg/dL, and non-HDL-C <90 mg/dL (Table 9 and Fig. 1).

Grade A; BEL 1

Recommendation 5.8—Statins are recommended for the initial treatment of hypercholesterolemia. Monitor efficacy every 6 to 12 weeks and increase the dose or intensity of statin as needed and tolerated to achieve LDL-C, apo B, and/or non-HDL-C goals based on individual ASCVD risk. Once lipid targets are achieved, lipid panel or apo B can be monitored less often (Fig. 1).

Grade A; BEL 1

Recommendation 5.9—Combine the cholesterol absorption inhibitor ezetimibe with statin therapy when the desired lipid targets are not achieved with a maximally tolerated

statin dose. If lipid targets are not achieved on this combination, add or substitute a proprotein convertase subtilisin/kexin type 9 (PCSK9)-lowering agent. Alternatively, add bempedoic acid to the maximally tolerated statin or consider adding icosapent ethyl (in persons with triglycerides 135 to 499 mg/dL) for ASCVD risk reduction.

Grade A; BEL 1

Recommendation 5.10—Management of hypertriglyceridemia in persons with high ASCVD risk or very high ASCVD risk should begin with intensive lifestyle modification and statin therapy. In persons treated with a maximally tolerated statin who have triglyceride concentrations ≥200 mg/dL and HDL-C <40 mg/dL, add a fibrate or high-dose omega-3 fatty acid to achieve the desired apo B or non-HDL-C goal. Icosapent ethyl can be considered in persons with high or very high ASCVD risk (Fig. 2).

Grade A; BEL 1

Evidence Base 5: How should dyslipidemia be managed in persons with DM?

Dyslipidemia Screening—All persons should receive information about the benefits of enduring lifestyle changes, including daily physical activity, regular exercise (several times a week), and nutritional guidance designed to improve glucose, lipid, and BP profiles and maintain a healthy weight.[266–274] Adherence to healthy lifestyle behaviors should be assessed frequently, with educational support from a registered dietitian, a CDCES, and/or a behavioral psychologist as needed to intensify therapeutic lifestyle change.

All persons with prediabetes, T1D over the age of 40 years, or T2D should be screened at diagnosis and monitored yearly with a lipid panel to include total cholesterol, triglycerides, HDL-C, and LDL-C. Fasting lipid panels, though helpful, are not necessary for therapeutic decisions, and nonfasting lipid panels may aid compliance with timely blood draws.[275]

Additional biomarkers, including apo B, lipoprotein(a), high-sensitivity C-reactive protein (CRP), coronary artery calcification score, and ankle-brachial index, are independent risk factors associated with increased risk of ASCVD events and may be helpful when the lipid management goal is unclear.[276–285] These biomarkers may enhance understanding of an individual's risk and inform decisions of initiating or intensifying pharmacotherapy.[286] However, sequential monitoring of some of these biomarkers is not recommended at this time; high-sensitivity CRP is not mechanistically linked to the pathophysiology of atherosclerosis, coronary artery calcium changes are unlikely to be reversed, and lipoprotein(a) as a targetable marker requires validation by future outcome trials.[287–289] In addition, repeat measures of these biomarkers add to costs and may result in unproven therapeutic strategies.

Where the decision for need to intervene with pharmacotherapy based upon the above risk factor assessments remains unclear, we recommend the use of a risk calculator[290–296] (Table 8). In persons younger than 40 years, initiation of statin therapy for primary prevention of CVD in both men and women needs to be individualized, based on other risk factors and comorbidities.[273] The use of various 10-year or lifetime risk calculators is an option

to decide the intensity of treatment (Table 8). By definition, these calculators are based on observational data for risk prediction but have been verified for prediction accuracy using large databases. The use of a statin choice decision aid also may assist in shared decision-making between clinicians and persons considering statin treatment choices.[297–299]

Persons who have T1D with persistent proteinuria are at increased risk of premature atherosclerosis.[300] In addition, the rising prevalence of overweight and obesity may contribute to increased rates of abnormal lipoprotein patterns related to insulin resistance among persons with T1D.[301,302] Despite limited observational and RCT data, we recommend treating persons with T1D and proteinuria and those over the age of 40 in a similar fashion to those with T2D.

Very low-density lipoprotein (VLDL) is secreted by the liver and is strongly influenced by insulin and carbohydrate intake, whereas chylomicrons are derived from the intestine and are secreted in response to dietary fat intake. VLDL remnants (apo B-100) are atherogenic and the primary particles accumulating when triglycerides are between 250 to 500 mg/dL. VLDL and chylomicrons may coexist in hypertriglyceridemia >500 mg/dL, though chylomicron remnants (apo B-48) predominate with significantly increasing triglyceride levels >500 mg/dL.

Multiple disturbances in lipoprotein metabolism in individuals with prediabetes and T2D result from the combined effects of insulin deficiency, insulin resistance, and hyperglycemia.[303–308] T2D dyslipidemia is characterized by increased levels of triglyceriderich lipoproteins (VLDL), intermediate-density lipoprotein, and remnant particlesdall apo Becontaining particlesd which metabolically lead to low levels of HDL-C and increased levels of small, dense LDL-C.[278,309–311] Hypertriglyceridemia is indirectly linked with changes in HDL-C and LDL-C composition that are conducive to accelerated atherogenesis.[312,313] Accumulating evidence favors the need to assess apo Becontaining lipoproteins to account for remnant lipoproteins and small dense lipoproteins responsible for residual ASCVD risk not seen with a standard lipid panel of total cholesterol, LDL-C, and HDL-C.[314–316]

Lipid Targets—Treatment targets for dyslipidemia in persons with DM or prediabetes and without ASCVD or target organ damage are based on the duration of DM and the presence of traditional ASCVD risk factors including advancing age, hypertension, CKD stage 3a, cigarette smoking, family history of premature ASCVD in men <55 years and women <65 years, low HDL-C, or high non-HDL-C (Fig. 1 and Table 9). T2D carries a high lifetime risk for developing ASCVD.[317] In individuals with T2D, ASCVD risk should be assessed and stratified as *high* (persons with T1D <40 years of age or T2D duration <10 years and less than 2 additional ASCVD risk factors), *very high* (persons with T2D >10 years or T1D >20 years and age >40 plus 2 or more traditional ASCVD risk factors), or *extreme risk* (DM or prediabetes plus established ASCVD or target organ damage, including left ventricular systolic or diastolic dysfunction, estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m^2, and ankle-brachial index <0.9) to help define lipid treatment targets and direct appropriate lipid-lowering therapy.[318] Risk stratification in this manner can guide management strategies as well as laboratory testing to ensure efficacy of therapy. We

recommend the use of apo B measurements as this is more accurate than non-HDL-C and predicts ASCVD risk more accurately than LDL-C.[319] In persons at high risk, the lipid targets should be LDL-C <100 mg/dL, apo B <90 mg/dL, and non-HDL-C <130 mg/dL.[314,315,320–325] In persons at very high risk for ASCVD, the lipid targets should be LDL-C <70 mg/dL, apo B <80 mg/dL, and non-HDL-C <100 mg/dL.[306] In persons with DM at extreme risk of ASCVD events, the lipid targets should be LDL-C <55 mg/dL, apo B <70 mg/dL, and non-HDL-C <90 mg/dL.[322–324,326] Note that the risk categories vary in name and definition in the references cited. The choice of statin and other lipid-lowering therapies prescribed should be based upon their relative intensity in lowering LDL-C required for lowering risk of ASCVD (Table 9 and Table 10).

Dyslipidemia Therapeutic Recommendations—To date, no RCT dedicated solely to lipid lowering in persons with T2D has examined secondary CVD prevention. However, several statin trials with large T2D subpopulations, including the GREACE (GREek Atorvastatin and Coronary-Heart-Disease Evaluation) study, TNT (Treating to New Targets) study, and PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial, have shown significant reductions in mortality and CVD events.[327–330] It should be noted that the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus of 2410 participants with T2D randomized to 10 mg atorvastatin or placebo did not show any reduction in the composite CV endpoint for primary prevention.[331] In low-risk persons with DM, whether DM per se leads to elevation of CV risk has been questioned.[332] In very high-risk persons with T2D who have had a prior ASCVD event or those who have T2D plus 2 or more additional major ASCVD risk factors (advancing age, hypertension, CKD stage 3a, cigarette smoking, family history of premature ASCVD in men <55 years and women <65 years, low HDL-C, or high non-HDL-C), a high-intensity statin (Table 10) should be started along with therapeutic lifestyle changes regardless of baseline LDL-C level.[333–335] Lipids should be rechecked within 12 weeks of initiating therapy, and the primary target is to attain apo B or non-HDL-C in goal.[314,315,336–338] If the LDL-C or non-HDL-C concentration remains >70 mg/dL or >100 mg/dL, respectively, the statin dose should be increased with the goal of lowering LDL-C to <70 mg/dL and non-HDL-C to <100 mg/dL (Fig. 2 and Table 10). If these targets cannot be achieved with maximally tolerated statin therapy, then treatment considerations should include a more potent statin or the addition of ezetimibe.[286,324–326,339–341] Where treatment goals are not met despite these strategies, bempedoic acid, or pharmacotherapy targeting PCSK9 should be considered.[340,342]

The *high-risk* ASCVD category (noted as moderate risk in some guidelines) describes persons with DM without known ASCVD and <2 major CV risk factors (advancing age, hypertension, CKD ≥ stage 3a, cigarette smoking, family history of premature ASCVD in men <55 years and women <65 years, low HDL-C, or high non-HDL-C). In such persons, treatmentshould beginwith therapeuticlifestylechanges for an initial 6- to 12-week trial. Goals for the primary targets LDL-C and non-HDL-C are <100 mg/dL and <130 mg/dL, respectively.[245,343–346] The additional primary target of apo B lowering (<90 mg/dL) may also be considered for judgingtherapeutic efficacy.[314,319,326] When the recommended goals are not being achieved after lifestyle interventions, statin therapy should be initiated,

starting with a moderate-intensity statin. For persons older than 40 years without diagnosed ASCVD, but who have 2 or more additional major ASCVD risk factors (very high ASCVD risk), statin therapy may be considered even if the LDL-C concentration is <100 mg/dL.[245,343–345] In persons with statin intolerance or unacceptable adverse drug effects, a bile acid sequestrant should be considered alone or in combination with statin tolerated at a lower dose [347,348] or a cholesterol absorption inhibitor.[349–355] No study has yet been designed to investigate the CV outcomes benefit of adding bile acid sequestrants or cholesterol absorption inhibitor to statins in persons whose atherogenic markers (LDL-C, non-HDL-C, and apo B) are not already at target levels. Addition of PCSK9 inhibitors has been shown to be highly effective for lowering LDL-C and apo B, and for lowering CV event rates, but to date have not translated to overall mortality benefits.[354]

In persons with end-stage kidney disease to include hemodialysis treatment and in those with advanced HF, there is no clear evidence that LDL-Celowering therapy provides ASCVD benefit.[356] Persons with eGFR <45 mL/min/1.73 m^2 who are not dialysis-dependent are at very high to extremely high risk for ASCVD events and should be treated to achieve LDL-C, non-HDL-C, and apo B goals with a statin and ezetimibe,[357] because higher doses of statins alone have not been proven to be safe in the setting of CKD. Such persons should be monitored closely to determine whether statin dose adjustment is necessary depending on comorbidities, drug interactions, and renal status.[356] Increasing evidence now shows that older persons gain significant benefits from lipid lowering for primary prevention, and these benefits are even more impactful in persons with DM.[358–361]

In persons at LDL-C goal and who have a fasting triglyceride level ≥150 mg/dL or HDL-C level ≤35 mg/dL, glycemic control and lifestyle changes to maintain a healthy weight are recommended.[324,343] In persons with fasting triglycerides of 200 to 499 mg/dL, despite tight adherence to a healthy diet (to include reduced intake of simple carbohydrates and avoidance of fruit juices and alcohol) and optimized glycemia control, prescribe statin therapy to the maximum tolerated dose to achieve goals for non-HDL-C or apo B, since all apo B–containing particles are potentially atherogenic.[312,313,324,362,363] Nonstatin therapies in combination with statins are often required in these settings.[364]

In persons with persistently elevated fasting triglycerides >200 mg/dL who are receiving maximally tolerated LDL-Celowering statin therapy, adding triglyceride-lowering drugs such as a fibrate or high-dose omega-3 fatty acid may be helpful to further reduce non-HDL-C.[365–368] The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial used icosapent ethyl added to statin-treated persons and reported a significant beneficial CV outcome in participants with hypertriglyceridemia, though this effect was independent of triglyceride lowering.[369] To date, aside from icosapent ethyl, fish oil therapy has not been shown to prevent CV adverse events.[313,370,371]

If the fasting triglyceride concentration is ≥500 mg/dL (ie, severe hypertriglyceridemia), begin treatment with a very low-fat diet and initiate a fibrate or high-dose omega-3-fatty acid treatment. Dietary therapy should be strongly emphasized as it remains the most poorly adherent triglyceride-lowering intervention, and all these therapies may be required in combination to control severe hypertriglyceridemia.[372] Niacin use is not encouraged

as it leads to dysglycemia but may be considered in refractory cases. Observational data and retrospective analyses support triglyceride-lowering therapy for prophylaxis against acute pancreatitis.[373] Rule out other secondary causes and reassess lipid status when the triglyceride concentration is <500 mg/dL. Additional statin therapy and possibly other agents are usually required to achieve the primary LDL-C, apo B, and non-HDL-C goals.[374–376] No RCT has yet been reported to investigate the benefit of reducing severe (>500 mg/dL) or moderate (>200 mg/dL) hypertriglyceridemia to prevent CVD.[313,370,371]

Modification of triglycerides with the proliferator activated receptor-alpha agonist fenofibrate failed to reduce ASCVD events in 2 separate trials in persons with T2D: (Fenofibrate Intervention and Event Lowering in Diabetes [FIELD][377] and ACCORD-Lipid),[367] although the mean baseline triglyceride levels were 153 mg/dL in FIELD[377] and 162 mg/dL in ACCORD-Lipid.[367] Post hoc and prespecified subgroup analyses and meta-analyses of 5 major fibrate trialsdHelsinki Heart Study, Veterans Affairs HDL Intervention Trial, Bezafibrate Infarction Project, FIELD, and ACCORD-Lipiddhave shown a CV benefit in persons with moderate dyslipidemia (triglycerides >200 mg/dL and HDL-C <40 mg/dL, either isolated or together) but not in persons without dyslipidemia.[286,378–381]

Two separate RCTs tested the HDL-C–raising hypothesis inpersons with coronary artery disease optimally treated with statins with or without ezetimibe. In the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes trial, the atherogenic markers LDL-C, non-HDL-C, and apo B were 74, 108, and 81 mg/dL, respectively, prior to randomization.[382] Before randomization in Heart Protection Study 2dTreatmentof HDL to Reduce the Incidence of Vascular Events, LDL-C, non-HDL-C, and apo B were 63, 84, and 68 mg/dL, respectively, and triglyceride and HDL-C levels were 120 mg/dL and 44 mg/dL, respectively.[383] In each of these trials, the addition of niacin resulted in small improvements in lipids, but these changes were not accompanied by any significant reduction in ASCVD events.[382,383] Thus, niacin cannot be recommended as adjunctive therapy if LDL-C, non-HDL-C, and apo B goals are already met. Niacin may have a role when optimized therapy fails to control triglycerides >1000 mg/dL.

Managing Dyslipidemia—If lipid goals are not achieved after initiating treatment, lipid-lowering therapy should be intensified, and apo B determination may also be useful to confirm goal attainment.[73,286,314] LDL-C, calculated non-HDL-C (total cholesterol – HDL-C), and apo B are the primary targets of therapy, with respective goals set according to ASCVD risk stratification (Fig. 1). If LDL-C is at goal but non-HDL-C or apo B remain above goal after maximally tolerated statin therapy, consider additional apo B or triglyceride-lowering therapies, such as ezetimibe, a cholesterol absorption inhibitor, or PCSK9 inhibitor or PCSK9-interfering therapy.[73,286,342]

Lipid Management in Prediabetes—The principles and goals of lipid management in individuals with prediabetes are the same as those with DM described previously (Fig. 1). No randomized intervention trials dedicated to persons with prediabetes use ASCVD events as outcome measures. Lifestyle change for a healthy diet, daily activity and regular

weekly exercise, and healthy weight maintenance should be emphasized for all persons with prediabetes.

Moderate-potency or high-potency statins, possibly combined with cholesterol absorption inhibitors or bile acid sequestrants, are effective for achieving LDL-C, non-HDL-C, and apo B goals in persons with prediabetes.[324] Low HDL-C is also common in prediabetes, and low HDL-C and high triglycerides are both associated with increased atherogenic lipoprotein particles. Niacin is effective in raising HDL-C, but it also increases insulin resistance and may accelerate the appearance of overt DM. Fibrates may be considered, but the use of gemfibrozil is discouraged owing to its interaction with statin clearance and the risk for severe rhabdomyolysis.

Meta-analyses of statin RCTs indicate that statin use is associated with significant increases in the risk of progression to T2D among persons with prediabetes: a 9% increase with moderate statin dosing and 12% increase with high statin dosing.[384,385] Persons with prediabetes should be warned of the potential added risk of conversion to DM with statin use. The net comparison of benefit vs risk is >4 ASCVD events prevented for one conversion from prediabetes to DM.[386] This risk-benefit analysis, considering the individual risk of converting to DM vs prevention of ASCVD, should be discussed when initiating statin therapy.

Question 6: How should DKD or CKD in DM be managed?

DKD refers to kidney disease attributable to DM. DKD replaced the older term, “diabetic nephropathy,” which referred to specific glomerular lesions of nodular glomerulosclerosis and glomerular basement membrane thickening, because of emerging evidence for a variety of other types of structural kidney injury caused by DM.[197]

DM and CKD or CKD in DM refer to DM accompanied by low eGFR and/or albuminuria/proteinuria without specification for cause. This is the inclusion criteria used for most of the large outcomes trials for kidney disease in DM. Therefore, though many study participants may have had DKD, others could have had CKD from another cause in the setting of DM.

Recommendation 6.1—Annual assessment of serum creatinine to determine the eGFR and urine albumin-to-creatinine ratio (UACR) is recommended to identify, stage, and monitor progression of DKD, also referred to as CKD in DM. Begin annual DKD assessment 5 years after diagnosis in persons with T1D or at diagnosis in persons with T2D.

Grade B; BEL 2

Recommendation 6.2—Advise persons with CKD in DM about optimal glycemic control, BP control, lipid control, and smoking cessation to reduce risks of development and progression of CKD and CVD. (See also **R 4.1 to R 4.5** on BP control, **R 5.1 to R 5.10** on lipid management, and **R 12.1.1 to R 12.2.19** on glycemic control.)

Grade A; BEL 1

Practice Points
In moderate-to-severe CKD (stages 3 to 5), check UACR and eGFR more frequently (eg, every 3 to 6 months), depending on rate of progression and comorbidities.
Measure UACR and eGFR after medication additions or adjustments (eg, ACE inhibitors, ARBs, SGLT2is, finerenone, nonsteroidal anti-inflammatory drugs, proton pump inhibitors) or change in clinical status that may affect kidney function (eg, iodinated contrast administration, acute illness).
Assess for complications of CKD, including anemia and bone and mineral metabolism disorders, in severe CKD (stages 4 to 5).
Referral to a nephrologist is recommended by CKD stage 4 or earlier if there are concerns about kidney disease diagnosis, rapid progression, complications, or management.

Recommendation 6.3—RAAS blockade with an ARB or an ACE inhibitor is recommended for persons with albuminuria (T1D or T2D) to reduce risk of DKD or CKD in DM progression (see Fig. 3 for category definitions).

Grade A; BEL 1

Recommendation 6.4—An SGLT2i with proven benefit is recommended as foundational therapy for persons with T2D and CKD with eGFR ≥20 mL/min/1.73 m^2 to reduce progression of CKD and risk of CVD.

Grade A; BEL 1

Recommendation 6.5—A GLP-1 RA with proven benefit is recommended for persons with T2D and DKD or CKD in DM with eGFR ≥15 mL/min/1.73 m^2 for glycemic control and to reduce risk of ASCVD and progression of albuminuria.

Grade A; BEL 1

Recommendation 6.6—A nonsteroidal mineralocorticoid receptor antagonist (finerenone) with proven kidney and CVD benefit is recommended for persons with T2D, an eGFR ≥25 mL/min/1.73 m^2, normal serum potassium concentration, and albuminuria (UACR 30 mg/g) despite a maximum tolerated dose of a renin-angiotensin system inhibitor.

Grade A; BEL 1

Practice Points
Serum potassium levels and eGFR should be monitored within 2 to 4 weeks after initiating an ACE inhibitor, an ARB, an SGLT2i, finerenone, or with changes in these medications.
Finerenone can be used for persistent albuminuria in addition to an ACE inhibitor or an ARB and SGLT2i, or in people with CKD in DM who cannot take an SGLT2i.
In the absence of albuminuria and with normal BP, ACE inhibitors or ARBs do not prevent DKD onset.
ACE inhibitors and ARBs should not be used together due to increased risks of adverse effects, particularly hyperkalemia and AKI.
ACE inhibitors and ARBs are not safe for use in pregnant women.

Evidence Base 6: How should DKD or CKD in DM be managed?

DKD or CKD in DM accounts for nearly half of all cases of kidney failure that require kidney replacement therapy (dialysis or transplant) in the United States and

occurs in about 40% of persons with T2D and 30% of those with T1D, increasing with duration of DM.[387–389] Classical diabetic nephropathy is represented histologically by the presence of basement membrane thickening, mesangial expansion, podocyte loss, and nodular or diffuse glomerulosclerosis.[197,390] Many other pathological changes (tubulointerstitial inflammation and fibrosis, arteriolar hyalinosis, mesangiolysis, glomerular capillary aneurysms) may also occur as a consequence of DM.[391] The pathologic changes may be present prior to development of albuminuria or low eGFR.[390,392] Consequently, the term DKD is now preferred to diabetic nephropathy. Prevention of microvascular complications including DKD should be a managementgoal as earlyas the time of diagnosis of DM. In general, AACE concurs with guidelines by the Kidney Disease: Improving Global Outcomes (KDIGO) working group[393] and the Kidney Disease Outcomes Quality Initiative Committee[394] for the diagnosis and management of CKD in persons with DM, also known as DKD.

The KDIGO guidelines recommend phasing out the term micro-albuminuria and replacing it with the term albuminuria. Testing for the presence of albuminuria can be done using a spot urine sample or a timed collection, although the former is now preferred for reliability and simplicity. UACR levels >30 mg/g indicate kidney damage and are also a marker of CV risk.[393,394] Increased urinary albumin may be seen in the setting of urinary tract or systemic infection, after exercise, or in the presence of hematuria, so confirmation is necessary to establish the diagnosis of DKD or CKD in DM. A UACR of >300 mg/g indicates greater damage and greater risk for progression to kidney failure and development of CKD complications such as anemia, CVD, and infections. Sudden onset or rapidly increasing albuminuria should prompt additional tests to assess for other types of kidney disease. Table 11 lists correlations between albuminuria, urine dipstick, and tests of total protein excretion.

eGFR should be calculated from the serum creatinine by the Chronic Kidney Disease Epidemiology (CKD-EPI). The CKD-EPI equation is more accurate for calculation of eGFR above 60 mL/min/1.73 m^2 than the prior Modification of Diet in Renal Disease equation, and the CKD-EPI equation is currently preferred.[393] Importantly, the CKD-EPI equation has been updated to a new version that is race agnostic and termed CKD-EPI 2021. The American Society of Nephrology and the National Kidney Foundation have recommended immediate implementation for CKD-EPI 2021 as an important strategy to advance CKD care and reduce health disparities by racial identification.[395–397] Figure 3 depicts the classification system for CKD that incorporates both eGFR and albuminuria in the risk assessment. Note that in Figure 3, stage 3 CKD has been divided into 2 categories: G3a for eGFR 45 to 60 mL/min/1.73 m^2 and G3b for eGFR 30 to 45 mL/min/1.73 m^2. The terminology used to describe CKD provides a composite picture by integrating the cause, eGFR, and UACR. For example, a person with DM, an eGFR of 40 mL/min/1.73 m^2, and an UACR of 250 mg/g creatinine would be categorized as “diabetes/G3b/A2.” The “heat grid” shown in Figure 3 indicates the terminology, the level of risk for CVD events and progression of kidney disease by color intensity, and the recommended frequency for monitoring UACR and eGFR.[393,398,399] Progression of CKD is considered rapid if the decline in eGFR is ≥5 mL/min/1.73 m^2 per year or if the person has a rapid increase in albuminuria.

High levels, as well as variability, of both BG and BP are important risk factors for DKD.[89,184,400–403] Prevention of the development of DKD includes optimal control of glycemia and BP with RAAS inhibition as first-line therapy.[394,404,405] Intensive glucose control (A1C levels <7% in T2D and <7.5% in T1D) in several clinical trials was found to reduce the risk of incident albuminuria (A2) and DKD onset.[70,78,90,406–410] However, intensive glucose control has not been shown to diminish DKD or CKD in DM progression and may increase risk of CVD mortality in persons with established DKD or CKD in DM. Moreover, glycemic targets need to be individualized due to increased risk of hypoglycemia in persons with DKD or CKD in DM.

The KDIGO guidelines recommend that persons with CKD in general be treated to a BP <120/70 mm Hg, but <130/80 mm Hg may be appropriate in people who have DM or DKD or CKD in DM.[209] Although care must be taken to avoid orthostasis and drug side effects, AACE recommends individualized BP targets, with a goal of <130/80 mm Hg for most persons (see **Q4. How should hypertension be managed in persons with DM?**).

Smoking cessation and lipid lowering are also important interventions for prevention of CVD complications of DM, which are increased at every level of CKD.[398] Therapy with statins reduces the relative risk of major vascular events in persons with DM by 17% for every 39 mg/dL decrease in LDL-C.[333] Persons with DM and CKD up to stage 4, including those who have had kidney transplants, receive CVD benefit from lipid-lowering with statins. However, the beneficial effect of statins is not apparent in persons who require dialysis.[333,357,411–413]

Slowing the progression of DKD or CKD in DM is critical for reducing risks of kidney failure and CVD, including HF, atherosclerotic events,[414–422] and related causes of death. Therapies shown to positively affect albuminuria and declining eGFR include ACE inhibitors, ARBs, SGLT2is, GLP-1 RAs, and the nonsteroidal mineralocorticoid antagonist finerenone.[197,209,239,242,393,423–435] Persons with albuminuria and T1D or T2D should be treated with an ACE inhibitor or ARB at the highest tolerated dose based on the drug label for approval.[188,197,430,436–439] Data are lacking on the effectiveness of ACE inhibitors and ARBs in persons with DM and reduced eGFR who do not have albuminuria. However, AACE recommends RAAS blockade in all persons with DM who have CKD categories G2, G3a, G3b, and G4. The RAAS-blocking drugs may potentiate hyperkalemia and AKI when used with nonsteroidal anti-inflammatory drugs. Risk of AKI is also increased in persons with volume depletion or bilateral renal artery stenosis who use ACE inhibitors or ARBs. RAAS-blocking drugs are not safe for use in pregnancy. Combination therapy with an ACE inhibitor and an ARB or with a renin inhibitor added to another RAAS-blocking agent does not prolong survival or prevent progression of CKD.[263,440,441] In persons with advanced CKD (G3b and higher), combination therapy increases the risk of hyperkalemia and AKI and is therefore not recommended.[263,441,442]

On top of the prevailing standard of care with an ACE inhibitor or an ARB, there has been a major upsurge in new highly effective therapies for people with T2D to reduce risks of DKD or CKD in DM progression, kidney failure, HF, ASCVD, and death for some agents. An SGLT2i with proven kidney protection is recommended for people with T2D who have

an eGFR >25 mL/min/1.73 m^2 irrespective of albuminuria to reduce risks of DKD or CKD in DM and CVD.[425,443–469] In those with HF, one agent in the class, empagliflozin, can be used with an eGFR as low as 20 mL/min/1.73 m^2.[470] If the eGFR drops below this level on treatment, the SGLT2i does not have to be stopped unless the person proceeds to kidney failure requiring kidney replacement therapy by dialysis or kidney transplant. The recognized side effects of SGLT2 inhibition, including genital mycotic infections, volume depletion, DKA, or hypoglycemia when used with insulin or insulin secretagogues, are not greater in persons with lower levels of eGFR.[471] Initial reports of higher rates of lower extremity amputation with canagliflozin have not been substantiated in subsequent studies of this agent or other SGLT2is. However, people with DKD or CKD in DM are at higher risk of lower extremity amputations in general, making good diabetic foot care essential (see R 8.6 on diabetic foot exams). Risk mitigation strategies for SGLT2is are the same as for other individuals with DM (Table 12). SGLT2is also tend to lower serum potassium, which may mitigate risks of hyperkalemia and allow greater use of other kidney and heart protective agents such as ACE inhibitors, ARBs, and mineralocorticoid antagonists. Additionally, the risk of AKI is actually reduced by 25% with SGLT2i use in persons with T2D.[461]

A GLP-1 RA is recommended as another option to reduce risks of ASCVD, macroalbuminuria, and eGFR decline in T2D.[429,472–479] In advanced CKD (eGFR <30 mL/min/1.73 m^2), GLP-1 RAs retain glycemic efficacy without increased risk of hypoglycemia and can be used to control BG with an eGFR as low as 15 mL/min/1.73 m^2, depending on the agent.[429] Similar to the SGLT2is, side effects of GLP-1 RAs are not different in persons with lower levels of eGFR (Table 12). Because gastrointestinal (GI) symptoms such as nausea, vomiting, and diarrhea may occur more frequently when kidney function is reduced, consider slowing uptitration of drug doses. As for other persons with DM, adjustment of other glucose-lowering agents may be needed to prevent hypoglycemia.

The nonsteroidal mineralocorticoid antagonist finerenone is also recommended for kidney and heart protection in T2D with eGFR >25 mL/min/1.73 m^2, normal serum potassium concentration, and albuminuria (UACR ≥ 30 mg/g) despite a maximally tolerated dose of a renin-angiotensin system inhibitor, because it reduced risks of substantial GFR decline, kidney failure, HF and ASCVD events, and related deaths in a broad T2D population ranging from those with microalbuminuria to advanced CKD. [434,435,480–482] The main side effect of finerenone is hyperkalemia, which usually can be managed with dietary restriction and concurrent use of diuretics or SGLT2is (Table 12). Potassium-binding agents such as partiromer or sodium zirconium cyclosilicate are also a consideration for control of hyperkalemia.

Dietary protein management may add benefit to risk factor control and drug therapies for CKD. KDIGO recommends limiting protein intake to 0.8 g/kg per day (the recommended daily allowance in the United States) in persons with DKD or eGFR <30 mL/min/1.73 m^2.[430] As described above, dietary approaches also help to control high levels of potassium as well as phosphorus. Sodium intake should be limited to 2 g per day in persons with DM who require antihypertensive medications. With obesity being a risk factor for hypertension and incident CKD, weight management including diet, physical activity, and other weight-

loss strategies (eg, US Food and Drug Administration [FDA]-approved pharmacotherapy, bariatric surgery, GLP-1 RAs) may be considered for persons with DM.

Persons with CKD or CKD in DM are at risk for various types of drug toxicity and AKI. Glucose-lowering therapies may need to be modified to reduce hypoglycemia.[483] Many other drugs should be avoided or used with caution in persons with low eGFR. Individuals should be informed of their CKD diagnosis and should avoid dehydration and imaging that requires gadolinium, high phosphate-containing bowel preparations, or high doses of iodinated contrast agents.

Persons with CKD in DM should undergo annual or more frequent assessment of electrolytes to assess potassium and acid-base status; blood counts to assess anemia status; and calcium, phosphorus, 25(OH) vitamin D, and parathyroid hormone (PTH) measurements to assess mineral metabolism.[209] Hyperkalemia may be managed by dietary restriction, potassium binding agents, and adjustment of antihypertensive medications. For those with a serum bicarbonate level <22 mEq/L, the addition of oral sodium bicarbonate is recommended to correct the serum bicarbonate level. Anemia, defined as hemoglobin <13 g/dL in men and <12 g/dL in women, should be further investigated with iron, transferrin saturation, ferritin, vitamin B_{12}, and folate levels.[484] Deficiencies should be replaced and a transferrin saturation target of ≥30% achieved, regardless of ferritin level[484]. Iron given intravenously may produce better results than oral replacement. AACE recommends adequate calcium intake and achievement of 25(OH) vitamin D levels of >30 ng/dL in all persons. Supplementing vitamin D_2 or D_3 may reduce PTH in persons with CKD and secondary hyperparathyroidism.[484,485] Active vitamin D preparations are usually necessary to keep the PTH level from increasing as eGFR declines. Hyperphosphatemia should be corrected into the normal range with dietary modification and use of phosphate binders.

Referral to a nephrologist is appropriate when the presentation is atypical, progression of albuminuria or decline in eGFR is rapid, or when secondary manifestations of CKD require expert advice. Referral of persons with stage 4 CKD to a nephrologist allows time for sufficient planning to accommodate individual personal needs.[486] Kidney transplantation is the preferred kidney replacement therapy for persons with DM because long-term outcomes are superior to those achieved with dialysis. For persons with T1D, the possibility of combined kidney-pancreas transplantation delivers considerably better outcomes.[487]

Question 7: How should retinopathy be managed in persons with DM?

Recommendation 7.1—It is recommended that persons with T2D or adult-onset T1D should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of diagnosis or shortly after diagnosis. Individualized subsequent screening can be based on type and duration of DM, A1C or mean BG, BP, and the presence and grade of retinopathy.

Grade A; BEL 2 and expert opinion of task force

Recommendation 7.2—In persons with T1D, an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist should be performed within 5 years of diagnosis in children and adolescents.

Grade B; BEL 4 and expert opinion of task force

Recommendation 7.3—Women who are pregnant and have preexisting T1D or T2D should be monitored with eye examinations every trimester during pregnancy and in the postpartum period as determined by the severity of retinopathy during pregnancy.

Grade B; BEL 2

Recommendation 7.4—Persons with greater than mild nonproliferative retinopathy should have examinations at least once a year and more frequently as advised by their eyecare specialist.

Grade B; BEL 4 and expert opinion of task force

Recommendation 7.5—Follow-up with eyecare specialists typically should occur on an annual basis, but persons with T1D or T2D who have had a normal ocular examination may be screened every 2 to 3 years.

Grade B; BEL 2 and expert opinion of task force

Recommendation 7.6—Optimal glucose, BP, weight, and lipid control should be implemented to slow the progression of retinopathy.

Grade B; BEL 1

Recommendation 7.7—Artificial intelligence systems, authorized by the FDA for detecting greater than mild diabetic retinopathy, can be used as an alternative to traditional screening approaches. These systems can facilitate diagnosis of vision-threatening retinopathy and identification of persons who require ophthalmologic visits for treatment.

Grade B; BEL 1

Evidence Base 7: How should retinopathy be managed in persons with DM?

Diabetic retinopathy is the leading cause of blindness in adults. The stages of diabetic retinopathy include nonproliferative retinopathy, preproliferative retinopathy, and proliferative retinopathy, with macular edema occurring at any stage. The prognosis for retaining vision has improved dramatically over the past 40 years owing to improved metabolic and BP control.[78,432,488–490] Diabetic retinopathy is present in 25% to 45% of persons with T2D, and between 2% and 8% of persons with T2D have proliferative retinopathy and/or macular edema.[491] Diabetic retinopathy is present in approximately 20%, 40%, and 70% of persons with T2D after <10, 10 to 20, and >20 years of the disease, respectively, with prevalence rates of proliferative retinopathy and/or macular edema around 2%, 10%, and 25% at the respective durations.[492] A 2020 meta-analysis of data from Europe

revealed that any retinopathy was present in 25.7% of persons and diabetic macular edema occurred in 3.75%.[493] The prevalence of diabetic retinopathy is predicted to continue to increase through the next 2 decades.[494]

Moreover, teenagers and young adults with T1D and T2D diagnosed during childhood (mean 7.8 years duration) have a prevalence of retinopathy of 9.1% and 5.6%, respectively.[417,495] Higher levels of glycemia and BP, as well as the presence of nerve and renal diabetic complications, are associated with a greater likelihood of developing retinopathy.[496,497] Nonhealing ulcers and bacterial infections increase the rate of progression of retinopathy,[496,498] so persons with infections may merit close ophthalmologic care during this period; African American and Hispanic populations have increased likelihood of diabetic macular edema compared with non-Hispanic Whites.[499]

Like other complications, it is important to detect greater than mild nonproliferative retinopathy before vision is threatened. Ophthalmoscopy without pupil dilation is suboptimal so referral to an experienced ophthalmologist or optometrist for an annual dilated eye examination is recommended.[500] Annual examinations have long been recommended as the standard approach, but data suggest that individualized risk assessment and persons with well-controlled DM and no retinopathy at baseline can be safely examined at 2- to 3-year intervals.[501,502] The ophthalmologic examination can also detect other common conditions such as cataracts, glaucoma, and macular degeneration. The use of nonmydriatic fundus cameras equipped with digital transmission technology enables large-scale point-of-care (POC) screening for retinopathy.[503] Screening programs have been most successful in defined populations with government-organized health care systems, such as in the United Kingdom and Scandinavia and in American Indian tribes rather than in the general population of the United States.[503–506] Persons with abnormal retinal photographs are referred to an ophthalmologist for a complete eye examination. This two-step approach can be an effective strategy for retinopathy screening at the population level, particularly in remote areas.[507]

Artificial intelligence approaches to screening for diabetic retinopathy have progressed to the point of utility and cost-effectiveness.[508–513] Given the relatively low prevalence of proliferative retinopathy and/or macular edema in persons with T2D during the first decade after diagnosis, however, the suggestion is now being made that persons with T2D who have had a negative ophthalmologic examination may safely have the screening interval increased to 2 or 3 years.[514–517] Retinopathy develops over a period of 5 or more years from initial hyperglycemia, so screening should be initiated within 5 years of diagnosis in persons with T1D.[518] Pregnancy is a risk factor for progression of retinopathy, and ophthalmologic examinations should be performed repeatedly during pregnancy and for 1 year postpartum.[519] Persons with active lesions may be followed more frequently, whereas those who have had repeatedly normal eye findings can be seen less frequently. Elevated prepregnancy A1C and duration of T1D >10 years predict progression.[520] Teenage girls may have more difficulty controlling T1D than do teenage boys and thus risk more complications.[521] Thus, multiple systemic factors influence the risk of the development and progression of diabetic retinopathy.

Management of retinopathy requires attention to multiple systemic and ocular factors. Optimization of glucose and BP are the proven strategies for primary prevention of diabetic retinopathy and for slowing the progression of preexisting nonproliferative retinopathy.[78,185,186,193,522,523]

Other options that can stabilize retinopathy include lifestyle intervention or bariatric surgery in persons with T2D or physical activity in persons with T1D.[524–527] One study suggested that dietary marine omega-3 fatty acids may slow sight-threatening retinopathy, but further investigation is needed.[528]

In addition, pharmacologic treatment approaches may have specific benefit in diabetic retinopathy, including ACE inhibitors, ARBs,[529,530] and fibrate lipid-lowering agents.[531–533] Research into other novel pharmacologic agents with potential benefits may lead to additional medical treatments.[534]

The ophthalmic treatment of proliferative retinopathy has evolved in the past decade. Panretinal laser photocoagulation has been the primary treatment for decades because it provides enduring effects. Anti-vascular endothelial growth factor (VEGF) antibodies also inhibit neovascularization.[535] However, after 5 years of follow-up, the rate of visual field sensitivity is equivalent in the drug- and laser-treated groups.[536] Moreover, persons who fail to return for continued anti-VEGF treatments are at risk of losing vision.[537,538] Therefore, treatment should be individualized, in some cases combining panretinal photocoagulation and anti-VEGF therapy.[539] Vitrectomy effectively restores vision for many persons with persistent vitreous hemorrhage, vitreous scarring, and detachment.[540] Diabetic macular edema in the absence of proliferative retinopathy is most commonly treated with repeated anti-VEGF injections.[541]

Question 8: How should neuropathy be diagnosed and managed in persons with DM?

Recommendation 8.1—Diabetic peripheral neuropathy (DPN) is a clinical diagnosis. A comprehensive differential diagnosis should be considered to rule out nondiabetic neuropathies.

Grade B; BEL 2

Recommendation 8.2—Screening for DPN should be done at diagnosis of T2D, within 5 years of the diagnosis of T1D, and subsequently annually or whenever symptoms occur, by performing a clinical history and physical exam.

Grade B; BEL 2

Recommendation 8.3—Assessments for DPN should include a careful history to assess target symptoms and a combination of at least two of the following: vibration sensation using a 128-Hz tuning fork, pinprick sensation, temperature discrimination, 10-g monofilament testing on the dorsal aspect of the great toe bilaterally, and ankle reflexes. All these assessments should follow the typical DPN pattern, starting distally (the dorsal aspect of the hallux) on both sides and move proximally until a sensory threshold is identified.

Grade A; BEL 2, upgraded by expert opinion of task force

Recommendation 8.4—Screening for CV autonomic neuropathy (CAN) should be considered at diagnosis of T2D and at 5 years after the diagnosis of T1D, including youth. Screening for CAN should also be considered in the presence of DPN, DKD, 2 or more CV risk factors, hypoglycemia unawareness, high glucose variability, in persons with HF, peri-operatively, or in individuals presenting with autonomic symptoms. A careful differential to exclude other comorbidities or drug effects/interactions that could mimic CAN should be performed.

Grade B; BEL 2

Recommendation 8.5—CV reflex tests (deep breathing, Valsalva, supine to standing) remain the gold standard and are recommended for assessment of CAN. Indices of heart rate variability (HRV) derived from electro-cardiogram recordings could also be used as an easier alternative for screening for CAN.

Grade A; BEL 2, upgraded by expert opinion of task force

Recommendation 8.6—Diabetic foot exams should be performed at every visit (in person or virtual) to identify deformities and to identify those at risk for late complications such as ulcerations and amputations.

Grade A; BEL 1

Recommendation 8.7—Intensive glucose control applied as early as possible is recommended to prevent the onset of DPN and CAN in T1D. Achieving optimal control of glucose, BP, and lipid levels along with lifestyle interventions, including weight loss and exercise, are recommended to prevent DPN and CAN in T2D. Lifestyle interventions are effective for DPN and CAN prevention in persons with prediabetes/metabolic syndrome.

Grade A; BEL 2, upgraded by expert opinion of task force

Recommendation 8.8—Pregabalin, duloxetine, and capsaicin 8% patch are recommended for the treatment of neuropathic pain due to DM and have received regulatory approval in the United States. Current evidence shows that these agents are effective in reaching 30% to 50% reduction in pain in many individuals (**Grade A; BEL 1**). However, gabapentin and some tricyclic antidepressants may be as effective to achieve a clinically meaningful reduction in diabetic neuropathic pain (**Grade B; BEL 1**). Combining two or more agents from different classes may have enhanced benefits with lower adverse effects and risks than maximizing the dose of one medication or using opioids. The use of opioids, including tapentadol or tramadol, is **NOT RECOMMENDED** due to high risk of addiction and other complications.

Grade A; BEL 1

Recommendation 8.9—Lifestyle interventions including a combination of regular aerobic, strengthening, and balance exercises, reduction of sedentary behavior, and dietary modification aimed at reducing calorie intake and increasing plant-based and polyunsaturated fats are recommended. Neuromodulatory techniques such as high-frequency spinal cord stimulation and combining pharmacological with nonpharmacological approaches should be considered in those with refractory painful DPN.

Grade B; BEL 1

Evidence Base 8: How should neuropathy be diagnosed and managed in persons with DM?

Diabetic neuropathy affects about half of all persons with DM, contributing to substantial morbidity and mortality and resulting in a huge economic burden for DM care due to the increased risk of associated complications such as pain, sleep disturbances, falls and fractures, reduced QoL, polypharmacy, and socioeconomic consequences.[417,418,542–552] Persons with prediabetes and/or obesity may also develop DPN.[547,548,553]

Consensus in the field is that diabetic neuropathies are defined by the presence of symptoms and/or signs of peripheral and autonomic nerve dysfunction in people with DM after the exclusion of other causes confirmed through clinical examination and appropriate differential tests. Among the various forms of diabetic neuropathy, distal symmetric polyneuropathy and diabetic autonomic neuropathies, particularly CAN, are by far the most studied.[547] There are several atypical forms of diabetic neuropathy as well. A comprehensive classification of diabetic neuropathies was updated by the ADA's 2017 position statement on diabetic neuropathy.[547]

Symptoms of DPN vary depending on the class of sensory nerve fibers involved. The earliest affected nerve fibers are usually the small myelinated and unmyelinated fibers; thus, the most common early symptoms are pain and dysesthesias (unpleasant sensations of burning).[547,554,555] Neuropathic pain may be the first symptom that prompts persons to seek medical care and is present in up to 25% to 30% of individuals with DPN.[547,555–559] Characteristically, the pain is burning, lancinating, tingling, or shooting (electric shock-like), with paresthesia, occurring in varying combinations, and is typically worse at night[547] Neuropathic pain may be accompanied by an exaggerated response to painful stimuli (hyperalgesia) and pain evoked by contact, with socks, shoes, and bedclothes (allodynia) for example.[547,556,557,560,561] Neuropathic pain can lead to interference with daily activities, disability, psychosocial impairment, and reduced health-related QoL.[547,552,562,563] The direct and indirect economic burden associated with neuropathic pain is substantial.

The involvement of large fibers may cause numbness, tingling without pain, and loss of protective sensation.[547] Persons can also initially present with a completely insensate, numb foot, stating their feet feel like they are wrapped in wool or that they are walking in thick socks.

There are several established clinical tests that may be easily used to assess small- and large-fiber function. In clinical care, assessment of pinprick and temperature (mostly

cold) sensation provide reliable information on small-fiber function, whereas assessment of vibration perception (with a 128-Hz tuning fork), proprioception, light touch to 10-g monofilament, and ankle reflexes allow assessments of large-fiber function (Table 13) all in a “stocking and glove” distribution. Assessment of light touch perception using a 10-g monofilament should be performed on the dorsal aspect of the great toe bilaterally as recommended.[547] However, it is important to consider that the 10-g monofilament is a useful clinical tool mainly for detecting advanced neuropathy and identifying persons at increased risk of ulceration and amputation.[547,564] Loss of ankle reflexes occurs early, and later weakness of small foot muscles and dorsiflexors are also observed.[547]

The diagnosis of DPN is principally a clinical one. A combination of typical symptomatology and symmetrical distal sensory loss, or typical signs in the absence of symptoms, in a person with DM is highly suggestive of DPN and may not require additional evaluations or referral.[547,565–567] Tests for small fibers such as pinprick and temperature discrimination are recommended for diagnosis to document the deficits in the same DPN specific pattern.[547,556] Electrophysiological testing or referral to a neurologist is rarely needed for diagnosis, except in situations where the clinical features are atypical, the diagnosis is unclear, and a different etiology is suspected.[547,554,565] However, the presence of atypical features including motor deficits greater than sensory, asymmetry of symptoms and signs, and rapid progression warrant a timely referral.[547] Skin biopsy and/or standardized quantitative sensory testing are sensitive tests for small-fiber neuropathy and should be considered if the clinical features are atypical and a different etiology is suspected.

It is also important to remember that several peripheral neuropathies due to causes other than DM may coexist in persons with DM, mimic diabetic neuropathy, and may be treatable.[547] Thus, undertaking a thorough family and medication history and performing relevant investigations are helpful to assess other potential etiologies, such as alcohol abuse, genetic neuropathies, neoplasia, toxic exposure, and amyloidosis. Laboratory screening includes vitamin B_{12} levels to test for B_{12} deficiency (particularly in persons treated with metformin), thyroid function tests, complete blood count, metabolic panel, and serum immunoelectrophoresis with immunofixation to test for a monoclonal gammopathy.[547]

As recommended by the Toronto Consensus on Diabetic Neuropathy,[568] for research purposes, a diagnosis of confirmed diabetic neuropathy requires a combination of symptoms, signs, and abnormality of objective tests such as changes in nerve conduction studies. The symptoms and signs of DPN have been broadly covered above in the clinical section. However, for research, a range of assessments, including more objective measures and importantly, person-reported outcomes, has been developed over time and validated. The use of validated clinical instruments such as the Michigan Neuropathy Screening Instrument (most widely used in large cohorts of persons with T1D and T2D),[69,417,546,550,569–571] the modified Toronto Clinical Neuropathy Scale,[572] the Utah Early Neuropathy Scale,[573] or the Neuropathy Disability Score[574] are feasible and can be done in a standardized fashion in large cohorts of persons with DM. Instruments for painful DPN also have been validated.[556,558]

In addition to screening for DPN, a comprehensive foot examination at all outpatient office visits is necessary to identify foot ulcerations, infections, vascular insufficiency, and deformities that could lead to limb loss or mortality.[575] The global burden of foot complications, including ulcerations, infections, and ischemia that may lead to amputation, is between 2.2% to 6.3% of persons with DM per year, and the lifetime risk of any foot complication is up to 34% in persons with DM.[576,577] Recurrence of foot ulcerations after healing is common, up to 50% at 3 years.[576] Most foot ulcerations have a neuropathic component[577] and are preventable by foot care that includes daily inspection, nail and skin care, correction of foot deformities, and/or provision of appropriate footwear to accommodate structural changes.[578] In-office examination should include inspection for vascular insufficiency, musculoskeletal deformities, skin breakdown, or abnormal skin callus formation in addition to the DPN examination.[579] Referral to podiatry or others on a multispecialty team may prevent infections and ulcerations from progressing to limb loss.[580] Risk assessment for diabetic foot problems is integral to comprehensive care of persons with DM.[575]

Prevention of Diabetic Peripheral Neuropathy—Prevention of diabetic neuropathies focuses on glucose control and lifestyle modifications. Enhanced glucose control in people with T1D dramatically reduces the incidence of DPN (78% relative risk reduction),[78,542,547,549] and glucose control remains the strongest risk factor for DPN in T1D even in contemporary cohorts.[417,542–544,547] Despite socioeconomic barriers being associated with DPN, one should aim to achieve near-normal glycemia in persons with T1D at risk of DPN.[544] In contrast, enhanced glucose control in people with T2D reduces the risk of developing DPN more modestly.[547,557] The ACCORD trial in individuals with T2D reported a modest but significant DPN risk reduction with intensive glycemia intervention after 5 years of follow-up,[69] but other trials reported inconclusive effects.[547] Specific glucose-lowering strategies may contribute to the discrepancy. For example, participants, particularly men, in the BARI 2D trial treated with insulin sensitizers had a lower incidence of DPN over 4 years than those treated with insulin/SUs.[570] There is also emerging evidence that lifestyle modifications either as exercise alone (supervised aerobic with or without resistance training), combined dietary modification and exercise, or other behavioral interventions may have beneficial effects on preventing DPN in some persons with T2D or prediabetes.[547,526,582,583,581–586] Emerging evidence shows a potential benefit of bariatric surgery on reducing risk of DPN.[587]

Management of Diabetic Peripheral Neuropathy—Despite major advances in elucidating the pathogenesis of diabetic neuropathy, there remains a lack of disease-modifying treatment options in individuals with DM; hence, there is an urgent need for more targeted research.

Currently, there is no convincing evidence supporting glucose control or lifestyle management as therapies for neuropathic pain in DM or prediabetes. At present, among pharmacological options, pregabalin[588–598] and duloxetine[594,595,599,600] are oral agents that have received regulatory approval for the treatment of neuropathic pain associated with DPN by the FDA and are effective for DPN pain reduction when using patient-reported

outcomes.[547] In addition, based on evidence from 2 large 12-week randomized multicenter trials in 2020, the FDA approved the cutaneous concentrated capsaicin 8% patch that works by desensitizing and interfering with the function of the transient receptor potential vanilloid 1 receptor, a protein involved in pain signaling. However, the patch needs to be applied for ~30 minutes and can be done only in the office with a physician present.[601,602] The opioid, tapentadol, has received regulatory approval in the United States and Canada, but evidence for its use is, at best, inconclusive,[603,604] and the ADA and other organizations strongly recommend against using any opioids for management of DPN pain.[547] Reviewing evidence for the variety of agents that can modify DPN pain, one should use a stepwise approach and consider an individual's comorbidities, socioeconomic status, and potential drug interactions.[547,605] Nonsteroidal anti-inflammatory agents should be avoided for chronic pain management in persons with DM due to adverse kidney effects. Given the high risk of addiction, abuse, sedation, and other complications and psychosocial issues, even with short-term opioid use, opioids are not recommended in the treatment of painful DPN.[547] High frequency (eg,10 kHz) spinal cord stimulation is a nonpharmacological approach that may be effective in persons with painful DPN that failed at least one medication, as suggested by a recent large RCT, leading to FDA approval in 2021 (Fig. 4).[606,607]

Regular aerobic, strengthening, and balance exercise, alone or in combination; reduction of sedentary behavior; and dietary modification aimed at reducing calorie intake and increasing plant-based foods and polyunsaturated fats have all demonstrated positive outcomes for individuals with DPN, including for neuropathic pain reduction.[581–583,586,608–610] Small-fiber neuropathies should be managed with foot protection (eg, padded socks); supportive shoes with orthotics, if necessary; regular foot and shoe inspection; prevention of heat injury; and use of emollient creams.[547] Regular foot and nail care by a trained professional is recommended. Advanced stages of large-fiber neuropathies may require a multidisciplinary approach to include strategies to enhance muscle strength, gait, and balance training; titrate any pain or other medications that could promote dizziness and other side effects affecting gait and balance; orthotics to treat and prevent foot deformities; tendon lengthening for pes equinus from Achilles tendon shortening; and/or surgical reconstruction in case of deformities.[547,609]

Autonomic Neuropathies—Autonomic neuropathies affect the autonomic neurons (parasympathetic, sympathetic, or both) and are associated with a variety of condition-specific symptoms and signs that should be evaluated during the medical history and physical examination of all individuals with DM.[547] CAN is the most studied and clinically relevant of the diabetic autonomic neuropathies, whereas GI, genitourinary, and sudomotor dysfunction may also develop during the course of DM and impact a person's QoL and optimal management.[547]

CV Autonomic Neuropathy—Prevalence rates for CAN vary from ~3% to 5% in early T1D, to 44% over 23 years of mean follow-up, even with the current standard of care.[417,542] Prevalence rates as high as 60% have been reported in earlier cohorts with long-standing T2D or more advanced disease.[547,611] Furthermore, even in more contemporary cohorts with

recent-onset T2D prevalence rates of up to 25% have been observed,[545,546] including in youth[417,612–615] or at different degrees of glucose intolerance.[616]

Timely detection of CAN may help implementation of tailored interventions to prevent its progression and mitigate the risk of associated complications, including CVD, cardiac arrhythmias, myocardial dysfunction leading to congestive heart failure (CHF), CKD, and all-cause mortality.[547,614,617–625] Unfortunately, CAN is frequently overlooked in clinical practice due to its characteristic subtle presentation earlier in disease.[547,614]

Screening and Diagnosis of CV Autonomic Neuropathy in Clinical Care—It could be quite challenging to detect CAN in its early stages in routine clinical care, as persons may be completely asymptomatic (subclinical CAN) and may only present with decreased HRV.[547] The most common symptoms of CAN occur upon standing and include lightheadedness, weakness, palpitations, faintness, and syncope.[547,614] Targeted questions to unveil these symptoms should be included with a medical history. The specificity of these symptoms for CAN is quite low as they may occur in many other endocrine disorders, CVD, or with use of various medications, requiring an appropriate differential.[547] In addition, these symptoms occur late in the disease course. Clinicians should consider screening persons at risk for developing CAN for hypoglycemia unawareness and vice versa, as this may be associated with CAN.

Clinical Signs of CV Autonomic Neuropathy—Persons with subclinical CAN present with a decrease in HRV, usually with deep breathing or change in posture, considered the earliest clinical indicator of CAN.[547,614] Although HRV testing is largely confined to the research setting, the CV reflex tests that assess changes in HRV during standardized clinical challenges such as deep breathing, Valsalva maneuver and supine-to-standing position remain the gold standard tests and are available for clinical care as well.[547,614,626] However, even these relatively simple methods could be challenging in some clinical settings, highlighting the need for easily accessible diagnostic tools and/or biomarkers for screening and diagnosis of CAN for general clinical care.[547,627] Indices of HRV derived from standard short electrocardiogram recordings have been recently validated as an alternative approach.[627] Other evaluations requiring a variety of expensive devices have a low sensitivity and specificity for CAN and are not recommended for use in clinical care.[614]

As CAN progresses, persons may present with resting tachycardia with fixed heart rate (>100 bpm), exercise intolerance, nondipping BP and reverse dipping BP, and in most advanced cases with orthostatic hypotension (a fall in systolic or diastolic BP by >20 mm Hg or >10 mm Hg, respectively, upon standing without an appropriate increase in heart rate).[547] Orthostatic hypotension is usually easy to document in the office by measuring the BP supine and after standing. However, as with symptoms, the specificity of the signs for CAN is low, and thorough differential is required.[547] In a symptomatic person with a history of poor glucose control presenting with resting tachycardia or postural hypotension, clinicians may not need to perform additional CAN tests given costs and burden after excluding other potential causes.[547]

Management of CV Autonomic Neuropathy—Intensive glucose control is most effective to prevent CAN in T1D as documented by a 45% reduction in risk with intensive glucose control in the Diabetes Control and Complications Trial, a benefit that persisted during the Epidemiology of Diabetes Interventions and Complications study with a 30% reduction in incident CAN over an additional 14 years of follow-up.[542,628,629] Glucose control as part of a multifactorial intervention that also targeted hypertension, dyslipidemia, and lifestyle demonstrated a 63% reduction in the rate of progression to CAN in a small T2D cohort participating in the Steno-2 trial.[630] Analyses from the ACCORD trial reported that, after adjusting for multiple other risk factors, intensive glucose treatment significantly reduced CAN risk by 16% compared to standard intervention in a large cohort of more than 8 000 participants with T2D in the ACCORD trial over a mean 5-year follow-up.[611] As for DPN, lifestyle modifications with diet and exercise have shown benefit in CAN prevention.[631]

Management of orthostatic hypotension involves both behavioral and pharmacological interventions. Behavioral supportive measures include: (1) avoiding abrupt changes in body position; (2) avoiding actions that elevate intraabdominal and intrathoracic pressures; (3) avoiding medications that would exacerbate hypotension such as tricyclic antidepressants, phenothiazines, and diuretics; (4) raising the head of the bed during sleep; (5) following a schedule of small and frequent meals to minimize postprandial hypotension; (6) considering physical counterpressure maneuvers such as leg crossing and squatting; and (7) hydrating with fluids and salt, if not contra-indicated.[547] Pharmacological therapy includes midodrine and the more recent droxidopa, both of which are FDA approved for the management of orthostatic hypotension and may be considered in persons who fail nonpharmacological interventions. However, it is recommended to proceed with a very slow titration and use the minimally effective dose to avoid undesirable side effects. In selected severe cases, low-dose fludrocortisone may be also an option.[547]

Gastrointestinal Autonomic Neuropathy—GI neuropathies may involve any portion of the GI tract with manifestations including esophageal dysmotility, gastroparesis (delayed gastric emptying), constipation, diarrhea, and fecal incontinence.[547] Among these, gastroparesis may the most common condition providers may consider in clinical practice.

Earlier prevalence data on gastroparesis are limited and inconsistent. However, more recent data from larger community-based studies reported that cumulative incidence of gastroparesis over 10 years was 5% in T1D compared with T2D (1%) and controls (1%). The prevalence of GI symptoms that could mimic gastroparesis increased substantially in recent years in the United States and other countries, although these are nonspecific.

Screening and Diagnosis in Clinical Care—A careful history may unveil symptoms such as early satiety, fullness, bloating, nausea, vomiting, dyspepsia, and abdominal pain. However, all these symptoms are nonspecific and resemble many other conditions, do not correspond with the severity of gastroparesis, and are poorly associated with abnormal gastric emptying.[547] Thus, gastroparesis may be clinically silentin the majority of cases and symptoms and many persons may only present with unexplained early postprandial hypoglycemia followed by later hyperglycemia.[547]

Importantly, besides organic causes such as gastric outlet obstruction or peptic ulcer disease, hyperglycemia, hypoglycemia, and acute changes in BG are well documented to alter gastric emptying.[547] A critical consideration is that several medications widely used in persons with DM, especially opioids, that have been unfortunately prescribed extensively for pain management, and GLP-1 RAs, directly affect gastric emptying and could mimic gastroparesis or cause iatrogenic gastroparesis.[547] Therefore, a thorough differential to exclude all these factors known to affect gastric emptying (including esophagogastroduodenoscopy and/or a barium study of the esophagus, stomach, and upper GI tract), careful documentation of medication intake, and performing CGM if available should always be considered before conducting more specialized testing for gastroparesis and a firm diagnosis is established.

The diagnostic gold standard is the measurement of gastric emptying with scintigraphy of digestible solids at 15-minute intervals for 4 hours after food intake. Optimization of glucose levels prior to scanning is needed to avoid false-positive results. However, this test is burdensome, time consuming, not readily available, and costly. Recently, the use of 13C-octanoic acid breath test has been FDA approved and emerged as a much easier to use alternative.[547]

Other Forms of Diabetic Neuropathies—Other forms of diabetic neuropathies are mononeuritis such as cranial nerve palsies or entrapment neuropathies (eg, carpal tunnel syndrome, ulnar entrapment, and peroneal entrapment, among others).[632–635] There may also be atypical variants of diabetic neuropathy such as small-fiber neuropathies, which present predominantly with pain and autonomic features.[636,637] Risk factors include metabolic syndrome, IFG, and IGT.[638–640]

Question 9: How should antihyperglycemic agents be prioritized in persons with T2D at high risk for or with established CVD?

Recommendation 9.1—In persons with T2D and established ASCVD or at high risk for ASCVD, use GLP-1 RAs with proven CV benefits to reduce the risk of myocardial infarction, stroke, or CV death regardless of other glucose-lowering or CV therapies and independent of A1C.

Grade A; BEL 1

Recommendation 9.2—In persons with T2D and established ASCVD or very high ASCVD risk, use SGLT2is with proven CV benefits to reduce the risk of hospitalization for HF, major adverse CV events (MACE), or CV death regardless of background glucose-lowering therapy, CV therapy, or A1C.

Grade A; BEL 1

Recommendation 9.3—In persons with T2D and established HF (regardless of ejection fraction, background glucose-lowering or HF therapies, or A1C), use SGLT2is with proven HF benefits to reduce the risk of hospitalization for HF or CV death, and to improve HFerelated symptoms.

Grade A; BEL 1

Recommendation 9.4—In persons with T2D and ASCVD or at high risk for ASCVD, use GLP-1 RAs with proven benefit for reduction in the risk of stroke. In persons with insulin resistance, prediabetes, or T2D and a prior transient ischemic attack or stroke, pioglitazone should be considered to reduce the risk of recurrent stroke.

Grade A; BEL 1

Evidence Base 9: How should antihyperglycemic agents be prioritized inpersons with T2D athighriskforor withestablished CVD?

Evidence Base 9.1: DM and ASCVD—ASCVD remains the leading cause of morbidity and mortality in persons with T2D; therefore, prevention of ASCVD events is a key clinical priority. Multiple CVOTs have demonstrated that the use of GLP-1 RAs significantly lowers the risk of MACEdtypically defined as a composite of nonfatal MI, nonfatal stroke, or CV deathdin persons with T2D and either established ASCVD or at high risk for ASCVD. The category of “high risk” varies between studies, but in general includes persons with T2D, target organ damage, and/or risk factors for ASCVD. In specific, large trials of injectable GLP-1 RAs, once-daily liraglutide, and once-weekly albiglutide, semaglutide, dulaglutide, and efpeglenatide have all shown significant reduction in the risk of MACE.[242,427,472,641–643] The trial of once-weekly exenatide demonstrated a directionally favorable effect on MACE but narrowly missed statistical significance.[644] The outcome trial of once-daily lixisenatide was neutral.[645] Initial CVOT of oral semaglutide demonstrated CV safety but was not powered for superiority.[646]

A 2021 comprehensive meta-analysis of 8 major GLP-1 RA CVOTs, comprising more than 60 000 participants, demonstrated that these agents reduce the risk of MACE by 14% (HR, 0.86; 95% CI, 0.80–0.93; $P < .0001$) as well as individual components of MACE, including MI, stroke, and CV death.[643] In addition, GLP-1 RAs also reduced the risk of death from any cause by 12% (HR, 0.88; 95% CI, 0.82–0.94; $P = .0001$) and produced a modest but significant decrease in hospitalization for HF (HR, 0.89; 95% CI, 0.82–0.98; $P = .013$).[643] Importantly, these benefits were consistent in persons with or without established ASCVD and did not differ based on GLP-1 RA structural homology (human vs exendin based), baseline A1C, or background antihyperglycemic therapy (Fig. 5).

Evidence Base 9.2: DM and HF—The risk of HF is 2- to 4-fold higher in persons with DM compared with those without DM.[647] Thus, prevention of HF is critically important. Multiple large CVOTs and kidney outcome trials of SGLT2is have demonstrated robust and consistent reductions in the risk of hospitalization for HF in persons with T2D.[239,423,425,426,648] These trials tested different agents in the class (including empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin), and included both persons with and without established ASCVD, HF, and kidney disease.

A comprehensive meta-analysis of 6 major SGLT2i trials in individuals with T2D, comprising nearly 50,000 participants showed a 32% reduction in the risk of hospitalization for HF (HR, 0.68; 95% CI, 0.61–0.76), a 22% reduction in the composite of hypertensive

HF and CV death (HR, 0.78; 95% CI, 0.73–0.84), and a 15% reduction in CV death (HR, 0.85; 95% CI, 0.78–0.93) with SGLT2is vs placebo.[649] In addition, there was also a modest but significant 10% reduction in the risk of MACE (HR, 0.90; 95% CI, 0.85–0.95).[649] All of these benefits were consistent regardless of presence or absence of ASCVD. Secondary analyses across several of these trials also showed that HF prevention benefits of SGLT2is are present regardless of baseline CV or antihyperglycemic therapies (including metformin) (Fig. 5).[649]

Evidence Base 9.3: DM, ASCVD, and HF—Persons with HF (regardless of left ventricular ejection fraction) have a high risk of death and hospitalizations and experience a high burden of debilitating symptoms, physical limitations, and a poor QoL. The prognosis is particularly unfavorable in persons with HF who have concomitant T2D. Several large RCTs, which in combination enrolled over 8000 persons, have demonstrated that SGLT2is significantly reduce the risk of CV death or worsening HF and improve symptoms, physical limitations, and QoL in persons with heart failure with reduced ejection fraction (HFrEF). In the DAPA-HF (Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure) trial, dapagliflozin reduced the primary endpoint of CV death or worsening HF by 26%, whereas in EMPEROR-REDUCED (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction), empagliflozin significantly reduced the risk of CV death or hospitalization for HF by 25%.[457,470] Both of these studies, as well as a smaller RCT of dapagliflozin (DEFINE-HF [Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in Patients with HF with Reduced Ejection Fraction]) also demonstrated significant improvement in HF-related symptoms with SGLT2is.[650,651] The benefits were highly consistent in persons both with and without T2D; however, because persons with T2D had higher absolute risk, they experienced a greater absolute benefit with SGLT2is vs placebo.

More recently, empagliflozin also was shown to significantly reduce the risk of CV death or hospitalization for HF in nearly 5000 persons with HF and heart failure with preserved ejection fraction (HFpEF) by 21%.[443] Furthermore, the PRESERVED-HF trial of 324 persons with HFpEF demonstrated a large, clinically meaningful, and significant improvement in symptoms, physical limitations, and exercise function with dapagliflozin, as compared with placebo.[652] Similar to HFrEF trials of SGLT2is, in both HFpEF trials the benefits were consistent in persons with and without T2D.

In the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure) trial, which recruited ~1200 persons who were either hospitalized with HF or were recently discharged following hospitalization for HF, and all of whom had T2D, a mixed SGLT1/2 inhibitor sotagliflozin also significantly reduced the primary endpoint of total HF hospitalizations or CV death but is not yet FDA approved.[653]

Collectively, these data indicate that SGLT2is address all key goals of care in HF: reducing death and hospitalizations and improving symptoms, physical limitations, and QoL across the broad range of ejection fraction, and that persons with T2D derive a greater absolute benefit from these agents due to their higher baseline absolute risk (Fig. 5).

Evidence Base 9.4: DM and Stroke—Stroke is a devastating CV event, leading to disability, cognitive and physical dysfunction, recurrent strokes, and death. Persons with DM have a significantly higher risk of stroke, which is particularly pronounced in the elderly. In a cross-sectional study of 4346 persons aged ≥60 years using the National Health and Nutrition Examination Survey 2013–2018 dataset, the presence of DM increased the risk of stroke (OR, 28.019; 95% CI, 19.139–41.020) dramatically.[654] Additionally, the risk of death from stroke in persons with DM is 1.6 to 1.9 times the death rate for persons without DM.[655] The National Health Interview Survey conducted from 2000–2009 included participants with DM (8.2%) and showed that death attributable to cerebrovascular disease was significantly higher (HR, 1.48; 95% CI, 1.18–1.85) among those with DM compared to those without DM.[656] In the large Trial Evaluating Cardiovascular Outcomes with Sitagliptin study population, 1084 deaths were adjudicated from the study population of 14,671 persons with DM and ASCVD.[657] Death due to stroke (n = 65) was more common than death due to MI (n = 48) but less common than sudden death (n = 145).[657]

After the initial cerebrovascular accident (CVA), whether transient ischemic attack or stroke, the risk of recurrence and mortality increases. In an analysis of repeat hospitalization after first-ever lifetime stroke, DM was noted to increase the risk of repeat hospitalization for all causes.[658] Among persons aged <65 years who were stroke survivors and admitted to a comprehensive stroke center in Ontario, Canada (N 8293), preexisting DM was associated with increased risk of in-hospital death (adjusted OR, 1.46; 95% CI, 1.14–1.87) or direct discharge to long-term care (adjusted OR, 1.65; 95% CI, 1.07–2.54).[659] Among those discharged (N 7847), preexisting DM was associated with increased rate of death (adjusted hazards ratio [aHR], 1.68; 95% CI, 1.50–1.88), admission to long-term care (aHR, 1.37; 95% CI, 0.21–1.54]), and incident dementia (aHR, 1.44; 95% CI, 1.17–1.77).[659] Clearly, prevention of incident and recurrent stroke is a high priority in the care of persons with DM. Comprehensive risk factor management for reduction of ASCVD including stroke is discussed in **R 9.1** and **R 9.4** of this document.

Glucagon-like Peptide-1 Receptor Agonists and Stroke: Recent randomized, placebo-controlled clinical trials with adjudicated CV outcomes have been informative regarding the impact of GLP-1 RAs on the risk of fatal and nonfatal stroke. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial randomized 9340 persons with T2D with CVD or at high risk for CVD and demonstrated lower risk for the composite outcome (MI, stroke, CV death) (HR, 0.86; 95% CI, 0.78–0.97; P < .001 for noninferiority, P = 0.01 for superiority).[427] The HR for nonfatal stroke (HR, 0.89; 95% CI, 0.72–1.11; P = .30) provided the first indication that GLP-1 RAs could have a positive effect on stroke.[427] SUSTAIN-6, the semaglutide CVOT, tested once-weekly injectable semaglutide and found a more pronounced effect on stroke (HR, 0.61; 95% CI, 0.38–0.99; P = .04).[242] PIONEER-6, the CVOT for oral semaglutide, showed noninferiority for MACE and numerically fewer nonfatal strokes.[646] Dulaglutide was tested in 9901 participants with DM and prior ASCVD or at high risk for ASCVD and showed reduction in MACE (HR, 0.88; 95% CI, 0.79–0.99; P = .026) and reduction in nonfatal stroke (HR, 0.76; 95% CI, 0.61–0.95; P = .017).[642] In the CVOTs Harmony Outcomes (albiglutide vs placebo), EXSCEL (exenatide LA vs placebo), and AMPLITUDE-O (efpeglenatide vs

placebo), there were numerically fewer strokes, but HRs were not significant.[472,641,644] ELIXA (lixisenatide vs placebo after acute coronary syndrome) showed noninferiority for MACE but no effect on fatal or nonfatal stroke.[645] Two meta-analyses of CVOTs of GLP-1 RAs vs placebo reported MACE outcomes, including stroke.[643,660] A 2021 meta-analysis analyzed 7 RCTs (*N* 56,005 participants) with 174,163 patient years of follow-up and found that GLP-1 RAs reduced nonfatal stroke (RR, 0.85; 95% CI, 0.77–0.95) without statistically significant heterogeneity among the trials.[660] A comprehensive meta-analysis of the 8 completed CVOTs of GLP-1 RAs vs placebo in persons with DM and either prior ASCVD or at high risk for ASCVD reported risk reduction for fatal or nonfatal stroke (HR, 0.83; 95% CI, 0.76–0.92; *P* = .0002).[643] The number needed to treat, calculated over a weighted average median follow-up of 3.0 years to prevent one fatal or nonfatal stroke, was reported as 241 (120–1694).[643] Another meta-analysis evaluated the efficacy and safety of GLP-1 RAs for stroke prevention in 8 RCTs comprising 56,251 participants and found that compared with placebo, GLP-1 RAs reduced nonfatal strokes (OR, 0.84; 95% CI, 0.76–0.94; *P* = .002) and all strokes (OR, 0.84; 95% CI, 0.75–0.93; *P* = .001).[661]

Currently, FDAeapproved indications for the GLP-1 RAs exenatide QW, lixisenatide, and oral semaglutide are to improve glycemic control in adults with T2D. Dulaglutide has an additional indication to reduce MACE for people with T2D with and without established CVD. Liraglutide and semaglutide SC are approved to reduce the risk of MI, CVA, or CV death in adults with T2D and CVD.[662] No other antihyperglycemic agents have an FDAeapproved indication for CVA or stroke prevention (Fig. 5).

Pioglitazone and Stroke: Pioglitazone was arguably the first glucose-lowering medication to be tested in a placebo-controlled, dedicated CVOT. In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive Study), 5238 persons with T2D and prior ASCVD were randomized to receive pioglitazone or placebo with follow-up of an average of 34.5 months.[663] Although the primary composite endpoint was not significant, the main secondary endpoint consisting of all-cause mortality, nonfatal MI, and stroke was positive with an HR of 0.84 (95% CI, 0.72–0.98; *P* = .027).[663] The HR for stroke was 0.81 (95% CI, 0.61–1.07), suggesting but not proving benefit.[663] PROactive was followed by the IRIS trial (Pioglitazone after Ischemic Stroke or Transient Ischemic Attack), which randomized 3876 persons with insulin resistance but not DM to pioglitazone or placebo, with a follow-up of 4.8 years.[664] The primary outcome of fatal or nonfatal stroke or MI was reduced (HR, 0.76; 95% CI, 0.62–0.93; *P* = .007).[664] A post hoc analysis of the IRIS trial in the subset of participants with prediabetes and good adherence (A1C 5.7%-6.4%, *N* 1454) showed that pioglitazone reduced the outcomes of stoke (HR, 0.64; 95% CI 0.42–0.99) and stroke/MI (HR, 0.57; 95% CI, 0.39–0.84).[665] Adverse events of HF, edema, and bone fracture were increased with pioglitazone.[664] A meta-analysis of these trials plus others of varying size and duration reported that the use of pioglitazone reduced the risks of MACE and MI significantly, whereas there was a trend toward reducing recurrent stroke (RR, 0.81; 95% CI, 0.65–1.01) in persons without DM, similar to the result in persons with DM (RR, 0.78; 95% CI, 0.62–1.02).[666] Another meta-analysis of the risk of recurrent stroke in persons with prior transient ischemic attack or stroke (*N* 4980 with insulin resistance, prediabetes, or DM) found that pioglitazone reduced the risk of recurrent stroke (HR, 0.68; 95% CI, 0.50–0.92; *P*

= .01) and future major vascular events (HR, 0.75; 95% CI, 0.64–0.87; P = .0001) without heterogeneity across clinical trials (Fig. 5).[667]

Clinicians should discuss the risks and benefits of GLP-1 RAs with proven ASCVD risk reduction in persons with DM who are at high risk for stroke or who have had a prior stroke. This recommendation is concordant with evidence reviews and recommendations of other national and international bodies.[199,431,662] Alternatively, consider pioglitazone for stoke prevention after the risks and benefits of this therapy have been evaluated clearly and presented to persons with DM so that adverse effects can be avoided. Additional study of these antihyperglycemic agents in persons at risk for stroke is clearly warranted.

Question 10: How should obesity be managed in persons with DM?

Recommendation 10.1—Persons with prediabetes, T1D or T2D, and obesity/adiposity-based chronic disease (ABCD) have 2 diseases, and each should be treated effectively with the goal of optimizing their respective outcomes.

Grade B; BEL 2 and expert opinion of task force

Recommendation 10.2—The diagnosis and evaluation of ABCD in persons with prediabetes, T1D, or T2D should include both anthropometric and clinical components. The anthropometric evaluation should include body mass index (BMI), confirmed by physical examination that excludes excess muscle mass, edema, or sarcopenia. Waist circumference (WC) should be measured as a marker of cardiometabolic disease (CMD) risk.

Grade B; BEL 2 and expert opinion of task force

Recommendation 10.3—For most adults, BMI values that indicate excess body weight are 25 to 29.9 kg/m^2 for overweight and ≥30 kg/m^2 for obesity, and WC threshold values ≥102 cm for men and ≥88 cm for women.

Grade B; BEL 4 and expert opinion of task force

Recommendation 10.4—The clinical evaluation of persons with both prediabetes, T1D, or T2D and ABCD should assess the presence and severity of weight-related complications including cardiometabolic complications such as dyslipidemia, hypertension, nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH), CVD, HF, and CKD; biomechanical complications such as obstructive sleep apnea (OSA), osteoarthritis, gastroesophageal reflux disease, and urinary incontinence; abnormalities involving sex steroids, such as infertility, polycystic ovary syndrome, and hypogonadism; as well as impact on psychological disorders and QoL.

Grade B; BEL 2 and expert opinion of task force

Recommendation 10.5—Persons with T2D and ABCD should be treated with weight-loss interventions which will both improve glycemic control and prevent or treat ABCD complications. The target for weight loss should be >5% to ≥10% of baseline body weight.

Grade A; BEL 1

Recommendation 10.6—Persons with T2D and ABCD should be instructed and supported in therapeutic lifestyle interventions that include a reduced-calorie healthy diet generally designed to produce a ≥500 kilocalorie daily energy deficit, daily physical activity, regular exercise (several times a week), and behavioral health practices.

Grade A; BEL 1

Recommendation 10.7—The Mediterranean, low-fat, low-carbohydrate, very lowecarbohydrate, vegetarian, vegan, and DASH diets are recommended, safe, and effective for short-term (1–2 years) weight loss, though evidence of long-term risk reduction for CVD events and mortality exists only for the Mediterranean diet.

Grade A; BEL 1

Recommendation 10.8—Persons with T2D and obesity/ABCD with BMI ≥27 kg/m^2 should be treated with DM medications associated with weight loss (GLP-1 RAs, SGLT2is). In addition, for persons with prediabetes, T1D, or T2D who have obesity/ABCD, consider FDAeapproved weight-loss medications as an adjunct to lifestyle intervention to achieve lowering of A1C, reduction of CVD risk factors, treatment, or prevention of other ABCD complications, and improvement in QoL.

Grade A; BEL 1

Recommendation 10.9—Persons with a BMI ≥35 kg/m^2 and one or more severe obesity-related complications remediable by weight loss, including T2D, high risk for T2D (insulin resistance, prediabetes, and/or metabolic syndrome), poorly controlled hypertension, NAFLD/NASH, OSA, osteoarthritis of the knee or hip, and urinary stress incontinence, should be considered for a bariatric procedure.[668]

Grade C; BEL 3

Recommendation 10.10—Persons with BMI 30 to 34.9 kg/m^2 and T2D with inadequate glycemic control despite optimal lifestyle and medical therapy should be considered for a bariatric procedure.[668]

Grade B; BEL 2

Evidence Base 10: How should obesity be managed in persons with DM?

Diagnosis of Obesity—Increased adiposity occurs as a positive energy imbalance driven by dysregulated interactions involving central nervous system satiety factors, resulting in increased caloric intake and excess adipose tissue mass.[669] Although lean individuals can have insulin resistance and CMD, weight gain together with CMD exacerbates insulin resistance and leads to greater storage of fat in the intra-abdominal depot, ectopic accumulation of fat in liver and muscle cells, and heightened dysregulation of adipocytokines and systemic inflammation.[670–673] Weight gain increases risk of overt T2D

by increasing insulin resistance, thereby placing greater metabolic stress on the pancreas b cells in individuals predisposed to b-cell fatigue. BMI is currently used as a general screening tool to diagnose overweight (BMI 25 to 29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2), but these BMI cutoffs do not capture risk of adiposity among varied ethnic groups, nor do they identify individual CMD risk. ABCD is a medical diagnostic term that recognizes that excessive weight gain engenders abnormalities in the mass, distribution, and function of adipose tissue and leads to chronic complications that confer morbidity and mortality.[672,673] Thus, persons with T2D and ABCD have 2 diseases that interact to worsen outcomes, and each requires effective therapy. Weight loss not only addresses glycemic control but also addresses both the prevention and treatment of other cardiometabolic and biomechanical complications of obesity.

The comprehensive diagnosis of ABCD requires both anthropometric and clinical components[674,675] The anthropometric component is largely satisfied by BMI, which is used to diagnose individuals as lean (BMI 18.5 to 24.9 kg/m^2), overweight (BMI 25 to 29.9 kg/m^2), or obese (BMI ≥30 kg/m^2). BMI can be further categorized as obese class I (BMI 30 to 34.9 kg/m^2), obese class II (BMI 35 to 39.9 kg/m^2), and obese class III (BMI ≥40 kg/m^2). In South Asian, East Asian, and Southeast Asian populations, health is adversely affected at lower levels of BMI, and alternate criteria have been advocated, with BMI 18.5 to 22.9 kg/m^2 indicative of normal weight, 23 to 24.9 kg/m^2 overweight, and ≥25 kg/m^2 obese.[674] Clinical correlation is required because BMI may not reflect adipose tissue mass in individuals with increased muscle mass, sarcopenic obesity, paraplegia, frailty, edema, or other conditions that affect body composition. WC thresholds indicate increased risk of CMD and exhibit regional and ethnic variations.[676] Distribution of fat to the abdominal/visceral compartment can be assessed by WC, using cutoff points of ≥102 cm for men and ≥88 cm for women in the United States and Canada and ≥94 cm in men and ≥80 cm in women in many other populations. In South Asian, Southeast Asian, and East Asian adults, WC ≥85 cm in men and ≥74 cm in women indicate excess abdominal fat.[676,677]

The limitation of BMI as a diagnosis of obesity is that BMI does not indicate the impact of excess adiposity on overall health.[675] The health effects of excess adiposity are manifest by the development of adverse weight-related complications that are the cause of morbidity and mortality.[672,673] Complications or relevant risk factors determine disease staging and indicate the need for more aggressive therapy to improve individual health. In persons with ABCD and T2D, this involves an assessment of the severity of T2D as well as other cardiometabolic and biomechanical complications because all individuals with T2D would be designated stage 2 (at least one severe complication) ABCD.

Weight-loss Therapy and Lifestyle—Weight loss of >5% to ≥10% or more is needed to achieve progressive and optimal improvements in A1C, BP, and lipids in persons with T2D and ABCD.[678,679] Weight loss of 10% or more is required to remedy other common complications of ABCD, such as OSA [680–682] and NASH.[683–685] The treat-to-target objectives for the degree of weight loss should be individualized both for improvement of glycemia and for improvements in ABCD complications, to include BP, lipids, osteoarthritis, urinary stress incontinence, NAFLD/NASH,[686] and OSA. The reader is referred to the 2016 AACE guideline for care of persons with obesity for evidence attesting to the

amount of weight loss needed and efficacy of weight-loss therapy for addressing ABCD complications.[674]

All persons with T2D and ABCD complications should be instructed and supported in therapeutic lifestyle interventions that include a healthy diet with emphasis on weight management, daily physical activity, and regular exercise (several times a week). Consultation with a psychologist or CDCES is recommended as needed to support long-term behavior change. The most important feature for diet modification is a reduced-calorie meal plan, which is essential for effective weight loss.[687–690] The initial dietary prescription should generally be designed to produce a 500 kilocalories daily energy deficit. Very lowecalorie diets and meal substitutes can be considered and have the potential for T2D remission.[689,691,692] The following reduced-calorie meal plans have been shown to be safe and effective for weight loss in the short term (1–2 years) in persons with T2D and ABCD: Mediterranean,[693–700] low fat,[689,690,701–704] low carbohydrate, very low carbohydrate,[694,702–715] vegetarian and vegan,[716–720] and DASH diets.[721–723] However, evidence of long-term protection against CVD events and mortality exists only for the Mediterranean diet.[698,724–726] Minimal differences in weight loss between reduced-calorie diets with different macronutrient composition allow health care professionals to personalize recommendations for foods and macronutrients on the basis of individual medical conditions, cultural and personal preferences, lifestyle, and behaviors.[679]

A second lifestyle modification may pertain to the potential challenges and barriers for increased physical activity and exercise that may exist in persons with T2D and high BMI. Physical activity and aerobic exercise guidelines are similar in persons with T2D independent of lean vs overweight/obese BMI.[431,674,727,728] It is important to evaluate persons with T2D for contraindications, disabilities, and/or other physical limitations that may accompany increased adiposity. A physical activity and exercise program should be individualized for each person according to their personal preferences, goals, and physical limitations.[727] Importantly, increased physical activity is a main component in any lifestyle program for achieving and maintaining weight loss. In the Look AHEAD (Action for Health in Diabetes) trial, 1-year results revealed a significant association between increased minutes of physical activity and degree of weight loss.[689]

A systematic review and meta-analysis of 10 RCTs assessing lifestyle interventions vs standard care in persons with T2D found a pooled effect of 3.33 kg average weight loss associated with a 0.29% decline in A1C.[687] Another meta-analysis of 11 RCTs with 6754 participants employing lifestyle intervention (calorie restriction, regular physical activity/exercise and frequent contact support from health care professionals) duration of at least 1 year, showed significantly better effects on A1C, lipids, and BP in those with >5% weight loss compared to those with <5% weight loss.[688]

The benefits of an intensive lifestyle and behavioral weight-loss intervention in persons with T2D was rigorously examined in the Look AHEAD trial.[678,689,690,729] This study randomized 5145 persons to an intensive lifestyle intervention or standard DM support and education. The intensive lifestyle group were placed on a low-fat and reduced-calorie diet ranging from 1200 to 1800 kilocalories per day based on initial weight. Liquid meal

replacements were made available to participants who found this helpful for portion control to enhance adherence to the caloric goal. The physical activity goal was at least 175 minutes per week consisting of activities similar in intensity to brisk walking. The participants had frequent group and solo visits with support staff, and behavioral strategies were stressed, such as self-monitoring, goal setting, and problem-solving. Intensive lifestyle intervention resulted in 1-year weight loss of 8.6%, and 4-year weight loss of 4.7% compared with 1.1% in the standard group, and was accompanied by lower A1C with less need for DM medications, DM remission in ~10% of persons, lower diastolic and systolic BP, improved lipids (higher HDL-C, lower triglycerides), improvements in OSA as reflected by lower apnea hypopnea index scores, increased mobility, slower progression of nephropathy, and improved QoL.[678,680,690,729–733] The magnitude of weight loss after 1 year in Look AHEAD was related to the frequency of using meal replacements, amount of physical activity performed, and attendance at behavioral support sessions.[689] The principal outcome measure in Look AHEAD was CVD events, and the study was discontinued prematurely when an interim analysis showed no difference between treatment groups after 9.6 years median follow-up. Even so, in subanalyses, persons losing more than 10% of weight at 1 year experienced a 21% reduction in the composite CVD outcome.[734]

The Primary Care-Led Weight Management for Remission of Type 2 Diabetes (DIRECT) trial reported on persons with T2D and ABCD followedinprimary-care clinics inthe United Kingdomrandomized to a very lowecalorie diet vs standard care.[691,692] The very lowecalorie diet group lost 10 kg after 1 year and experienced a DM remission rate of 46% compared to 1 kg weight loss and 4% remission rate in the control group. Remission of T2D was directly related to the amount of weight lost with the remission rate rising to 86% inpersons losing ≥15 kg at 1 year.[691] After 2 years, 36% of persons with T2D remained in remission compared to 3% who received standard care.[692]

The Look AHEAD and DiRECT studies attest to the powerful benefits of lifestyle interventions and weight loss in persons with T2D and ABCD. These composite data indicate that weight loss should be a primary treatment modality in persons with T2D and ABCD.

Obesity and Diabetes Medications—Weight loss >5% to ≥10% is required for optimal treatment of most persons with T2D to optimally improve glycemia and address the risk, presence, and severity of ABCD cardiometabolic and biomechanical complications.[678–683] Since this degree of sustained weight loss is not commonly achieved by lifestyle interventions alone,[687,688] weight loss medications should be routinely considered as an adjunct to lifestyle inpersons with T2D and ABCD. These medications are approved when used in conjunction with a reduced-calorie diet plan for any person with BMI 27 to 29.9 kg/m^2 who have at least one ABCD weight-related complication, to include T2D, or for any person with BMI ≥30 kg/m^2 regardless of ABCD complications.

The addition of weight-loss medications has been shown to achieve significantly more weight loss than lifestyle interventions alone and produce greater A1C lowering and improvements in cardiometabolic risk factors. The mechanism of action for all weight loss medications (except orlistat) is to blunt appetite at the level of the central nervous

system hypothalamic satiety centers, which thereby helps individuals adhere to a reduced-calorie diet. All FDAdapproved medications for chronic weight management have also been demonstrated to be effective and safe in both RCTs and a meta-analysis involving persons with T2D.[735–742] The design of these studies was consistent in that all persons with T2D were treated with lifestyle intervention and then randomized to placebo vs weight-loss medication. The study's weight-loss medication arms consistently resulted in: (1) greater weight loss than lifestyle alone, (2) lower A1C values despite less need for DM medications, (3) reductions in BP, (4) lower triglycerides and higher HDL-C, (5) decreased levels of hepatic transaminases, and (6) improvements in inflammatory and other biomarkers such as CRP, fibrinogen, and adiponectin, when compared to the control arms treated with lifestyle intervention plus placebo.

Medications used for weight loss include several sympathomimetic amines (phentermine, benzphetamine, and phendimetrazine) approved for short-term use (≤12 weeks), which makes these drugs ineffectual for treatment of ABCD as a chronic disease. There is a lack of rigorous long-term safety data available for the sympathomimetic amines because this criterion was not required at the time of their approval. Placebo-subtracted weight loss approximates 5.1% in individuals without T2D,[743] and although longer-term cohort studies have been reported,[744] there is a lack of clinical trial data assessing efficacy and safety in persons with T2D.

Orlistat at a dose of 120 mg 3 times per day taken with meals produced placebo-subtracted weight loss of ~4% after 1 year in persons without T2D[745] and has been shown to be effective in those with T2D.[735–737,739] Weight loss produced by orlistat led to A1C reductions of 0.75% after 1 year (baseline value 8.9%) in persons with T2D who were overweight or obese. In a meta-analysis of 7 RCTs involving 1 249 persons with overweight/obesity and T2D treated with orlistat, 23% of persons lost ≥5% weight and exhibited pooled mean weight loss of 8.6 kg with decrements of 1.16% in A1C, 5.3% in total cholesterol, and 5.2 mm Hg in systolic BP.[739] A CVOT has not been performed for orlistat.

Phentermine/topiramate-extended release (ER) resulted in placebo-subtracted weight loss of ~8% to 9% in phase 3 RCTs that enrolled participants without T2D.[746–748] In persons with T2D, phentermine/topiramate-ER administration led to placebo-subtracted weight loss of 9% to 10% at 1 year, and reduced A1C by 0.4% in persons with a baseline mean A1C of 7.0% and by 1.6% in those with a baseline mean A1C of 8.6% who had long-standing T2D treated with multiple medications.[740,749] Weight loss was accompanied by improvements in lipids, BP, and CVD risk biomarkers. Importantly, these improvements were significantly greater than the lifestyle intervention alone and occurred despite greater reductions in the need for conventional DM drugs. A CVOT has not been performed for phentermine/topiramate-ER.

Naltrexone/bupropion-ER produced placebo-subtracted weight loss of ~4–5% in persons without T2D[750–752] and in those with T2D led to a reduction in A1C of 0.6% vs 0.1% compared with placebo, with improvements in triglycerides and HDL-C.[738] There was no weight loss benefit for BP and the drug is contraindicated in individuals with uncontrolled

hypertension. A CVOT for naltrexone/bupropion-ER was terminated early, and there was insufficient data to assess CV safety.[753]

Liraglutide is an acylated human GLP-1 RA that is injected subcutaneously once per day. Liraglutide doses up to 1.8 mg/day are approved for glycemic control and to reduce the risk of major adverse CVD events in adults with T2D. The liraglutide dose-response for weight loss is greater than that for glycemic control, and 3 mg per day is approved for chronic weight management. In 3 studies of 56-week duration involving persons with obesity and dyslipidemia or hypertension, weight loss ranged from 6.2% to 8.0% with 3 mg liraglutide vs 0.2% to 2.9% with placebo.[754–756] In persons with T2D, liraglutide 3 mg significantly reduced weight over 56 weeks by 6.0% and to a greater extent than liraglutide 1.8 mg (4.7%) and placebo (2.0 %).[741] Reductions in A1C were also greater with liraglutide 3 mg (-1.3%) compared to liraglutide 1.8 mg (-1.1%) and placebo (0.3%). These differences in A1C were achieved while actively treating to an A1C target for liraglutide, with a greater number of persons requiring fewer DM medications or less need to increase DM medications with liraglutide 3 mg compared to liraglutide 1.8 mg. Liraglutide 3 mg, but not liraglutide 1.8 mg, significantly improved levels of total cholesterol, VLDL-cholesterol HDL-C, triglycerides, plasminogen activator inhibitor 1, and UACR compared with placebo.[741] In clinical trials of liraglutide 3 mg, the incidence of cholelithiasis was greater than placebo.[741,754]

The GLP-1 RA semaglutide is acylated for binding to albumin and has an amino acid substitution to prevent degradation by DPP-4 that prolongs its half-life to allow once weekly subcutaneous injection. It is approved at doses of 0.5 mg and 1.0 mg per week for glycemic control in adults with T2D and to reduce the risk of major CVD events. Oral semaglutide 7 mg and 14 mg is approved for glycemic control but is not currently approved for chronic weight management, though a higher dose formulation is under development for obesity.

Subcutaneous semaglutide at the higher dose of 2.4 mg/week has been approved for chronic weight management based on results from 4 pivotal Semaglutide Treatment Effect in People with Obesity (STEP) trials.[742,757–759] The STEP 1 Trial enrolled persons without T2D and demonstrated placebo-subtracted weight loss was 16.9% with on-treatment analysis (analogous to completers) and 14.9% weight loss with in-trial analysis (analogous to last observation carried forward with imputation).[757] The STEP 1, 3, and 4 trials used semaglutide in conjunction with a lifestyle program and resulted in 16.9% to 18.2% weight-loss (using a completers-type analysis), which is superior to phase 3 trial results for other weight-loss medications, though without head-to-head drug comparison. A phase 2 study in persons with biopsy-proven NASH using a daily injection equivalent to semaglutide 2.4 g/week demonstrated 13% weight loss and improvement in hepatic fibrosis stage in 43% of participants compared to 1% weight loss and 33% fibrosis score improvement with placebo.[760]

The STEP 2 trial enrolled persons with T2D and ABCD and included 3 randomization groups, treatment with semaglutide at the dose approved for obesity (2.4 mg/week), semaglutide at the dose approved for T2D (1.0 mg/week), and placebo (Table 14).[742] Placebo-subtracted weight loss was greater in persons taking semaglutide 2.4 mg (6.2%) compared to semaglutide 1.0 mg (3.6%), and semaglutide 2.4 mg in conjunction with

lifestyle changes led to 10.6% weight loss in a completers-type analysis. In STEP 2, A1C lowering was relatively similar in both groups, though persons treated with semaglutide 2.4 mg achieved improvements in cardiometabolic risk factors, including WC, A1C, spontaneous bacterial peritonitis, lipids, UACR, CRP, and liver parameters.[742]

Although efficacy has been documented for weight-loss medications compared to placebo-subtracted weight loss, it is important to consider there is a wide range of weight loss reported in studies among these medications. Moreover, the 1-year efficacy can be predicted based on early response to weight loss.[761] If certain thresholds for early weight loss are not met, the FDA prescribing recommendation is to either stop the medication, continue the medication and intensify lifestyle behaviors for diet and exercise, or switch to a different medication. Phentermine/topiramate-ER and naltrexone/bupropion-ER have 2- and 4-week time periods of dose uptitration, respectively, with a weight cut-off to stop the drug if <5% weight loss occurs at 12 weeks. Liraglutide 3 mg has a 4-week dose uptitration period and based on clinical trial data, the weight cutoff for stopping the drug is <4% weight loss at 16 weeks. The FDA prescribing information for orlistat and semaglutide 2.4 mg does not contain weight cutoff rules. Weight-loss medications should be considered and available to prescribe for any individual unless contraindicated to enhance the likelihood that a drug will be found effective for successful weight loss. Semaglutide 2.4 mg has the greatest placebo-subtracted weight loss in clinical trials, with only 14% of persons losing only <5% body weight.[757,758] Persons with T2D are reported to have less weight loss in clinical trials than individuals without T2D, and in persons with T2D treated with semaglutide 2.4 mg, up to 27% have lost <5% weight.[742]

Benefits of phentermine/topiramate-ER in persons with T2D include lower A1C and less need for DM medication compared to placebo, as reported in the OB-202/DM-230 study in persons with T2D duration of 8 to 9 years, baseline A1C 8.7%, and an average 1.6 DM medications per person, and as reported in the CONQUER study in a subset of persons with T2D duration <5 years and baseline A1C 6.8%.[740]

FDA-approved weight-loss medications should be used with caution and monitored closely in adults aged ≥65 years with T2D and ABCD due to a relative lack of data addressing safety concerns. Additionally, persons aged ≥65 years with T2D and ABCD who are being considered for medical or surgical weight-loss therapy should be evaluated for bone loss (osteopenia/osteoporosis) and sarcopenia.

Despite the clinical benefits realized with weight-loss therapy in persons with T2D, there is more difficulty achieving and maintaining weight loss than in individuals without T2D.[762] It is important to be aware that several medications used to treat DM result in weight gain.[73,763,764] For achieving glycemic targets in individuals with T2D and ABCD, DM medications associated with weight loss (eg, GLP-1 RA, SGLT2is), or those associated with weight neutrality or minimal weight loss (metformin, DPP-4 inhibitors), should be considered over medications associated with weight gain (eg, insulin, SUs, meglitinides, thiazolidinediones [TZDs]) when possible, to the extent they are needed to achieve A1C targets.

Current DM medications associated with weight loss (eg, SGLT2is and GLP-1 RAs at doses approved for T2D) often do not usually produce sufficient weight loss for optimal treatment of ABCD. None of the current DM medications associated with weight loss, including GLP-1 RAs and SGLT2is, have resulted in more than 5.6% weight loss in clinical trials, and this includes dulaglutide,[765] exenatide,[766] exenatide-ER,[767] liraglutide 1.8 mg,[768] lixisenatide,[769] semaglutide 1.0 mg/week,[770,771] semaglutide 1.0 mg/week added to SGLT2i,[772] oral semaglutide 14 mg,[773] canagliflozin,[774] dapagliflozin,[775] and empagliflozin.[776] These DM drugs do not achieve adequate weight loss for optimal treatment of ABCD in the majority of persons. In persons with T2D and ABCD, improvements in A1C, BP, and lipids require >5% weight loss and are progressive up to and exceeding 15% weight loss,[678,679] whereas other common complications of ABCD, such as OSA and NASH, may require >10% weight loss for clinical benefits.[680–685] Health care professionals who treat persons with T2D with GLP-1 RAs and SGLT2is without further consideration of other ABCD complications may not be effectively treating that person's composite CMD risk.

Metabolic (Bariatric) Surgery and Endoscopic Devices—Bariatric surgery and endoscopic procedures are important therapeutic options in persons with T2D and ABCD.[777–781] In clinical trials comparing bariatric surgery vs medical treatment in persons with T2D, bariatric surgery results in greater short-term and long-term lowering of A1C, including remission of T2D in some persons.[777–783] Persons with T2D and ABCD who undergo bariatric surgical procedures must have careful evaluation pre- and peri-operatively due to anesthesia and surgical risks, and post-operatively because of risks of micronutrient deficiencies and hypoglycemia, particularly following malabsorptive procedures such as Roux-en-Y gastric bypass or biliopancreatic diversion.

While recommendations are adopted from the 2019 AACE/TOS/ASMBS bariatric surgery guideline,[668] several key studies involving persons with T2D warrant mention. The STAMPEDE (Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently) trial showed that metabolic surgery, when compared with intensive medical therapy (lifestyle counseling, weight management, self-monitoring of glucose, drug therapy), significantly improved outcomes for weight loss, DM remission, glycemic control, need for DM medications, lipid and BP medications, and QoL[777] Five-year outcomes from a 2020 RCT reported that Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding achieved remission of T2D in 30% and 19% of persons, respectively, compared with 0% of controls undergoing intensive lifestyle weight intervention.[784] Ten-year data from a single-center RCT in Italy showed that 37.5% participants randomized to a surgical intervention maintained DM remission (25% for Roux-en-Y gastric bypass and 50% for biliopancreatic diversion) compared with 5.5% of participants treated with medical therapy.[783] In the prospective SOS (Swedish Obese Subjects) cohort study, bariatric surgery produced DM remission rates of 72% and 30% after 2 and 15 years, respectively, and was associated with a reduction in micro- and macrovascular DM complications, including risk of CV death.[779,780] At a median follow-up of 20 years, the HR was 0.77 ($P < .001$) for death, with reduced death from CVD and cancer compared with the control cohort in the SOS cohort study.[785] Thus, there are ample data to support bariatric surgery as an effective therapeutic

approach in persons with T2D, obesity, and uncontrolled DM refractory to lifestyle and pharmacotherapy.

In addition to carrying over 3 recommendations from the 2019 bariatric surgery guideline,[668] a new recommendation is added unique to the current guideline regarding endoscopic and orally ingested devices for weight loss in persons with T2D. The 2019 AACE/TOS/ASMBS bariatric surgery guideline reviewed evidence regarding endoscopic devices for treating obesity but did not make any recommendations for use due to lack of an adequate evidence base as of 2019. Various bariatric devices function by: (1) reducing the stomach's capacity via space-occupying devices, such as intragastric balloons or orally ingested hydrogels, (2) inhibiting gastric emptying via a transpyloric shuttle, (3) evacuation of stomach contents following meals (aspiration therapy), or (4) preventing nutrient absorption across the duodenal mucosal surface.[668] Some endoscopic and orally delivered devices have been approved by the FDA for treatment of obesity, including hydrogel capsules,[786] intragastric balloon systems,[787–788] a transpyloric shuttle that blocks gastric emptying,[789] and gastric aspiration therapy that evacuates partial gastric contents following meals via a variation of a percutaneous endoscopic gastrostomy tube.[790]

None of these devices have been approved to treat T2D, though some trials included some persons with T2D. The hydrogel capsules are well tolerated and in the Gelesis Loss of Weight (GLOW) study produced 2% placebo-subtracted weight loss.[786] However, 59% of participants treated with these hydrogel capsules achieved non-eplacebo-subtracted weight loss ≥5%, and persons with prediabetes or drug-naïve T2D were more likely to achieve a favorable weight-loss response.[786] The intragastric balloon and transpyloric shuttle trials included some persons with T2D, but numbers were inadequate to assess safety and efficacy in those with T2D.[787–789] Duodenal mucosal resurfacing involves a catheter-based hydrothermal ablation of the duodenal mucosa followed by subsequent regeneration of healthy new mucosa with therapeutic effects lasting up to 1 year. In April 2021, the duodenal mucosal resurfacing approach was given an FDA Breakthrough Device Designation for treatment in persons with T2D, which should accelerate its development and review.[791] Clinical trials have demonstrated A1C lowering of 0.9% to 1.2% over 6 to 12 months irrespective of weight loss.[792–794] Problems of duodenal stenosis treatable by endoscopic balloon dilation have been reduced via changes in catheter design. There is potential for duodenal mucosal resurfacing to be an option for therapy and an adjunct to oral medications in persons with T2D.

Persons Aged ≥65 Years with Type 2 Diabetes and Obesity—It is important to mention T2D and ABCD in persons aged ≥65 years due to the increasing number of persons in this category. Because relatively low numbers of elderly individuals have been included in clinical trials, there is a lack of rigorous efficacy and safety data, particularly regarding weight-loss medications. Weight-loss therapy should be used cautiously and monitored frequently in the elderly[674,795] with clear health-related goals in mind, including glycemic control in T2D, prevention of T2D in persons with prediabetes, BP lowering, and improvements in osteoarthritis, mobility, and physical function, because available evidence supports weight-loss therapy in these conditions. As reviewed in the 2016 AACE guideline for care of persons with obesity,[674] persons aged ≥65 years being considered for weight-loss

therapy or bariatric surgery should be screened for sarcopenia by examining muscle strength and performing a review of systems assessing functionality. Endurance and resistance exercise becomes a valuable addition to lifestyle intervention because it preserves lean muscle mass during weight loss. Elderly individuals should receive adequate calcium and vitamin D for skeletal health, especially after bariatric surgery[796] and should be screened for bone loss per usual guidelines[797] because weight loss results in loss of bone mass[798] and may increase risk for fracture.[799,800] Weight-reduction interventions in elderly persons with ABCD and prediabetes or T2D should consider their nutritional status, eating habits, food availability, social support systems, risk of hypoglycemia, and cognitive abilities.

Section 3: Management of Prediabetes, T2D, and T1D With Selection of Glycemic Targets, Lifestyle Interventions, and Antihyperglycemic Pharmacotherapy (Insulin Therapy for all With T1D and Select Individuals With T2D); Prevention, Identification, and Treatment of Hypoglycemia; Treatment of Hospitalized Persons With DM or Those With Hyperglycemia Without Diagnosis of DM; and Women With GDM

Question 11: How should prediabetes be managed?

Recommendation 11.1—Prediabetes is a metabolic and vascular disorder, and clinicians should actively treat people with prediabetes in order to prevent or at least delay progression to T2D and development of CVD complications.

Grade A; BEL 1

Recommendation 11.2—In persons with prediabetes and/or metabolic syndrome or identified to be at high risk of T2D based on validated risk-staging instruments, the prevention of T2D can be addressed by lifestyle modifications that include a healthy meal plan, regular physical activity, and behavioral health practices and weight loss in persons with ABCD. The Mediterranean diet should be considered to reduce progression to T2D and risk of CVD. Low-fat, vegetarian, and DASH meal patterns can also be considered for prevention of T2D.

Grade A, BEL 1

Recommendation 11.3—Clinicians should manage and monitor CVD risk factors in prediabetes and metabolic syndrome, including elevated BP, dyslipidemia, and excessive weight, with the same targets as for a person with T2D.

Grade B; BEL 2

Recommendation 11.4—Lifestyle intervention should include aerobic and resistance physical activity in all persons with prediabetes and/or metabolic syndrome. The initial aerobic prescription may require a progressive increase in the volume and intensity of exercise, and the ultimate goal should be ≥150 minutes/week of moderate exercise

performed during 3 to 5 sessions per week (**Grade A; BEL 1**). Resistance exercise should consist of single-set exercises that use the major muscle groups 2 to 3 times per week (**Grade A; BEL 1**). An increase in nonexercise and active leisure activity should be encouraged to reduce sedentary behavior (**Grade B; BEL 2**).

Recommendation 11.5—Obesity medications, namely phentermine/topiramate ER, liraglutide 3 mg, or weekly semaglutide 2.4 mg, in conjunction with lifestyle therapy, should be considered in persons with prediabetes and/or metabolic syndrome with ABCD, whether overweight (BMI 27 to 29.9 kg/m^2) or with obesity (BMI ≥30 kg/m^2), when needed to achieve and sustain 7% to 10% weight loss for prevention of T2D.

Grade A; BEL 1

Recommendation 11.6—Although no medications have been approved for the treatment of prediabetes, diabetes medications including metformin, acarbose, pioglitazone, or GLP-1 RA can be considered in persons with prediabetes or in persons who also have ABCD and remain glucose-intolerant following weight loss using lifestyle and/or weight-loss medications.

Grade A; BEL 1

Evidence Base 11: How should prediabetes be managed?

Prediabetes can be identified by the presence of IFG (FPG value of 100 to 125 mg/dL), or IGT (OGTT result of 140 to 199 mg/dL 2 hours after ingesting 75 g of glucose), or an A1C value of 5.7% to 6.4%.[9] Metabolic syndrome, based on National Cholesterol Education Program IV Adult Treatment Panel III (NCEP ATP III) criteria, may be considered a prediabetes equivalent.[801] Both prediabetes and metabolic syndrome confer increased risk of T2D and CVD.[802–804] The risk of progressing from prediabetes to overt T2D are greatest for those persons with a history of GDM, strong family history of T2D, progressive increments in glycemia within the prediabetes range, and who meet criteria for a combination of IFG, IGT, or metabolic syndrome (any 2 out of 3).[9,805,806]

Goals of therapy in persons with prediabetes and metabolic syndrome
✓ Prevent progression to T2D
✓ Prevent progression to NASH
✓ Improve CVD risk factors via aggressive control of:
- elevated BP
- LDL-C
- dyslipidemia

✓ Treat obesity or prevent excessive weight gain
✓ Improve functionality and
✓ QoL

In treating prediabetes and metabolic syndrome, it is important to consider that these clinical states are integral to a chronic progressive pathophysiological process termed CMD, which, as the term implies, gives rise to both metabolic and vascular disease end-stage manifestations.[670] At the core of CMD is the insulin-resistant state characterized by a glucoregulatory defect (ie, normal or elevated glycemia in the face of

hyperinsulinemia) accompanied by multiple biochemical abnormalities involving molecular signaling, gene expression, oxidative stress, mitochondrial dysfunction, and accumulation of inflammatory macrophages in adipose tissue that alters release of adipocytokines into the circulation.[671,807,808] These molecular processes have systemic consequences producing abnormal glucose tolerance, ectopic lipid accumulation within muscle and liver cells, systemic inflammation, dyslipidemia, vascular stiffness, elevated BP, and accelerated atherogenesis. Early in the course of CMD progression, the insulin-resistant state is largely subclinical. However, over time, disease progression gives rise to clinically identifiable states, namely prediabetes and metabolic syndrome, which indicate the presence of CMD and mark individuals at high risk of future T2D, NASH, hypertension, myocardial dysfunction, CVD events, and CKD. Furthermore, with the development of T2D, there is further amplification of vascular disease progression and risk of CVD events.[670]

Obesity plays a key role in CMD because it can exacerbate insulin resistance and impel this disease progression. AACE[672] and the European Association for the Study of Obesity[673] have advocated for the use of ABCD as a medical diagnostic term for obesity. The disease is adiposity based because it involves abnormalities in the mass, distribution, and function of adipose tissue, and is a chronic disease that gives rise to complications, both biomechanical and cardiometabolic, which confer morbidity and mortality. Therefore, ABCD indicates what we are treating and why we are treating it and underscores a complications-centric approach to treatment consistent with the 2016 AACE guideline for care of persons with obesity.[674] Thus, ABCD is clinically meaningful in contradistinction to the BMI-based diagnosis that provides no indication of the impact on health[675] and avoids multiple meanings and stigmatization associated with the term obesity.[672] In this context, treatment of ABCD employing weight-loss therapy is highly effective for treating persons with prediabetes, metabolic syndrome, T2D, and CVD risk factors who also have overweight or obesity.[809]

The natural history of CMD has important implications regarding the treatment of prediabetes and metabolic syndrome. Aggressive preventive interventions are required to halt progression toward all end-stage manifestations of the disease.[809] Thus, comprehensive risk factor management is required for the treatment and prevention of both metabolic and vascular outcomes. With this in mind, the goals of treatment in persons with prediabetes and/or metabolic syndrome are shown in the text box.[75,805] Optimal management of lipids and BP in prediabetes equates with the recommendations for T2D itself (ie, a DM equivalent), as described in the 2017 AACE Guidelines for the Management of Dyslipidemia and Prevention of CVD[286] and 2020 AACE Algorithm for Management of Dyslipidemia,[318] because accelerated atherosclerosis predates the development of overt hyperglycemia and diagnosis of T2D.[810]

In all persons with prediabetes and/or metabolic syndrome, whether lean or with ABCD, dietary and physical activity aspects of lifestyle therapy are cornerstones of risk management in preventing progression to T2D.[811–813] The most robust research available regarding eating/meal patterns for T2D prevention in prediabetes pertains to Mediterranean-style diets.[698,724–726,814–816] In a subgroup analysis of the PREDIMED trial, nondiabetic persons with metabolic syndrome traits who were randomized to Mediterranean diets enriched with

olive oil without restrictions on energy intake experienced a significant reduction in the progression to DM compared with standard dietary advice to avoid fats (HR [0.60; 95% CI, 0.43–0.85]).[814,815] In addition, the PREDIMED trial showed that a Mediterranean-style eating pattern intervention enriched with olive oil or nuts over 4.8 years reduced the composite primary endpoint of MI, stroke, or CV death compared with a low-fat diet in individuals at risk for CVD with or without DM.[724,725] The Lyon Diet Heart Study assessed the efficacy of Mediterranean diets for the secondary prevention of CVD events.[726] Persons who had a previous MI were randomized to a Mediterranean diet or a diet typically consumed in northern European countries, and after 4 years, the Mediterranean diet group had reduced rates of reinfarction and mortality. Adherence to this eating pattern is associated with decreased risk for metabolic syndrome, reduced inflammation, hepatic steatosis, and improved renal function. Mediterranean diets have also been shown to reduce rates of progression to T2D independent of weight loss, and, therefore, can be recommended in lean persons with metabolic syndrome or prediabetes.[814] An umbrella evaluation of meta-analyses affirmed that a higher adherence to a Mediterranean eating pattern was associated with lower incidence of mortality from T2D and CVD.[698] Thus, Mediterranean diets are a highly rational choice as the dietary component of long-term lifestyle therapy in persons with cardiometabolic risk.

With respect to other meal patterns, there are limited RCT data available that address prevention of CMD outcomes in persons with prediabetes or metabolic syndrome. The DASH diet has been shown to reduce BP and is particularly effective in individuals who were hypertensive at baseline and/or self-identified as African American.[817,818] Adherence to a DASH diet is also associated with a low prevalence of DM.[819–821] Low-fat meal plans in the context of a comprehensive lifestyle intervention have been shown to promote weight loss, improve glucose tolerance, and prevent DM in large RCTs enrolling persons with obesity and IGT.[811,822–828] A large number of cohort studies and epidemiological data demonstrate that vegetarian and vegan diets confer metabolic benefits and are associated with a lower risk of developing T2D.[820,829–833] In a meta-analysis of 11 cohort studies,[715] a low-carbohydrate diet was no different than a high-carbohydrate diet regarding incidence of DM[715,834] and could be harmful if fat sources are derived from red meat.[835] Given the limited evidence, it is unclear which meal pattern is optimal. There is a large body of data indicating that isocaloric substitution of specific macronutrients can improve insulin sensitivity assessed by clamp studies and CVD risk factors.[836] These data would generally support macronutrient intake as follows: (1) limitations on fat intake, (2) emphasis on poly/mono-unsaturated fats over saturated fats, (3) no trans fats,[835] (4) complex over simple carbohydrates, (5) whole grains over refined grains[934], (6) fruits and vegetables,[837] (7) dietary fiber,[838] and (8) reduced consumption of processed food.[839] Dietary enrichment of these macronutrients can enhance insulin sensitivity,[836] aligning with the Mediterranean diet and other meal patterns that are epidemiologically associated with reduced prevalence of T2D,[839] and predictably would be beneficial based on the role of insulin resistance in the pathophysiology of CMD. Indeed, these foods and macronutrients coincide with favorable scores on the Healthy Eating Index-2010 (HEI-2010), the Alternative HEI-2010 (AHEI-2010), the Alternative Mediterranean Diet Score, and the DASH scores, which are associated epidemiologically with lower prevalence of DM.[723,840]

There is a plethora of evidence in persons with prediabetes and metabolic syndrome that regular exercise can lower glycemia, improve CVD risk factors, and prevent or delay progression to DM, either in the form of an exercise program per se or as part of a comprehensive lifestyle plan.[841–851] As is the case for persons with T2D, studies have demonstrated beneficial effects of both aerobic and resistance exercise and additive benefits when both forms of exercise are combined.[727,847–852] The physical activity program optimally includes aerobic exercise, which should begin at a low level to allow a person to increase the intensity and duration of the exercise over time. Various guidelines have recommended that, ideally, a person should achieve at least 150 minutes per week of moderately intense aerobic exercise accomplished in 3 to 5 sessions.[674,852,853] High-intensity interval training can be used to achieve comparable metabolic benefits of moderate aerobic exercise with less of a time commitment.[854] A resistance exercise program should be added and should consist of single-set repetitions targeting the major muscle groups 2 to 3 times per week.[674,852,853] Despite these recommendations, less intense exercise and walking programs can reduce risk of DM.[846,855] A final component of a physical activity program is to reduce sedentary behavior and increase active leisure activity.[856–859] The physical activity prescription should be compatible with individual preferences and take into account any health-related or physical limitations.[674]

In persons with ABCD (both overweight or with obesity) and prediabetes and/or metabolic syndrome, weight loss is a highly effective way to prevent progression to T2D.[674] In addition, weight reduction prevents or treats multiple CVD risk factors and additional complications of ABCD.[674] Whether due to lifestyle therapy, obesity medications, or bariatric surgery, weight loss has been shown to (1) enhance insulin sensitivity; (2) prevent or delay progression to T2D particularly in high-risk persons with prediabetes or metabolic syndrome; (3) improve hepatic steatosis; (4) lower BP; (5) improve dyslipidemia; and (6) ameliorate biomarkers of CVD risk, including CRP, interleukin 6 and other markers of inflammation, fibrinogen levels, and serum adiponectin concentrations.[674] Thus, weight loss is perhaps the most effective therapeutic approach for preventing the progression of CMD to T2D and/or CVD events.

In persons with ABCD, the principles of lifestyle therapy are the same as those that generally apply in prediabetes and metabolic syndrome except that the meal plan is presented in a reduced-calorie format to achieve weight loss. Any one of the reviewed meal plans (Mediterranean, low-fat, low-carbohydrate, vegetarian, vegan, and DASH diets) can be used as diets that feature a healthy composition of foods and macronutrients that promote insulin sensitivity[836] and are associated with improvements in CMD outcomes as defined by the HEI[723,840] and other epidemiological data. Although any of these healthy eating patterns can safely be used in the short term for weight reduction and improvements in CVD risk factors, only the Mediterranean diet has been shownto be cardioprotective in the long term. To accomplish weight loss, the incorporation of very lowecalorie diets and meal substitutes into an overall dietary plan has been shownto be effective in achieving greater degrees of weight loss.[689,860]

Regarding lifestyle interventions in persons who have ABCD and prediabetes, 3 major RCTs, the Diabetes Prevention Program, the Finnish Diabetes Study, and the Da Qing

Study, all demonstrated that lifestyle/behavioral therapy featuring a reduced-calorie diet (eg, caloric deficits of 500 to 1000 calories/day) and physical activity are highly effective in preventing T2D.[811,822–828] These lifestyle interventions also improved other aspects of CMD including improvements in insulin sensitivity and CVD risk factors, such as BP, lipids, and markers of inflammation. In addition, long-term follow-up of participants in the Da Qing Study revealed that CVD events and mortality were reduced when comparing the combined subgroups treated with diet and exercise with the controls.[828] The Diabetes Prevention Program study randomized persons with IGT to ordinary care, metformin, and lifestyle intervention subgroups, and after 4 years, lifestyle modification reduced progression to T2D by 58% and metformin by 31%, compared with placebo.[811] Participants achieved approximately 6% mean weight loss at 2 years and 4% weight loss at 4 years in the lifestyle intervention arm, and there was a progressive 16% reduction in T2D risk with every kilogram of weight loss.[822] With observational follow-up after termination of the study, there was still a significant reduction in the cumulative incidence of T2D in the lifestyle treatment group at 10 years, despite the fact that BMI levels had equalized among the 3 treatment arms.[823,824] The Diabetes Prevention Program was a resource-intensive efficacy trial and was not designed to be directly deliverable in real-world settings. The translation of the structured lifestyle intervention used in the Diabetes Prevention Program to community-based programs, commercial programs, and programs using remote technologies have achieved less weight loss than observed in the Diabetes Prevention Program trial itself.[861–869] Despite limited weight loss, some efforts have produced modest improvements in metabolic parameters and, when measured, reductions in incidence of DM. A meta-analysis of 44 Diabetes Prevention Program translation studies reported an average 9.3-month weight loss of 3.77 kg from participants' baseline weight and a decrease in fasting glucose of 2.4 mg/dL.[865] Another meta-analysis of 63 real-world DM prevention efforts demonstrated a weight loss of 2.2 kg in participants and 0.8 kg in controls, but still led to a reduction in incident DM by 25%.[866] Since the degree of DM prevention is proportional to the degree of weight loss,[822] these efforts at translation would predictably be less effective regarding prevention of DM.

It is important to consider the degree of weight loss that is optimal for DM prevention. In the Diabetes Prevention Program, maximal prevention of DM over 4 years was observed at about 7% to 10% weight loss.[811,822] This is consistent with the study employing phentermine/topiramate-ER where weight loss of 10% reduced incident DM by 79% over 2 years, and any further weight loss to ≥15% did not lead to additional prevention.[870] Bariatric surgery produces greater weight loss than observed following lifestyle and pharmacotherapy interventions, yet, in 2 studies, there was a maximum of 76% to 80% reduction in DM rates,[871,872] similar to that observed with phentermine/topiramate-ER[870] and liraglutide 3 mg[873] despite lesser weight loss than achieved following bariatric surgery. These combined data suggest that 7% to 10% weight loss will reduce the risk of future T2D by ~80% and represents a threshold above which further weight loss may not result in additional preventive benefits. For this reason, 7% to 10% weight loss is the appropriate goal in preventing progression to T2D in persons with ABCD and prediabetes and/or metabolic syndrome,[674,679] whether as a component of a structured lifestyle intervention program or in conjunction with obesity medications.

The addition of obesity medications to lifestyle interventions produces more weight loss than attributable to lifestyle intervention alone and leads to greater reductions in incident T2D and improvements in CVD risk factors.[674] Currently approved obesity medications are shown in Table 14 and include phentermine for short-term therapy (≤3 months) and 5 medications approved for chronic obesity management. Orlistat diminishes intestinal fat absorption via lipase inhibition, but the remaining medications act centrally to suppress appetite. When used in combination with lifestyle therapy, orlistat produced greater weight loss compared with lifestyle changes plus placebo and reduced rates of DM by up to 52% among persons with IGT at baseline.[874] Naltrexone-ER/bupropion-ER reduced body weight and A1C in persons with T2D[738] but had minimal effects on fasting glucose in persons without DM;[875] a DM prevention study has not been performed for naltrexone-ER/bupropion-ER. Greater degrees of weight loss in RCTs involving phentermine/topiramate-ER[870] and liraglutide 3 mg[873] were associated with larger reductions in rate of DM and improvement of CVD risk factors. Phentermine/topiramate-ER in persons with prediabetes or metabolic syndrome reduced the annualized incidence rates of T2D by 70.5% and 78.7% among persons receiving the 7.5/46 mg and 15/92 mg daily doses, respectively, over 2 years.[870] These reductions were related to the degree of weight loss (10.9% and 12.1% in the low- and high-dose groups, respectively, vs 2.5% in the placebo group; $P < .0001$) and were accompanied by significant improvements in cardiometabolic parameters.[870] High-dose liraglutide (3 mg/day) in persons with prediabetes reduced weight by 6.1% from baseline over 160 weeks compared with 1.9% in those randomized to placebo, and the cumulative progression to DM was reduced by 72.7%.[873,876] In RCT phase 3 trials (STEP 1, 3, 4), semaglutide 2.4 mg once weekly has produced weight loss of 14.9% to 17.4% from baseline in persons with overweight or obesity compared with 2.4% to 5.7% in placebo.[757–759] In the STEP 1 trial, 45% of persons randomized to semaglutide 2.4 mg/week had prediabetes at baseline and treatment converted many to normoglycemia, reducing the percent with prediabetes to 8.3% by the end of study with improvements in CVD risk factors, compared to 40% and 26% with prediabetes, respectively, on placebo.[757] In addition, a greater number of persons progressed to overt T2D on placebo in the STEP 1 trial compared with semaglutide 2.4 mg,[757] although a study powered to assess DM prevention has not yet been conducted using semaglutide 2.4 mg. Given these high rates of DM prevention, persons with prediabetes and/or metabolic syndrome with ABCD (BMI ≥27 kg/m^2) should be considered for weight-loss therapy involving obesity medications. In addition, weight regain is frequently observed after lifestyle interventions accompanied by worsening of glucose tolerance and CVD risk factors.[811,877] Obesity medications used together with lifestyle changes can be used to sustain a greater degree of weight loss over time to preserve CMD benefits.[674,759]

The at-risk pool of persons at risk of T2D is large,[878,879] and it is not feasible or safe to treat all persons aggressively using all the tools of obesity medicine. However, the risk for developing T2D and CVD varies greatly among persons with ABCD. This presents opportunities for identifying and targeting persons at higher risk for more aggressive interventions.[290,728,806,880–885] For DM risk, clinicians can use the Framingham Risk Score,[880] the ADA Diabetes Risk Calculator,[9,881] and Cardiometabolic Disease Staging.[806,882,883] Cardiometabolic Disease Staging is based on the number and severity

of metabolic syndrome traits and employs two models: (1) a validated categorical approach indicating that persons who meet criteria for a combination of IFG, IGT, or metabolic syndrome (any 2 of the 3) are at greatest risk of both T2D and CVD,[806] and (2) a logistic regression equation providing a quantitative 10-year risk assessment, which has superior accuracy compared with ADA or Framingham risk scores.[882] Additional tools for predicting CVD risk in persons with CMD include the American College of Cardiology (ACC)/AHA Omnibus Risk Estimator,[728] Framingham Coronary Heart Disease Risk Score,[886] and the Reynolds Risk Score.[290] Given the rising personal and social cost of DM, clinicians and health care systems can use these strategies to identify persons at high risk for DM and employ more aggressive interventions in those persons who will most benefit. For example, the number-needed-to-treat to prevent one case of T2D using phentermine/topiramate-ER is markedly reduced among high-risk persons compared with low-risk using Cardiometabolic Disease Staging.[887]

There is strong evidence that oral glucose-lowering medications approved for DM reduce the progression of prediabetes to DM.[888–896] Even so, no medications sanctioned for use in DM or obesity are approved by the FDA solely for the management of prediabetes and/or the prevention of T2D. The Diabetes Prevention Program randomized persons with IGT to placebo, a structured lifestyle intervention, or metformin, and assessed progression to T2D with average follow-up of 2.8 years.[811] Metformin was effective as evidenced by a 31% decrease in progression to DM but was inferior to lifestyle that reduced DM incidence by 58% compared with placebo.[811] Metformin was particularly effective in persons with A1C 6.1% to 6.4%, BMI ≥30 kg/m^2, those aged <60 years, and women with prior GDM.[897] Metformin can also be combined with linagliptin to decrease DM incidence over that observed with metformin alone.[890] Additionally, acarbose may be associated with reduced risk of DM[891–894] as well as coronary heart disease as shown in the STOP-NIDDM trial.[892] More recent study did not show coronary benefit with acarbose but did show decreased progression to T2D.[1058] There is also robust RCT evidence demonstrating that TZDs decrease the likelihood of progression from prediabetes to DM in studies employing rosiglitazone[898] and ACT-NOW for pioglitazone.[895,896]

TZDs are the only medications that approach the effectiveness of weight-loss medications, such as phentermine/topiramate-ER[870] and liraglutide 3 mg,[873] to prevent DM in persons with prediabetes and obesity. Therefore, with respect to DM medications, metformin, acarbose, or TZDs can be used to prevent progression to T2D.[75,805] It is important for clinicians to consider side effects and CVD benefits in the choice of these DM medications.[664,892] A meta-analysis of 10 RCTs encompassing 20,872 participants, including both weight-loss/lifestyle and pharmacologic interventions, found that lifestyle approaches were superior to DM drug-based approaches in DM prevention and improved CVD risk factors.[812] Thus, DM drugs should be reserved for the higher-risk populations who remain glucose intolerant following failed weight-loss interventions involving structured lifestyle interventions and obesity medications, or in lean persons with CMD.[805] The preference for weight-loss therapy in persons with obesity is due to the high efficacy of weight loss or DM prevention, and this ameliorates the broad range of other obesity complications.

Question 12: How can glycemic targets be achieved in persons with T2D?

12.1 Therapeutic Lifestyle Changes

Recommendation 12.1.1: All persons with prediabetes or DM should be prescribed, instructed, and supported in lifestyle interventions that include a healthy meal plan, regular physical activity, and healthful behavior practices. Individualized medical nutrition therapy (MNT) should be provided at the time of diagnosis (with intermittent reeducation as needed during continued care) via evaluation and counseling by a trained registered dietitian, certified nutritionist, or a clinician knowledgeable in nutrition.

Grade A, BEL 1

Recommendation 12.1.2: MNT should consider the overall treatment plan including medications, DM complications, physical activity, body weight goals, and avoidance of hypoglycemia, as well as personal and cultural preferences, health literacy and numeracy, psychological factors, readiness for change, SDOH, and support systems. For people on insulin therapy, insulin dosage adjustments should match carbohydrate intake (eg, with use of carbohydrate counting).

Grade A; BEL 1

Recommendation 12.1.3: The meal plan should contribute to therapeutic goals for control of glycemia, BP, lipids, CVD risk factors, and the prevention of DM complications. In selecting optimal meal patterns, certain Mediterranean diets should be considered which, over the long term, can protect against CVD events and premature mortality. Although there is a lack of long-term studies addressing CVD outcomes, multiple other meal plans have been shown to be safe and can achieve short-term benefits (1–2 years) regarding glycemia, BP, lipids, and CVD risk factors. These meal plans include low-fat, low-carbohydrate, very-lowecarbohydrate, vegetarian, vegan, and DASH diets.

Grade A, BEL 1

Recommendation 12.1.4: Given the variety of meal plans demonstrated to be beneficial in management of DM, nutritional recommendations should consider personal and cultural dietary preferences. Until there is conclusive evidence comparing the benefits of different meal patterns and the availability of long-term safety data, health care professionals should emphasize foods and nutrients that contribute to high “diet quality” scores as assessed by the HEI; high HEI is associated with reduced risks of DM, CVD, and mortality and includes fruits, non-starchy vegetables, whole grains, nuts, legumes, and fish, with limited consumption of added sugars, refined grains, red meat, and processed meats.

Grade B; BEL 1

Recommendation 12.1.5: Lifestyle intervention in persons with DM should include an individualized prescription for physical activity involving aerobic and resistance exercise and reduction in sedentary behavior. The initial prescription for aerobic physical activity may require a progressive increase in the volume and intensity of exercise, and the ultimate

goal should be ≥150 min/week of moderate exercise performed during 3 to 5 sessions per week. (**Grade A; BEL 1**). Moderate exercise is considered to be activity that achieves a heart rate that is 50% to 60% higher than one's basal heart rate. The physical activity prescription also should include resistance exercise that use the major muscle groups 2 to 3 times per week (**Grade A; BEL 1**). Individuals should also incorporate flexibility and range-of-motion training. An increase in nonexercise and/or active leisure activity should be encouraged to reduce sedentary behavior (**Grade A; BEL 1**).

Evidence Base 12: How can glycemic targets be achieved in persons with T2D?

Evidence Base 12.1: Therapeutic Lifestyle Changes—MNT encompasses the delivery of evidence-based nutrition care for persons with DM in a manner that supports healthy eating behaviors, optimizing glycemic control, achieving and sustaining body weight goals, and reducing the risks of DM complications.[899–901] MNT has several essential components including assessment, nutrition diagnosis, interventions (eg, education and counseling), and monitoring with the provision of long-term follow-up, adjusting meal patterns as needed to accommodate changes in medications and the clinical course of the disease.[899,901] A registered dietitian nutritionist (RDN) is the ideal member of the health care team to provide MNT based on training and expertise,[679,899,901–905] and MNT constitutes the regulatory definition of nutrition counseling for DM by an RDN in the United States.[900,901] In T1D, T2D, and GDM, key objectives are to provide consistency in day-to-day carbohydrate intake, adjusting insulin doses to match carbohydrate intake (eg, use of carbohydrate counting), limitations in consumption of sucrose-containing or high-glycemic index foods, adequate protein intake, healthy meal patterns, weight management, regular physical activity, and adequate glucose monitoring.[679] MNT is individualized to accommodate differences in nutritional needs, medications and A1C goals, personal and cultural preferences, access to healthful foods and other SDOH, health literacy and numeracy, readiness for change and other psychological factors, family and community support systems, and existing barriers to change.[679,906–908]

Data support the effectiveness of MNT delivered by RDNs for improving A1C, with absolute decreases of 0.3% to 2.0% in T2D and of 1.0% to 1.9% in T1D at 3 to 6 months.[901] Ongoing MNT support is helpful in maintaining glycemic improvements[679,901,902,909–912] accompanied by cost savings in a person's care.[913–915] MNT is a covered Medicare benefit and should also be adequately reimbursed by insurance and health care systems or bundled in value-based care models.

T2D is an end-stage development of CMD, and, in this context, persons with T2D are also at risk of other sequelae of CMD including hypertension, dyslipidemia, NAFLD/NASH, CVD (coronary artery disease, stroke, nontraumatic amputation), CHF (both HFrEF and HFpEF), and CKD.[670] Therefore, the clinician should assess persons with T2D for the risk, presence, and severity of these disease manifestations and engage in comprehensive and aggressive prevention and treatment strategies. Furthermore, obesity can exacerbate insulin resistance and accelerate progression of CMD toward these end-stage developments, and weight loss is an effective intervention in preventing and treating T2D, as well as hypertension, dyslipidemia, NAFLD/NASH, CVD risk factors, and CKD.[674] The role of

obesity to worsen CMD is mediated by abnormalities in the mass, function, and distribution of adipose tissue (adiposity-based) causing progression to chronic end-stage complications (chronic disease).[901] For this reason, we will use the term ABCD, as recommended by AACE[672] and the EASO,[673] as the medical diagnostic term for obesity to indicate what is being treated and why it is being treated.

Lifestyle therapy is a foundational aspect of treatment in persons with DM who also may have or are at risk of other CMD outcomes. All persons with DM should be instructed and supported in lifestyle interventions centered around MNT.[679,899–901] The components of therapeutic lifestyle changes include healthful eating, regular physical activity, weight management in persons who have ABCD, sufficient sleep, avoidance of tobacco products, limited alcohol consumption, and stress reduction.

Successful lifestyle interventions also feature a package of behavioral interventions that are designed to promote adherence with the meal plan and physical activity prescriptions. Clinical trials have demonstrated the efficacy of lifestyle programs that include behavioral interventions and have underscored particular practices that are most likely to be associated with success.[690,811] For example, persons who self-monitor and record weight, food intake, or physical activity are more likely to achieve weight management goals. Patient education is also advantageous and can be delivered face-to-face, in group meetings, or using remote technologies (telephone, texting, and Internet). The program should also be able to provide for clear and reasonable goal setting, strategies for stimulus control, and systematic approaches for problem-solving and stress reduction. Other components can include cognitive restructuring (ie, cognitive behavioral therapy), motivational interviewing, behavioral contracting, and mobilization of social support structures. DM can often be associated with depression, disordered eating (eg, binge-eating disorder), anxiety, and other psychiatric disorders, which can impair the effectiveness of lifestyle interventions. For this reason, psychological counseling and psychiatric care may be necessary. The behavior intervention package is effectively accomplished by a multidisciplinary team that can include combinations of dietitians, nurses, health educators, physical activity trainers or coaches, and clinical psychologists. As with the meal plan and physical activity components, behavioral lifestyle intervention should be tailored to a person’s ethnic, cultural, socioeconomic, and educational background.

Meal plans for persons with DM should be designed to assure adequate intake of all nutrients, optimize glycemic control, achieve and sustain body weight goals, reduce the risks of DM complications, and improve CVD risk factors.[679,899–901] There should be consistency in day-to-day carbohydrate intake for persons on fixed medical regimens, or adjustments of insulin doses to meals that vary in carbohydrate content (eg, use of carbohydrate counting). The timing of meals and distribution of ingested calories through the day should be individualized with reference to medical therapy and physical activity and to avoid hypoglycemia. A physician and/or an RDN should discuss meal plan recommendations in plain language with persons at the initial visit after DM diagnosis and then periodically during follow-up outpatient visits[679,899–901] and should include information on specific foods and meal planning, grocery shopping, and dining-out strategies. MNT and diabetes self-management education and support (DSMES) should assure an understanding of

differences between protein, fat (saturated and unsaturated), and carbohydrates (sugars, starch, and fiber), and their effects on health and glucose excursions following meals.[916–918] Persons with DM should also understand nutrition facts label information.[916] MNT can address the metabolic needs of persons in more detailed discussions in terms of calories, grams, and other metrics, but should be individualized to accommodate differences in health literacy and numeracy, personal and cultural preferences, access to healthful foods, support systems, and other SDOH.

To achieve dietary goals in DM, studies have demonstrated that there is no ideal mix of macronutrients that can be broadly prescribed, and that current evidence has not established an ideal percentage of calories from carbohydrate, protein, and fat.[679,901,919] Regarding whole foods, multiple meal patterns have been shown to be advantageous for the management of DM, which promote reductions in glycemia, BP, and CVD risk factors.[679,901,920–924] These include the Mediterranean-style,[694,695,697–700,724–726,814,815,821,925,926] low-fat,[678,690,701–704,811,827,927,928] low-carbohydrate,[704,707–714,926,929,930] vegetarian and vegan,[716–720,831,833,931,932] and DASH[721–723] diets, as shown in Table 15. Thus, while current evidence has identified meal patterns that are clinically advantageous in DM, studies addressing the comparative benefits have not identified a superior mealpattern for control of glycemiathat can be universally applied to all persons with DM. However, the long-term safety data demonstrating protection against CVD events, CVD mortality, and all-cause mortality is only available for Mediterranean-style diets.[724,726] Thus, all meal plans in Table 15 can be used safely in the short term (1–2 years) to facilitate glucose control, lower BP, and improve lipids; however, long-term maintenance on a Mediterranean-style diet should be considered. In any event, meal plans and macronutrient distribution should be based on an individualized assessment of current eating patterns, personal preferences including health beliefs, economics and food access, cultural preferences (eg, tradition, culture, religion), as well as metabolic and clinical goals.[679,899–901] In an RCT comparing the Atkins, Ornish, Weight Watchers, and Zone diets, weight change did not differ between diets, and adherence to the diet was the single most important criterion of successful weight loss.[933] The key to adherence, then, is to individualize the dietary recommendation consistent with personal and cultural preferences, lifestyle, and behaviors.

Mediterranean.: In addition to the prevention of DM,[814,815,821] RCTs and cohort studies that included persons with T2D have demonstrated that Mediterranean-style diets lower A1C, body weight, and improve CVD risk factors.[694,695,697–700,724–726,821,925,926] In addition, RCTs have demonstrated primary[724] and secondary[726] protection against CVD events, CVD mortality, and all-cause mortality in study populations comprised of ~50% with DM.[724] In particular, the PREDIMED trial showed that a Mediterranean-style eating pattern intervention enriched with olive oil or nuts over 4.8 years reduced the composite primary end point of MI, stroke, or CV death compared with a low-fat diet in individuals at risk for CVD with or without DM.[724]

Low Fat.: Structured lifestyle interventions that include reduced-calorie low-fat diets in persons with overweight or obesity have been shown to prevent progression from

prediabetes to DM,[690,811,827] and to lower A1C, BP, and triglycerides in persons with T2D.[678,690,702–704,927,928] In both prediabetes and T2D, most of these benefits are attributable to weight loss. Although diets that emphasize low glycemic index foods may not affect A1C compared with high glycemic index foods,[701,901] the quantity of carbohydrate and anticipated glycemic response should be taken into account in adjusting rapid-acting insulin doses for any given meal.[679,899–901]

Low Carbohydrate.: Low-carbohydrate diets that reduce carbohydrates to 26% to 46% of daily calories and very lowecarbohydrate diets that restrict carbohydrates to 20 to 50 grams per day sufficient to induce ketosis are both safe for persons with T2D.[707–714,929,930] Several systematic reviews agree that reduced-carbohydrate diets can produce greater reductions in A1C and body weight compared with low-fat diets in the short term (~3 to 6 months); however, benefits equilibrate at 1 to 2 years when persons on both diets achieve similar A1C, BP, and lipid levels.[704,707–709] Even so, persons on low-carbohydrate diets may chronically experience the need for reductions in doses of DM medications.[711,712]

Vegetarian/Vegan.: Vegetarian and vegan diets are associated with lower risk of DM, and, in persons with DM, these diets have been shown to lower glycemia and improve CVD risk factors.[831,833,931,716–720,833,932] Low-fat vegetarian or vegan diets may be associated with additional improvements in metabolic parameters.[718,932]

DASH.: The DASH can also be used safely in persons with DM and can produce improvements in glycemia, BP, and lipids.[721–723]

Until there is more conclusive evidence regarding comparative benefits of different eating patterns in individuals, health care professionals should at least emphasize foods or nutrients that are common among these meal patterns demonstrated to be beneficial in persons with DM. These foods and macronutrients include: (1) limiting consumption of added sugars and refined grains, (2) emphasizing nonstarchy vegetables,[837] (3) intake of whole foods over highly processed foods, (4) increased fiber consumption,[838,934] and (5) avoidance of trans fats[835] and excess saturated fats with emphasis on mono- or polyunsaturated fats.[679,839] The meal plans in Table 15 share an emphasis on these foods and macronutrients. In addition, in isocaloric substitution experiments, these macronutrients have been shown to increase insulin sensitivity in studies employing glucose clamps.[836] Furthermore, a systemic review and meta-analysis assessed the association between diet quality as measured by the HEI, AHEI, and DASH score and multiple health outcomes.[723] In general, these diets also emphasize fruits, vegetables, whole grains, nuts, legumes, and fish, moderate dairy (<1000 grams/day), and limits on red meats and processed meats.[921] The meta-analysis found that diets scoring highly on the HEI, AHEI, and DASH were associated with significant reductions in the risk of all-cause mortality, CVD, cancer, T2D, and neurodegenerative disease by 22%, 22%, 16%, 18%, and 15%, respectively.[723] Thus, health care professionals should provide individualized meal plans in which the foods and macronutrients described above are emphasized, consistent with the meal patterns in Table 15.

In the absence of underlying insufficiency, routine supplementation of vitamins and minerals is not necessary; a healthful eating meal plan can generally provide sufficient

micronutrients.[679,935] Specifically, chromium; vanadium; magnesium; vitamins A, C, and E; CoQ10; and herbal supplements including cinnamon, curcumin, or aloe vera for improving glycemia in persons with DM are not supported by evidence, or the data are conflicting, and, therefore, are not recommended.[679,935]

Metformin administration can cause vitamin B12 deficiency, perhaps due to impaired absorption.[936] Clinicians should be wary of vitamin B12 deficiency, particularly in persons on metformin who develop peripheral neuropathy or anemia.[937] Supplementation doses of 1000 mg orally per day can be effective.[938]

Lifestyle Therapy: Physical Activity—Increased physical activity is an important component of lifestyle therapy.[674,727] Regular physical activity improves glucose control in persons with DM,[939–943] even in the absence of weight loss.[944–946] In addition to improving BG control, exercise has been shown to reduce CV risk factors, contribute to weight loss, and improve sense of well-being.[943,946–948] Moderate to high volumes of aerobic activity are associated with substantially lower CV and overall mortality risks in both T1D and T2D.[948,949] Structured exercise improves insulin sensitivity, cardiorespiratory fitness,[950,951] muscle strength, and mobility.[731] Physical activity is also an important component in weight loss and weight-loss maintenance. Individuals must be evaluated initially for contraindications and/or limitations to physical activity, and the physical activity prescription should be compatible with any health-related or physical limitations and consider patient preferences.

Studies have reported beneficial effects of both aerobic and resistance exercise, and additive benefits when both forms of exercise are combined on a regular basis.[853,945,947,952–954] For cardiometabolic conditioning, the guidelines proposed by the ACC/AHA,[728,852] AACE,[286,674] ADA,[199,679] European Society of Cardiology/European Association for the Study of Diabetes,[431] and the American College of Sports Medicine[727,853] are well aligned. The recommendations include 30 minutes of moderate intensity exercise 5 days per week for a total of 150 minutes/week, or 20 to 25 minutes of intense exercise 3 days per week for a total of 60 to 75 minutes/week, combined with resistance training involving each major muscle group 2 to 3 days per week.[955] Persons with T2D and ABCD can also benefit from high-intensity interval training involving shorter durations of time engaged in exercise.[854,956] Regular exercise not allowing more than 2–3 days to elapse between exercise sessions is recommended to maintain improvements in insulin sensitivity.[956] Persons with DM tend to have lower VO_2 max measurements, and the exercise prescription should initiate activities at a lower level as tolerated followed by a slow progression in the intensity, frequency, and duration of exercise.

The recommended targets for physical activity cannot always be achieved and individuals should be encouraged to engage in physical activity even if suboptimal. For example, studies have consistently shown that a walking program is associated with reductions in DM incidence,[855] and low-intensity exercise can improve glycemic control in T2D.[939,940]

People with and without DM should be encouraged to reduce the amount of time spent being sedentary (eg, working at a computer, watching television) with durations of sedentary

periods lasting less than 90 minutes and interrupted by >30-minute periods of activity such as standing, walking, or performing other light physical activities.[728,855,957–965] Participating in leisure-time activity and avoiding extended sedentary periods may help prevent T2D for those at risk[959,960] and may also aid in glycemic control for those with DM.[961–964] Persons with DM should be recommended to engage in flexibility and range of motion training, which can have significant impacts on A1C, flexibility, muscle strength, and balance, especially in older adults with DM.[943,962–964,947]

As individuals intensify their exercise program, medical monitoring may be indicated to ensure safety and evaluate the effects on glycemic management. Health care professionals and persons with DM should together establish a physical activity prescription with the goal of long-term adherence. Specific recommendations and precautions will vary by the type of diabetes, age, type of activity, and presence of DM-related health complications. Clinicians should assess individuals for disabilities and other conditions that might preclude certain types of exercise or predispose to injury, such as advanced age, limited exercise tolerance, uncontrolled hypertension, claudication, untreated proliferative retinopathy, autonomic neuropathy, diabetic foot disease, and Charcot foot. Recommendations should be tailored to meet the specific needs and capabilities of each individual,[947] and an incremental exercise prescription should be developed for each person according to both goals and limitations. Although routine testing for coronary artery disease may not be necessary,[41] health care professionals should perform a careful history, assess CV risk factors, and be aware of the atypical or silent ischemia. Screening for coronary artery disease should be performed in persons at risk.

12.2 Antihyperglycemic Pharmacotherapy for Persons with Type 2 Diabetes

Recommendation 12.2.1: Individualized pharmacotherapy for persons with T2D should be prescribed based on evidence for benefit that includes glucose lowering, avoidance of hypoglycemia and weight gain, and reduction of cardio-renal risk.

Grade A; BEL 1

Recommendation 12.2.2: Persons with T2D and their health care professionals should use patient-centered shared decision-making to agree on therapy targets and treatments as well as a regimen for glucose monitoring (ie, BGM, structured BGM, or CGM).

Grade B; BEL 2

Recommendation 12.2.3: Glycemic targets include A1C, BGM, and, for those using CGM, achievement of CGM targets such as TIR, percentage in low and very low range, time above range, and glycemic variability (Table 6). Nonglycemic targets include avoidance of hypoglycemia, control of BP, lipids, other CVD risk factors, and achieving and maintaining a healthy body weight.

Grade B; BEL 4

Recommendation 12.2.4: Independent of glycemic control, targets, or treatment, if there is established or high risk for ASCVD, HF, and/or CKD, clinicians should prescribe a GLP-1 RA or an SGLT2i with proven efficacy for the specific condition(s) of the person with T2D being treated (see also **R 6.1 to R 6.6** on DKD or CKD in DM and **R 9.1 to R 9.4** on ASCVD and HF).

Grade A; BEL 1

Recommendation 12.2.5: DM therapy should be individualized based on level of glycemia and the presence of comorbidities, complications, and access. Metformin is often the preferred initial therapy. Other agents may be appropriate as first line or in addition to metformin to reduce BG and/or to address specific comorbidities (such as ASCVD, HF, CKD, obesity, NAFLD), independent of glucose-lowering effects.

Grade A; BEL 1

Recommendation 12.2.6: For some recently diagnosed individuals with T2D and more severe hyperglycemia (A1C ≥7.5%), unlikely to attain the A1C target with a single agent, early combination pharmacotherapy should be considered, usually to include metformin plus another agent that does not cause hypoglycemia, especially a GLP-1 RA, SGLT2i, or DPP-4 inhibitor.

Grade A; BEL 1

Recommendation 12.2.7: For newly diagnosed persons with T2D and an entry A1C >9.0% and/or ≥1.5% above target, one should initiate, along with lifestyle modifications, dual- or possibly triple-combination pharmacotherapy usually including metformin. Basal insulin along with noninsulin therapy is recommended if there are significant signs or symptoms of hyperglycemia, especially including catabolism (eg, weight loss) or a very high A1C >10% (86 mmol/mol) or BG levels (≥300 mg/dL [16.7 mmol/L]).

Grade A; BEL 1

Recommendation 12.2.8: Clinicians should discuss with persons with T2D the likelihood that most persons with T2D ultimately require a combination of multiple complementary antihyperglycemic agents, in addition to lifestyle interventions, to attain and maintain optimal glycemic control.

Grade B; BEL 2

Recommendation 12.2.9: The diabetes care team should assess medication adherence and safety and glycemic control in persons with T2D quarterly or more frequently as needed. Subsequent visits will depend upon the metabolic targets achieved and the stability of metabolic control.

Grade D; BEL 4

Recommendation 12.2.10: Persons with T2D who start on metformin should continue it unless intolerance or contraindications occur. When intensification of antihyperglycemic treatment is needed, other agents should be added to metformin.

Grade B; BEL 2

Recommendation 12.2.11: Most persons with T2D who require intensification of antihyperglycemic therapy with a GLP-1 RA or insulin should initially be prescribed a GLP-1 RA. If further intensification is required, one should prescribe a basal insulin or a switch to a fixed-ratio combination of a basal insulin and a GLP-1 RA (insulin glargine U100 + lixisenatide [GlarLixi] or insulin degludec + liraglutide [IdegLira]).

Grade A; BEL 1

Recommendation 12.2.12: Insulin should be prescribed for persons with T2D when non-insulin antihyperglycemic therapy fails to achieve target glycemic control or when a person has symptomatic hyperglycemia.

Grade A; BEL 1

Recommendation 12.2.13: Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), degludec (U100 or U200), or detemir are preferred over intermediate-acting Neutral Protamine Hagedorn (NPH) insulin because analog insulins have demonstrated less hypoglycemia in some studies. Glargine U300 and degludec can be associated with less hypoglycemia than glargine U100 or detemir.

Grade A; BEL 1

Recommendation 12.2.14: Many persons with T2D receiving basal insulin and not at goal A1C can have significantly improved glycemia by the addition of a GLP-1 RA or being switched to a fixed-ratio combination basal insulineGLP-1 RA (GlarLixi or IdegLira). One of these changes should be considered before adding a meal-time insulin for postprandial glycemic control.

Grade A; BEL 1

Recommendation 12.2.15: When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or the rapid-acting inhaled human insulin powder) over regular human insulin (see Table 18). The former have a more consistent and a more rapid onset and offset of action with less risk of hypoglycemia.

Grade A; BEL 1

Recommendation 12.2.16: Ultra-rapid-acting insulins (faster-acting insulin aspart, lispro aabc, and [human insulin] inhalation powder) may allow a decrease in the time between

insulin administration and food intake and reduce the postprandial peak of PG as compared with rapid-acting insulins. The significance of this on long-term complications is unknown.

Grade A; BEL 1

Recommendation 12.2.17: Basal-bolus insulin regimens or CSII (ie, insulin pump) allow for adjustment of insulin doses according to carbohydrate intake and activity levels and are recommended for intensive insulin therapy in persons with T2D.

Grade B; BEL 1

Recommendation 12.2.18: Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for persons with T2D who have consistent dietary and exercise patterns and in whom adherence to more intensive insulin regimens is problematic. However, these preparations have reduced dosage flexibility and may increase the risk of hypoglycemia compared with basal insulin or basal-bolus regimens.

Grade A; BEL 1

Recommendation 12.2.19: In persons with T2D who are treated with basal-bolus insulin therapy, adding a GLP-1 RA, or switching to a fixed-ratio combination of a GLP-1 RA and a basal insulin, or adding an SGLT2i or pramlintide (less commonly used) may be able to reduce postprandial hyperglycemia, A1C, and weight. GLP-1 RAs may also allow reduction or discontinuation of bolus insulin in some individuals.

Grade A; BEL 1

Evidence Base 12: How can glycemic targets be achieved in persons with T2D?

Evidence Base 12.2: Antihyperglycemic Pharmacotherapy—The goal of antihyperglycemic treatment in persons with T2D is to achieve clinical and laboratory targets (eg, glycemic, BMI, BP, plasma lipids, eGFR) with as few adverse consequences as possible and reduce the risk of DM-related complications. As shown in Table 16, antihyperglycemic agents vary in their impact on A1C, FPG, PPG, insulin secretion, insulin sensitivity, weight, BP as well as the potential for hypoglycemia and other adverse effects. There are also differences in demonstrated evidence for CV and renal benefits among individual antihyperglycemic agents even within the same class. The choice of specific antihyperglycemic agents for those with T2D should be personalized and guided by each individual's medical needs, shared decision-making with their clinicians, treatment goals, weight, comorbidities, presence of or estimated risk for chronic complications, A1C, glycemic profile obtained by either BGM or CGM, and history of or risk for hypoglycemia or increased risk for adverse consequences from hypoglycemia.[966–968] These patient characteristics can be matched with an agent’s antihyperglycemic efficacy, tolerability, side-effect profile, ease of administration, convenience, cost-effectiveness, and extraglycemic effects.[966–970] Minimizing the risks of hypoglycemia and weight gain and maximizing

CV and renal benefits should be priorities. Affordability of and access to the prescribed medications also need to be considered.

As monotherapy, most noninsulin antihyperglycemic agents reduce A1C by 0.5% to 2.0%. Larger decrements are seen in persons with more marked A1C elevations, likely explaining the apparent greater efficacy of some older agents in their clinical trials vs newer ones.[73] Several GLP-1 RAs lower glucose more than other noninsulin antihyperglycemic agents.[971] The various classes of glucose-lowering agents differ widely in nonantihyperglycemic respects (Table 16).

Detailed descriptions of available antihyperglycemic agents, their mechanisms of action, glycemic efficacy, extraglycemic effects, and rationale for use in different clinical situations can be found in the AACE Comprehensive T2D Management Algorithm[73] and Table 16 as well as the 2022 ADA Standards of Care chapter on pharmacologic approaches to glycemic treatment[972] and the 2018 ADA/EASD consensus report[967] and its 2020 update.[973,974] In addition to lowering glucose, a priority in DM management is to avoid or minimize the risks for hypoglycemia. Choosing agents that are associated with weight loss or minimal weight gain is also desirable. AACE preferentially recommends agents that can achieve these goals.

Metformin is often the preferred initial therapy for most persons with new-onset T2D. Once initiated, metformin should be continued as long as it is tolerated and not contraindicated. Metformin carries a low risk of hypoglycemia, is weight neutral, produces durable antihyperglycemic effects, and some studies suggest CV benefit. It is equally efficacious across all weight categories (normal, overweight, and obese) in T2D.[975] However, it should not be used in persons with advanced renal impairment in which situation it can pose a risk of lactic acidosis.[407,976–978] Metformin should not be used in persons with eGFR <30 mL/min/1.73 m^2, and it should not be initiated in persons with an eGFR <45 mL/min/1.73 m^2.[73,979] However, once started, it can continue to be used in persons with stable eGFR >30 mL/min/1.73 m^2 although reduction in total daily dose (TDD) is prudent in persons with eGFR between 30 and 45 mL/min/1.73 m^2.

Metformin is sometimes associated with anorexia and weight loss and may cause GI adverse effects (eg, nausea, vomiting, dyspepsia, or diarrhea). Longer-term use of metformin may be associated with the development of vitamin B_{12} deficiency,[980] and B_{12} levels should be monitored periodically. When metformin is contraindicated or not tolerated, acceptable alternatives include GLP-1 RAs, SGLT2is, DPP-4 inhibitors, and alpha-glucosidase inhibitors. TZDs, SUs, and glinides may also be used, although caution should be exercised owing to the potential for weight gain, hypoglycemia (not with TZDs), or other risks. Metformin can be used in combination with virtually all other antihyperglycemic agents, including insulin, in persons who do not reach their glycemic target on monotherapy. There are single pill combinations with many other oral antihyperglycemic agents including SUs, DPP-4 inhibitors, SGLT2is, TZDs and glinides.

SUs increase insulin secretion in a glucose level-independent fashion. Appropriate candidates for treatment with SUs are persons with T2D whose duration of DM is <5 years and who do not have end-organ complications (eg, CKD), for whom cost of

antihyperglycemic agents is a major concern, and those who are willing to follow a healthy diet and exercise plan and perform BGM or CGM to reduce the likelihood or identify the occurrence of hypoglycemia.[981] The use of pharmacoeconomic analyses of medication utilization should help inform prescribers and health systems of the cost-effectiveness of a particular medication. For unknown reasons, not all persons with T2D respond to SUs (primary failure), and antihyperglycemic effectiveness declines after several years of treatment in many persons (secondary failure).[982,983] SU therapy may be associated with weight gain, but the main SU adverse event of concern is hypoglycemia, which can be more prolonged than that produced by insulin, particularly when longer-acting formulations (eg, glyburide) are used in older adults.[984] Decreased kidney function also increases the risk of SU-associated hypoglycemia. Glinides' mode of action and other properties are very similar to those of SUs, but the efficacy is less, and hypoglycemia potential is also less than with SUs.[985]

TZDs improve insulin sensitivity and can preserve or improve b cell secretory function in persons with T2D. In addition to their glycemic effects, these agents also improve a wide range of CV risk markers[986,987] and may help prevent central nervous system insulin resistanceerelated cognitive dysfunction.[988] Clinical studies and meta-analyses of RCTs reported that treatment with pioglitazone results in a statistically significant reduction in the composite outcome of nonfatal acute MI, stroke, and all-cause mortality (MACE).[663,989,990] TZDs have been shown to have benefit in some persons with NASH[686,991,992]; however, TZDs lead to weight gain comparable to that with SU and insulin therapy.[993] TZDs may also cause fluid retention (particularly in persons with cardiac or renal disease), which may contribute to TZD-associated weight gain and peripheral edema. The risk for both might be decreased by using lower doses of pioglitazone and avoiding the highest dose and/or perhaps use in combination with an SGLT2i and/or a GLP-1 RA.[994] TZDs are not recommended in persons with symptomatic HF and are contraindicated in persons with New York Heart Association (NYHA) class III or class IV CHF. TZDs can also reduce bone mineral density and are associated with increased risk for bone fractures, especially in women, with the majority of fractures in the distal upper limb or distal lower limbs.[995,996] The TZD rosiglitazone has been withdrawn from use in Europe and was severely restricted in the United States because of concerns over a possible increase in CVD risk.[997] However, the FDA later lifted this restriction because additional data, including one large RCT, showed it was not associated with an increased risk.[998,999] According to the FDA, pioglitazone, but not rosiglitazone, may be associated with increased rates of bladder cancer, although there is not enough evidence to support a clear association.[1000,1001] A cumulative exposure analysis involving data from 1.01 million persons from multiple countries over 5.9 million person-years found no association between exposure to pioglitazone and bladder cancers.[1002]

GLP-1 RAs and DPP-4 inhibitors increase insulin and decrease glucagon secretion in a glycemic level-dependent manner. In addition to glucose lowering, the GLP-1 RAs may slow gastric emptying, promote early satiety, reduce food intake, and frequently are associated with weight loss. GLP-1 RAs are also associated with a decrease in BP accompanied by a small increase in pulse rate. There also can be improvements in lipid levels.[1003,1004]

Currently approved GLP-1 RAs include dulaglutide, exenatide, exenatide-ER, liraglutide, lixisenatide, and semaglutide, which are administered by injection on a twice daily, daily, or once weekly basis. There is also a form of semaglutide that is orally administered. These agents are often used as add-on therapies for persons with inadequately controlled DM despite oral therapy.[242,642,1005-1020] Several clinical trials have compared the effects of adding a GLP-1 RA to insulin (glargine insulin or premixed insulin) in persons with inadequately controlled T2D on oral agents.[1021-1030] All of the studies show equivalent or slightly better A1C lowering by GLP-1 RA with the advantages of a 2- to 3-kg weight loss and little or no additional hypoglycemia. Additionally, liraglutide, semaglutide, and dulaglutide have demonstrated reduction in MACE in CVOTs.[242,642,1031] As a result, guidelines recommend use of GLP-1 RAs before initiation of insulin for most individuals with T2D (see **Evidence Base 9: How should antihyperglycemic agents be prioritized in persons with T2D at high risk for or with established CVD?**).

The most frequently experienced adverse effects with GLP-1 RAs are nausea, vomiting, and diarrhea, which may lead to discontinuation of the GLP-1 RA in 5% to 10% of persons, but usually these adverse symptoms diminish over time.[1032]

Although medullary thyroid carcinoma has not been shown to be caused by GLP-1 RAs in humans, all GLP-1 RAs except twice-daily exenatide and lixisenatide are contraindicated in persons with a personal or family history of medullary thyroid carcinoma and in persons with multiple endocrine neoplasia syndrome type 2. The FDA has stated that persons taking a GLP-1 RA do not need to be monitored for medullary thyroid carcinoma (eg, with calcitonin levels)[1033] (also see discussion of pharmacologic therapies for DM and cancer risk or prognosis under **Q27. How should potential increased cancer risk be managed in persons with obesity/T2D?**).

Pancreatitis appears to be a rare association with use of GLP-1 RAs and DPP-4 inhibitors.[1034,1035] Prescribing information for GLP-1 RAs and DPP-4 inhibitors generally states that these agents have not been studied in persons with a history of pancreatitis. Consider other antihyperglycemic therapies in persons with a history of pancreatitis.

Tirzepatide is a dual glucose-dependent insulinotropic peptide and GLP-1 RA recently approved by the FDA for improvement of glycemic control in persons with T2D. Individual trials have assessed the clinical profile of tirzepatide vs different comparators. A systematic analysis of seven completed trials with a total of 6609 participants[1036] confirmed a dose-dependent (5, 10, or 15 mg weekly subcutaneous administration) superiority on glycemic efficacy, and reduction in body weight was evident with tirzepatide vs placebo, GLP-1 RAs, and basal insulin. Tirzepatide was associated with increased incidence of GI adverse events but no increase in risk of hypoglycemia. Tirzepatide appears to be useful for those already on metformin therapy. Based on some early promising data and ongoing trials, including a CVOT, clinical indications for weight loss and/or CV risk reduction may be sought.[1037]

DPP-4 inhibitors do not cause weight gain; linagliptin can be administered in persons with CKD at full dosage since it is not cleared by the kidneys. Sitagliptin, saxagliptin and alogliptin are renally cleared and require appropriate dose adjustment in the presence of

decreased eGFR. DPP-4 inhibitors do not have significant GI adverse effects and may be used in early combination with metformin.[1038–1043] CVOTs with DPP-4 inhibitors achieved non-inferiority compared with placebo for the occurrence of MACE.[1044–1046] The trial comparing saxagliptin with placebo showed an increased likelihood of hospitalization for CHF[1045] without increase in mortality. (Prescribing information states: Consider the risks and benefits of saxagliptin in patients who have known risk factors for HF. Monitor patients for signs and symptoms.) The FDA also noted a trend toward increased hospitalization for CHF without increase in mortality with alogliptin and stated "There is limited experience with alogliptin therapy in patients with CHF of New York Heart Association (NYHA) functional classes III and IV. Alogliptin should therefore, be used with caution in these patients,"[1044,1047] Despite no evidence of increased risk in their CVOTs, the prescribing information for sitagliptin and linagliptin say because HF has been observed with other members of the DPP-4 inhibitor class, consider risks and benefits in patients who have known risk factors for HF. Monitor patients for signs and symptoms. The main adverse effects noted with DPP-4 inhibitors are a small increase in upper respiratory tract viral infections (rates of nasopharyngitis were 6.4% with a DPP-4 inhibitor vs 6.1% with comparators; risk ratio, 1.2; 95% CI, 1.0–1.4) and a rare hypersensitivity reaction.[1032] Severe and disabling arthralgia has been reported in individuals taking DPP-4 inhibitors.[1032]

SGLT2is are the newest class of oral antihyperglycemic agents approved for treatment of individuals with T2D. The glucosuric effect of these agents reduces both glycemia and weight in most persons. Most also experience decreases in systolic BP. Dehydration due to increased diuresis could lead to hypotension.[1048] Clinicians and persons with DM should be alert for the potential of postural hypotension, especially in older adults on loop diuretics. Although the antihyperglycemic effect can be diminished with decreasing eGFR, studies have shown that SGLT2is continue to exert their renal protective benefit for those with low eGFRs (eg, <45 mL/min/1.73 m^2).[423]

By increasing glycosuria, SGLT2is may increase the risk of fungal genital tract infection and much less frequently urinary tract infection. Risk of DKA is increased in persons using SGLT2is, especially in those being treated with insulin (especially if there has been a recent reduction in their insulin dose) and/or those with acute illnesses and prolonged fasting.[1049,1050] Small increases in LDL-C levels (4 to 8 mg/dL) occurred with canagliflozin, dapagliflozin, and empagliflozin in pivotal trials. Bone fracture has been described in post-marketing safety reporting.[1051] Multiple studies have shown renal and CV benefits of SGLT2is[239,424–426,444,1052–1054] (see also **Evidence Base 9: How should antihyperglycemic agents be prioritized in persons with T2D at high risk for or with established CVD?**). Empagliflozin and canagliflozin demonstrated reduction in MACE in CVOTs; empagliflozin also demonstrated decreased CV death and all-cause mortality. Empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin have shown a decrease in hospitalization for HF in their CVOTs. Dapagliflozin also has shown in people with HFrEF reduced risk of worsening HF or death from CV causes regardless of the presence or absence of DM.[457] Empagliflozin has also demonstrated reduction in composite of CV death or hospitalization for worsening HF in those with HFrEF with or without T2D.[470] More recently, empagliflozin was demonstrated to reduce the combined risk of CV death

or hospitalization for HF in persons with HFpEF, regardless of the presence or absence of DM.[239,425,426,443] Dapagliflozin has now been shown to reduce the combined risk of worsening HF or CV death in patients with HF and a mildly reduced or preserved ejection fraction.[1054a] Dapagliflozin received an FDA indication to reduce the risk of CV death and hospitalization for HF in adults with and without DM with HFrEF (NYHA Class II-IV). Empagliflozin received an indication for those with and without DM to reduce the risk of CV death and hospitalization for HF in adults with HF (HFrEF or HFpEF).

Based on the CREDENCE trial,[423] the FDA has given canagliflozin an indication to reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for HF in adults with T2D and diabetic nephropathy with albuminuria. Dapagliflozin based on the DAPA-CKD RCT[424] has received an FDA indication to reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, and hospitalization for HF in adults with CKD at risk of progression.

As a result of GLP-1 RA and SGLT2i studies above, independent of glycemic control or targets, individuals with T2D at significant risk for or with established ASCVD, HF, and/or CKD should be treated with a GLP-1 RA or SGLT2i with proven benefit for the individual's specific conditions.

Colesevelam, alpha-glucosidase inhibitors, and bromocriptine primarily affect PPG levels and are worth consideration in selected persons. Colesevelam carries a low risk of hypoglycemia and also reduces LDL-C, for which it was originally developed. It also modestly increases triglyceride levels, and its main adverse effect is constipation, but it is not systemically absorbed and therefore is not likely to have systemic adverse effects.[1055]

Alpha-glucosidase inhibitors also have a low risk for hypoglycemia, although persons may not tolerate the GI side effects (eg, bloating, flatulence, and diarrhea). These may be reduced by starting with a low dose and slowly titrating the dose as needed. Acarbose has been shown to lower A1C and cause weight loss.[1056,1057] Some clinical trials have suggested some CV benefit in persons with IGT or DM. However, in a large RCT[1058] of Chinese participants with coronary heart disease and IGT, acarbose did not reduce the risk of MACE, but did reduce the incidence of DM.[891,892]

The dopamine receptor agonist bromocriptine does not cause hypoglycemia. It can cause nausea and orthostasis and should not be used in persons taking antipsychotic drugs. Bromocriptine in one study with a small number of events was associated with reduced CV event rates.[1059]

Because many persons do not achieve adequate glycemic control with monotherapy or are at risk for early loss of efficacy with metformin or another monotherapy, combining antihyperglycemic agents is often appropriate.[1060] For some recently diagnosed individuals with T2D and more severe hyperglycemia, early combination pharmacotherapy should be considered, usually to include metformin plus another first-line agent that does not cause hypoglycemia, especially a GLP-1 RA or an SGLT2i, or DPP-4 inhibitor (see **R 12.2.6** and **R 12.2.7** and **R 9.1 to R 9.4** on CVD). In the VERIFY trial,[1040] initial combination therapy of metformin and the DPP-4 inhibitor vildagliptin was superior to sequential

addition of medications in prolonging the occurrence of primary and secondary failure. For newly diagnosed persons with T2D and an entry A1C >9.0% and/or ≥1.5% above target, one should initiate, along with lifestyle modifications, dual or possibly triple combination pharmacotherapy usually including metformin and considering basal insulin. If there are significant symptoms of hyperglycemia, especially including catabolism (eg, weight loss) or a very high A1C >10% (86 mmol/mol) or BG levels (300 mg/dL [16.7 mmol/L]), insulin is recommended. The Efficacy and Durability of Initial Combination Therapy study compared efficacy of initial metformin/pioglitazone/exenatide in new-onset T2D vs sequential addition of metformin followed by glipizide and insulin. The decrease in A1C from triple therapy was greater at 6 months than that of conventional therapy and the superiority was maintained at 3 years.[1061]

Metformin is quite effective when administered in combination with other agents, as long as one avoids its use in persons with CKD (eGFR <30 mL/min/1.73 m^2)[73] or GI intolerance. SUs, in contrast, may be problematic when used in combinations because they can cause hypoglycemia and may reduce, eliminate, or minimize the weight-loss benefit of drugs such as metformin, GLP-1 RAs, and SGLT2is.[993] See **R 12.2.4** and **Evidence Base 9: How should antihyperglycemic agents be prioritized in persons with T2D at high risk for or with established CVD?** for those with established or high risk for ASCVD, HF, and/or CKD for recommendations about antihyperglycemic medications that should be used often in combination with metformin. Even for those without these conditions who require intensification of therapy, one should consider adding a GLP-1 RA and/or an SGLT2i, which would provide good glycemic lowering (especially with GLP-1 RA), reduction in weight and BP, and a low risk for hypoglycemia. Other medications that have a low risk for hypoglycemia are DPP-4 inhibitors and TZDs. Medications that tend to be less expensive than others are SUs and TZDs.

Insulin Use in T2D: Insulin is usually initiated in those with T2D when combination therapy with other agents fails to attain or maintain glycemic goals, or when an individual, whether drug naïve or on a treatment regimen, presents with an A1C level >9.0% and symptomatic hyperglycemia.[73,1062] Once insulin is initiated, its beneficial A1C effect is stable for 2 to 4 years in the majority of persons.[1063] Most persons with T2D who require intensification of antihyperglycemic therapy with a GLP-1 RA or insulin should initially be prescribed a GLP-1 RA. Insulin could then be added if further intensification is required. Several RCTs show that GLP-1 RAs vs basal insulin have equal or better glucose lowering, low risk for hypoglycemia, and weight reduction vs weight gain.[1021,1064]

Insulin therapy may be initiated as a basal, basal-bolus, prandial, or premixed regimen, although for most persons with T2D, starting with a basal insulin analog added to the existing antihyperglycemic regimen is preferred[1065] (Tables 17 and 18). The combination of insulin with any antihyperglycemic agent raises the potential for hypoglycemia. Persons should be closely monitored, and those on SUs or glinides may require dosage reductions or discontinuation of the oral agent. TZDs can be associated with weight gain, edema, and increased risk of CHF in combination with insulin. Basal insulin analogs are preferred over NPH insulin because of a reduced risk of hypoglycemia.[1066–1071] Newer “ultra-long-acting” basal insulin analogues, insulin glargine U300, and insulin degludec have been shown to be

associated with less hypoglycemia than insulin glargine U100.[1072,1073] The insulin regimen to be prescribed and the exact treatment goals should be discussed with the person with DM.

Insulin-treated persons should be instructed in performance of BGM. Most insulin-treated persons with T2D should conduct BGM ≥2 times daily and ideally at least before each injection of insulin. The frequency and timing should be dictated by the particular needs and goals of the individual, as well as hypoglycemia risk. Emerging evidence suggests benefits of CGM use in insulin-treated persons with T2D[170,1074] (see **Q3. When and how should glucose monitoring be used?**).

Premixed insulins are popular with some persons, but they provide less dosing flexibility and have been associated with a higher frequency of hypoglycemia compared to basal and basal-bolus regimens in many, but not all studies.[1075–1079] Nevertheless, there are some persons for whom a simpler regimen is a reasonable compromise, and for this population, analog premixed insulins will provide better glycemic control with less hypoglycemia than the traditional, more affordable premixed NPH regimens.[1080] The analog premixed insulin insulin degludec/insulin aspart may provide reductions in nocturnal hypoglycemia compared to glargine U100,[1081] but a basal bolus regimen with an ultra-long-acting basal insulin analog and a rapid-acting prandial insulin analog may achieve more effective control with less hypoglycemia.[1082] Different concentrations of the rapid-acting analogue may be beneficial in some populations.[1083] With the BIAsp 30 preparation (premixed insulin analogue containing 30% soluble, rapid-acting insulin aspart and 70% intermediate-acting protamine-bound aspart in each injection), for higher A1C levels, a third injection prior to lunch may be preferable.[1084]

When mealtime glucose control is needed or when glycemic goals are not met on a basal insulin regimen plus oral agents or a GLP-1 RA, insulin therapy intensification to a basal-bolus regimen (using a rapid-acting insulin analog or inhaled insulin) should be considered (Table 19). Ultra-rapid acting insulins can reduce postprandial glycemic peak, but this effect on long-term complications is unknown.[1085,1086] In addition, insulin human inhalation powder, a rapid-acting inhaled insulin, is effective at reducing postprandial peak, and studies in persons with T1D demonstrated that hypoglycemia was reduced with use of this inhaled insulin relative to insulin aspart,[1087] but overall glycemic efficacy measured by A1C may not be as great as subcutaneous insulin.[1088,1089]

CSII or insulin pumps are options for persons with T2D taking basal and prandial injections (MDI) of insulin.[153,1090] Persons with T2D may also benefit from the use of a wearable device that delivers for basal insulin a continuous subcutaneous infusion of rapid-acting insulin and also allows 2-unit boluses of insulin when the wearer depresses a button.[1091]

Many people with T2D treated with MDI and CSII should also be using CGM, and a significant number of those treated using the wearable, patch-like device described above or receiving injections of basal insulin only would benefit greatly by use of CGM. More information about insulin pumps, CGM (including differences between rtCGM, isCGM), and open-loop and hybrid closed-loop (HCL) use of both insulin pumps and CGM can be

found elsewhere in this guideline and in the 2021 AACE Advanced Diabetes Technology guideline.[153]

Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in persons with T2D.[1092,1093] GLP-1 RAs and DPP-4 inhibitors have properties similar to those of pramlintide and also increase endogenous in- sulin secretion. The combination of basal insulin and incretin therapy decreases basal glucose and PPG and may minimize weight gain and the risk of hypoglycemia compared with basal-bolus insulin regimens. Pharmacokinetic and pharmacodynamic studies of combination GLP-1 RAs and basal insulin analogs have shown an additive effect on BG decreases.[1021,1094–1097] Similarly, in persons with T2D who are treated with basal-bolus insulin therapy, adding a GLP-1 RA or switching to a fixed-ratio combination of a GLP-1 RA and a basal insulin or adding an SGLT2i[1098] or pramlintide can serve as adjuncts to prandial insulin therapy to reduce postprandial hyperglycemia, A1C, and weight. GLP-1 RAs may also allow reduction or discontinuation of bolus insulin in some individuals. Long-acting GLP-1 RAs also reduce fasting glucose.[1099]

The combined use of DPP-4 inhibitors or SGLT2is with insulin can also help improve glycemic control with a relatively low risk of hypoglycemia, although the glycemic lowering is likely to be less than with GLP-1 RAs.[1100,1101]

U500 regular insulin (contains 500 units/mL of regular insulin) may improve glycemia in the therapy of persons with DM who have severe insulin resistance (eg, require >200 total units of insulin/day).[1102–1105] The pharmacokinetics of U500 insulin is more like NPH than regular insulin but is variable and can pose a hypoglycemia risk and be associated with weight gain. U500 insulin should only be administered with a U500 insulin syringe or a U500 insulin pen device.

Hypoglycemia and weight gain are the most common adverse effects of insulin therapy.[1106,1107] Rates and the clinical impact of hypoglycemia are frequently underestimated,[1108] but about 7% to 15% of insulin-treated persons with T2D experience at least 1 episode of hypoglycemia per year,[1109] and 1% to 2% have severe hypoglycemia.[1106,1108] The frequency of hypoglycemia increases with intensive insulin targets, use of SUs, decreased caloric intake, delayed meals, exercise, alcohol consumption, CKD, T2D duration, and cognitive impairment.[1108] Large, randomized trials have shown that participants with established T2D and a history of 1 or more severe hypoglycemic events had an approximately 2- to 4-fold higher rate of mortality for reasons that remain unknown.[87,1110] It has been proposed that hypoglycemia may be a marker for persons at higher risk of death rather than being its proximate cause[1108]; nevertheless, avoidance of hypoglycemia by appropriately reducing insulin dosages seems prudent. Basal inulin analogs are associated with less hypoglycemia than human basal insulin such as NPH. U300 glargine and insulin degludec have a lower risk for hypoglycemia than U100 insulin glargine[1031,1111] or insulin detemir.

Question 13: How should insulin therapy be used for management of persons with T1D?

Recommendation 13.1—Insulin must be used to treat all persons with T1D.

Grade A; BEL 1

Recommendation 13.2—Physiologic insulin replacement regimens, which provide both basal and prandial (meal-related or bolus) insulin, are recommended for most persons with T1D.

Grade A; BEL 1

Recommendation 13.3—Achievement of glucose targets using either MDI of insulin or CSII, is needed to prevent development of life-threatening crises, such as acute hyperglycemic crises (DKA and hyperglycemic hyperosmolar state) and catabolic state.

Grade A; BEL 1

Recommendation 13.4—A multi-component self-management diabetes education program is recommended for persons with T1D. Ideally, this is provided by a professional with expertise (ie, CDCES) in the topics of healthy lifestyle, insulin technique including prandial insulin dosing guided by carbohydrate counting, and diet adjustments for special situations, such as physical activity and prolonged fasting. Instruction is also needed in how to deal with sick days and prevention of DKA and hypoglycemia, and other relevant issues. Due to changes in DM self-management practices and each individual's medical history, personal and cultural background, and educational needs, specific education topics may need to be repeated at regular intervals.

Grade A; BEL 1

Recommendation 13.5—The ideal insulin regimen should be personalized to an individual's needs and glycemic targets, attempting to better emulate physiological insulin replacement to maintain near normoglycemia, to prevent the development and progression of DM complications, while minimizing hypoglycemia and providing flexibility for specific daily life situations/scenarios such as: exercise, sleep, acute illness, psychological stress, etc.

Grade A; BEL 1

Recommendation 13.6—Insulin regimens usually should involve the use of insulin analogs for most persons with T1D and include the following approaches:

a. MDI, which usually involve 1 to 2 subcutaneous injections daily of basal insulin to suppress ketogenesis and gluconeogenesis and to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or use of inhaled insulin before each meal to control meal-related glycemic excursions. CGM is the preferred method of glucose monitoring for all individuals with T1D.

Grade A; BEL 1

b. Insulin pump therapy (CSII) provides constant/continuous infusion of fast-acting insulin driven by mechanical force and delivered via a cannula inserted under the

skin. CSII can improve (or enhance) glycemic control and should be an option for insulin delivery for appropriate persons with DM. Ideally, these individuals should also use CGM as stated in **R13.6.a.**

Grade B; BEL 1

c. Automated insulin delivery (AID) systems, which include an insulinpump, an integrated CGM, and computer software algorithm, aim to better emulate physiological insulin replacement and achieve glycemic targets. This technology is recommended for many persons with T1D since its use has been shown to increase TIR while often reducing hypoglycemia or at least without causing increased hypoglycemia.

Grade A; BEL 1

d. Open-loop (use of a pump and sensor which do not communicate) and sensor-augmented pump (SAP) systems: (CGM communicates with pump facilitating needed adjustments to basal rate; temporary interruption of insulin delivery when glucose levels are low or forecast to be low within 30 minutes). Insulin pump with a CGM or an SAP is recommended to manage persons with DM treated with intensive insulin management who prefer not to use AID systems or have no access to them.

Grade D; BEL 4

Evidence Base 13: How should insulin therapy be used for management of T1D?

Based on the World Health Organization's Classification of Diabetes 2021,[1112] T1D is defined as b-cell destruction and absolute insulin deficiency. Hence, insulin therapy is necessary for life in all persons with T1D ("all or nothing").[1113] Absolute (or near-absolute) insulin deficiency can result in acute hyperglycemic complications, including DKA, hyperosmolar hyperglycemic state, hypertriglyceridemia, and hypercatabolic state, which can be life-threatening.[1114–1120] All persons with T1D should receive adequate basal insulin replacement, either via frequent injections or CSII, every day to prevent development of life-threating acute hyperglycemic complications.[1117,1121] Inadequate (incomplete) insulin replacement, beyond the use of basal insulin, results in chronic hyperglycemia which is a driver for micro- and macrovascular DM-related complications in T1D. Intensive glycemic control with insulin therapy reduces the risk of these complications.[200,1122,1123]

Since publication of the prior CPG in 2015, there has been extensive development on insulin formulations and delivery, particularly in persons with T1D. Several advantages have been published on newer insulin analogs for both basal and prandial insulin; CSII development with adjunctive use of CGM; and the latest development in the use of nonadjunctive CGM with CSII, also called AID systems, HCL systems, or artificial pancreas device systems (discussed below, in Figure 6, and in 2021 AACE Advanced Diabetes Technology guideline).[153]

Physiologic insulin regimens including both basal and prandial insulin, provided by either MDI or CSII, have not been formally tested in RCTs against nonphysiologic insulin

regimens (once or twice daily insulin). Rather, physiologic insulin regimens have been formally studied as one component of a comprehensive treatment strategy for persons with T1D.[1106,1124,1118] In comparisons of regimens of MDI with BGM (without CGM) vs CSII for T1D, there have been small improvements in A1C, but substantial reductions in severe and nocturnal hypoglycemia.[1113,1125–1127] However, in the REPOSE RCT, where all participants received a structured diabetes education program and adjusted insulin based on SBMG, treatment with CSII vs MDI resulted in reduction in severe hypoglycemia after 2 years in both groups, with a nonstatistically significant A1C benefit toward CSII, and better treatment satisfaction and QoL among CSII users.[1128] Regardless of the insulin delivery method (MDI vs CSII), glycemic control metrics, including A1C and CGM TIR, hypoglycemic events, QoL, and patient satisfaction are substantially improved when MDI or CSII is augmented with CGM, with better results when CSII is combined with CGM or integrated into AID systems, compared with using CGM.[158,160,1129–1131]

Basic Principles of Insulin Therapy in Type 1 Diabetes—Several trials have demonstrated that physiologic regimens using basal insulin analogs may reduce hypoglycemia, and bolus insulin analogs may result in better control of PPG excursions for most persons with T1D.[1132–1137] Hence, insulin analogs should be considered first-line choice for most persons with T1D (Table 19).

These effects were demonstrated initially when comparing first-generation insulin analogs to NPH insulin.[1132,1134,1138,1139] Further improvements were confirmed when comparing second generation of ultra-long-acting basal to first-generation insulin analogs,[1135,1137,1140–1145] which may translate into potential cost savings in real-world settings from avoiding severe hypoglycemic and hyperglycemic crises.[1146] There are limited data comparing the latest basal insulin analogs degludec and glargine U300.[1147,1148] The InRange RCT assessed the noninferiority of both basal insulins, as measured by CGM metrics.[1149] Furthermore, a novel ultra-long-acting weekly insulin icodec is under development for persons with T1D.[1150]

Similarly, the use of rapid-acting analogs has resulted in less hypoglycemia, with small reductions in A1C compared to using regular human insulin, including MDI using NPH as basal insulin.[1151–1153] The development of ultrarapid insulin analogs has resulted in better coverage of PPG excursions, compared with rapid-acting insulin analogs, as measured by BGM and CGM, but not all studies have resulted in A1C improvements or hypoglycemia reductions.[1154–1157] Inhaled insulin with a faster peak of action and shorter duration is also available as prandial insulin, with the requirement of using repeated inhaled correctional insulin doses after 1 to 2 hours postmeal.[1158,1159]

The starting dose of insulin is usually estimated based on weight, with doses ranging from 0.4 to 0.5 units/kg/day of total insulin, with higher amounts required for persons who are obese (increasingly common in T1D) or have a sedentary lifestyle, as well as during puberty, pregnancy, and acute medical conditions. Conversely, lower starting insulin doses (0.2 to 0.3 units/kg/day) are recommended for older adults, those with renal failure, malnutrition, or low BMI.[1124,1136]

In general, basal insulin requirements are usually 40% to 50% of TDD insulin. Basal insulin doses are titrated to personalized target fasting glucose. In the ideal prandial/bolus regimen, the dose of prandial insulin is usually determined by estimating the carbohydrate content of the meal. Persons with DM should have formal training on carbohydrate counting as part of a multicomponent DSMES program, provided by professionals (CDCES) if available.[1160–1164] Most would start with 1:15 insulin to carbohydrate (IC) ratio (1 unit for 15 g of consistent carbohydrates) or 450/TDD insulin if using regular insulin; 500/TDD if using rapid-acting IC ratio (eg, for someone using 50 units of insulin/day: 500/50 units = 1:10 IC ratio) as a starting point. The IC ratios can be adjusted based on an individual's response to the calculated boluses of insulin. Insulin sensitivity factor (ISF) approximates the glucose-lowering effect of 1 unit of insulin in a particular individual (1500/TDD units for regular insulin vs 1800/TDD rapid acting insulin). These formulas are just starting points and need to be modified empirically for each person. Numerous mobile applications are also being used to assist with IC ratios and ISF.

IC ratios usually range from 1:20 for the very insulin-sensitive to 1:5 for insulin-resistant persons. Similarly, correction dose insulin for premeal or between-meal hyperglycemia is based on the ISF, also called insulin correctional factor, which is based on the overall insulin sensitivity of a person, loosely estimated by the individual's TDD insulin. Although various formulas have been used to estimate the appropriate ISF, this parameter should only be viewed as an estimation due to numerous factors that can alter BG. The most commonly used formula is 1800/TDD insulin = number of mg/dL of glucose that will be reduced by 1 unit of insulin. Another key factor that should be appreciated is insulin action time. For most subcutaneous injections, this ranges from 4 to 6 hours. Ultrarapid insulins (ie, faster aspart, lispro aabc) have demonstrated earlier time of onset and action but similar duration of action.[1165]

With the knowledge of the IC ratio, ISF (insulin correctional factor), and insulin action time, persons with DM on MDI or CSII can calculate the appropriate correction dose of insulin. This is significantly simpler with CSII, as most pumps include bolus calculators to perform the calculations by pressing a few buttons. Most persons using MDI, however, will need to estimate the remaining "insulin on board" from the last injection of prandial insulin based on standard curves that can be provided to them.[1124,1136]

For persons using MDI or intensive insulin therapy, there are a variety of smart phone apps available that can assist persons with insulin dosing and calculations.[1166] Similarly, several smart insulin pens have been developed, including devices that are specific to one insulin brand and others that can be used with different formulations. RCTs have validated their use in persons with T1D, providing benefits for avoidance of extreme glycemic events.[1167–1169] This topic is reviewed in the 2021 AACE Advanced Diabetes Technology guideline.[153]

CSII should only be used by persons who are motivated and knowledgeable in DM self-care, including insulin adjustment. To ensure the safety of persons with DM, prescribing physicians must have expertise in CSII therapy, and CSII users must be thoroughly educated and periodically reevaluated. In 2018, an RCT using an open-loop CSII system found no glycemic benefit compared to MDI, although QoL scores were improved with pump

therapy.[1170] Training should be provided by personnel with expertise, particularly a CDCES or registered dietitian. Refer to **R 17** on DSMES in **Section 4** of this guideline.

Adjunctive Medications for Type 1 Diabetes—The amylin analog pramlintide, the only other medication approved for the treatment of T1D, is administered with prandial insulin. A1C reductions are consistently modest, and mild weight loss is common. Nausea is a common adverse effect. There is a potential risk of severe hypoglycemia if persons with DM do not appropriately reduce the prandial insulin dosage.[1171–1174] Tachyphylaxis is often seen after several years of therapy.

There has been much interest in the use of metformin as an adjunctive therapy for T1D. A meta-analysis of 13 randomized placebo-controlled trials with 1183 participants with T1D reported small reductions in BMI, insulin requirements, total and LDL-C, but no differences in A1C, HDL-C, or triglyceride levels.[1175] Given the lack of glycemic benefit and minimum other benefits on top of frequent GI side effects and a small risk of lactic acidosis, a recommendation for metformin use in T1D cannot be made at this time.

Another unapproved agent for T1D is the GLP-1 RAs, which have been studied for T1D for 2 indications. The first is b-cell preservation in newly diagnosed T1D. In conjunction with anti-IL-21 antibody, liraglutide was shown to provide small improvements of endogenous insulin secretion.[1176] Secondly, similar to pramlintide, these agents inhibit glucagon secretion, delay gastric emptying, and promote satiety and weight loss. The largest trial with this class in T1D was with liraglutide, which showed a reduction of A1C of 0.4% with the highest 1.8 mg dose in addition to a 5 kg weight loss and insulin dose reductions.[1177] Although this agent was more effective with those participants still producing endogenous insulin, the added hypoglycemia and ketosis noted has resulted in no attempt for FDA approval in T1D.

Of all of the unapproved adjunctive agents for T1D, there has been the most interest in the SGLT2i or SGLT1/2is. By inducing glycosuria, less hyperglycemic spikes, lower A1C levels, and weight loss could be expected. In one meta-analysis of 14 studies and with 4591 participants, A1C was reduced by 0.4% with a 2.7 kg weight loss and reductions in BP and insulin dosing.[1178] A 3.38-fold increased risk of DKA (often euglycemic, now generally defined as a BG less than 250 mg/dL)[1179] has resulted in no approval in the United States, although the European Medicine Agency has approved dapagliflozin (5 mg) and sotagliflozin (200 mg) for those with T1D and a BMI above 27 kg/m^2.[1180] Although there have been attempts to reduce risks,[1181] at the present time, no recommendation for use of these agents to manage T1D can be made until the high risk of DKA can be safely mitigated.

AID Systems—The integration of glucose monitoring with insulin pump therapy has been an important goal in diabetes technology. Although connectivity of glucose meters to insulin pumps were initially found to be convenient to assist in calculating the bolus dose delivery, the evolution of CGM with sophisticated computerized algorithms has resulted in SAPs and more recently AID systems.

CGM used completely independently of insulin pump therapy (“open-loop”) or in conjunction with an SAP system (where insulin can be interrupted before or when glucose drops below a hypoglycemic threshold) has been shown to benefit glycemic control for all age groups with T1D.[153,1182–1184] The use of SAP therapy has been shown to improve not just A1C or hypoglycemia but also glycemic variability and albuminuria[1185–1187] when compared with MDI. Furthermore, scores for QoL and treatment satisfaction are also superior with SAP systems compared with MDI and BGM.[1188–1191] This is important because not all areas of the world have access to AID systems.

HCL systems and AID systems: AID systems are recommended for all persons with T1D, since their use has been shown to increase TIR, especially in the overnight period, without causing an increased risk of hypoglycemia. For persons with DM with suboptimal glycemia, significant glycemic variability, impaired hypoglycemia awareness, or who allow for permissive hyperglycemia due to the fear of hypoglycemia, such AID systems should be considered.[153,1131,1182–1184,1192,1193]

Pivotal trials for 3 HCL systems have shown success in improving TIR and reducing hypoglycemia both in the pediatric and adult age group.[1182–1184] In terms of insulin algorithms, target glucose choices and clinicians’ understanding of the impact of basal rates, insulin action time, and insulin sensitivity is paramount. Some systems use automated basal only, while others also use automated bolus for sustained hyperglycemia. Exercise is also addressed differently in each system. A meta-analysis of both approved and unapproved systems have shown improvements in glycemic control with closed-loop systems.[1194] It is therefore important for clinicians to be familiar with each device. Do-it-yourself HCLs have also gained in popularity due to excellent glycemic results,[1195] but as of this writing are not approved by the FDA.

Question 14: How should hypoglycemia be managed?

Recommendation 14.1—Oral intake of rapidly absorbed glucose (eg, glucose tablets or dietary sugar like fruit juice) followed by a snack or meal containing both protein and carbohydrates (eg, cheese and crackers or a peanut butter sandwich) should be used to treat hypoglycemia (measured glucose <70 mg/dL [3.9 mmol/L]) if a person is able to safely swallow.

Grade A; BEL 1

Recommendation 14.2—Glucagon, in one of the currently available forms: intranasal, prefilled liquid stable nonaqueous formulation, prefilled aqueous liquid stable glucagon analogue or with reconstitution from powder, should be used to correct hypoglycemia if individuals are unable or unwilling to ingest carbohydrates orally. If there is no response after 15 minutes, an additional same dose may be administered. As soon as the individual is awake and able to swallow, they should receive a rapidly absorbed source of carbohydrate.

Grade A; BEL 1

Recommendation 14.3—Persons with severe hypoglycemia with altered mental status or with prolonged hypoglycemia need to be hospitalized. If an individual has hypoglycemic unawareness and hypoglycemia-associated autonomic failure, several weeks of hypoglycemia avoidance may at least partially reverse hypoglycemia unawareness and may reduce the risk or prevent recurrence of severe hypoglycemia. Adjustment of an individual's long-term antihyperglycemic regimen may be necessary to further avoid recurrence of hypoglycemia.

Grade B; BEL 1

Recommendation 14.4—In persons with T2D who develop hypoglycemia and are being treated with alpha-glucosidase inhibitors or with pancreatic diabetes, oral glucose or lactose-containing foods (dairy products) must be given because alpha-glucosidase inhibitors inhibit the breakdownand absorption of complex carbohydrates and disaccharides (eg, table sugars or starches).

Grade A; BEL 1

Recommendation 14.5—Persons at risk for hypoglycemia should perform frequent BGM or preferably use CGM devices (see **R 3.1-R 3.4** on monitoring).

Grade B; BEL 4 and expert opinion of task force

Evidence Base 14: How should hypoglycemia be managed?

Definition of Hypoglycemia—The classical definition of hypoglycemia is a low BG level accompanied by symptoms of hypoglycemia (eg, palpitations, diaphoresis, hunger) that are relieved by the ingestion of glucose (ie, the Whipple triad).[1196] A glucose of <70 mg/dL (3.9 mmol/L) is the classic threshold for hypoglycemia based on physiologic glucose regulation and neuroendocrine response in persons without DM.[1197] Hypoglycemia may be asymptomatic, and any BG <70 mg/dL is generally considered hypoglycemia.[1198] In persons with DM, hypoglycemia is separated into 3 levels. Level 1, a measurable glucose <70 mg/dL (3.9 mmol/L), but ≥54 mg/dL(3.0 mmol/L), can and should alert a person to act. Level 2 is a measurable glucose <54 mg/dL (3.0 mmol/L) that needs immediate action, as neurogenic and neuroglycopenic hypoglycemic symptoms begin to occur below this level. Level 3 is defined as a severe event characterized byaltered mental status and/or physical status requiring assistance.[1198,1199] In addition, hypoglycemia symptoms can occur in the normal glucose range in a person with very high glucose levels that drop quickly. BGM and CGM can be helpful but are not necessarily diagnostic because of possible instances of glucose meter and sensor inaccuracy.

Symptoms of Hypoglycemia—Hypoglycemia manifests as neurogenic and/or neuroglycopenic symptoms that range in severity from mild to life-threatening and include anxiety, palpitations, tremor, sweating, hunger, paresthesia, behavioral changes, cognitive dysfunction, seizures, and coma. Certain hypoglycemia-related responses (psychomotor function) are altered in older adults compared with younger persons. Although severe hypoglycemia generally results in recognizable symptoms, mild-to-moderate hypoglycemia

may remain asymptomatic and unreported in persons with DM. Even severe hypoglycemia is often unrecognized in those with hypoglycemia unawareness.[1198]

Etiology of Hypoglycemia—In persons with DM, iatrogenic hypoglycemia stems from an imbalance among insulin and/or insulinogenic (eg, SUs, glinides) therapy and food intake, physical activity, organ function (gluconeogenesis), and counter-regulation with glucagon and/or epinephrine (hypoglycemia-associated autonomic failure). Hyperinsulinemia, increased alcohol intake, starvation, and organ failure may be aggravating factors.[1108,1200,1201] Noniatrogenic hypoglycemia (ie, insulinoma) is beyond the scope of this guideline.

Risks of Hypoglycemia—The primary cause of hypoglycemia is intensification of antihyperglycemic therapy (almost always using SUs [or to a lesser extent glinides] and/or insulin) aimed at achieving lower A1C targets, as demonstrated by intensive therapy trials.[1202,1203] Over 3.5 years in the ACCORD study, severe hypoglycemia occurred at an annualized rate of 3.1% of persons in the intensive therapygroup (mean end point A1C 6.4%; target <6.0%) vs 1.0% per year in the standard therapy group (mean end point A1C 7.5%).[76] During the ADVANCE trial, in which the goal A1C of 6.5% was met in the intensive group, 0.7% of intensively treated persons experienced severe hypoglycemia on an annual basis compared with 0.4% of persons per year in the standard care group.[70] Finally, in the UKPDS, wherein intensive treatment led to a mean end point A1C of 7.0%, hypoglycemia occurred in 1.8% of insulin-treated persons per year in the intensive group vs 0.7% of conventionally treated persons per year.[407] The risk of hypoglycemia is greater in older adults and those with longer DM duration, kidney failure, or lesser insulin reserve. Dementia is another important risk factor for hypoglycemia, and recurrent hypoglycemia appears to increase the risk of dementia.[1204–1206] The failure to recognize symptoms of hypoglycemia can increase the risk of subsequent hypoglycemia by causing autonomic failure, leading to a cycle of recurrent hypoglycemia and hypoglycemia unawareness.[1200]

Sequelae of Hypoglycemia—Studies have suggested an association of hypoglycemia with adverse CV events. In the ADVANCE trial, severe hypoglycemia was associated with significant risk increases for CV events including death.[1110] In ACCORD, hypoglycemia was considered a suspect behind the increased mortality observed in the intensive-treatment arm. However, glucose levels at time of death were unknown, and the hypothesis remains unproven.[82,87] Moreover, the HR for hypoglycemia-related mortality was even higher in the standard therapy arm of that study (aHR in intensive treatment arm: 1.41, 95% CI, 1.03–1.93; in standard therapy arm: 2.30, 95% CI, 1.46–3.65).[87] A meta-analysis of prospective and retrospective clinical trials demonstrated that severe hypoglycemia doubled the risk of CV events, whereas an observational trial showed that, over a period of 5 years, mortality was 3.4 times higher among persons who reported severe hypoglycemia at baseline.[1207,1208] The proposed mechanism for these effects posits that hypoglycemia reduces baroreceptor sensitivity and increases sympathoadrenal system activity, which can trigger a fatal ventricular arrhythmia in the setting of reduced baroreflex sensitivity.[1209] Other short- and long-term consequences of severe hypoglycemia include neurologic conditions ranging from temporary cognitive impairment to dementia as well as major

vascular events such as stroke, MI, acute cardiac failure, ventricular arrhythmias, and sudden death.[1108,1200,1210] The complications of hypoglycemia are also associated with short-term disability and higher health care costs.[1211–1214]

Management of Hypoglycemia—Oral administration of rapidly absorbed glucose (15 g) should be used to treat hypoglycemia (measured glucose <70 mg/dL (3.9 mmol/L) if a person is able to safely swallow.[1215–1217] Subsequent confirmation of return of glucose levels to greater than normal range is recommended.

In persons with T2D being treated with alpha-glucosidase inhibitors, who develop hypoglycemia due to use of hypoglycemic agents, oral glucose or lactose-containing foods (dairy products) must be given because alpha-glucosidase inhibitors inhibit the breakdown and absorption of complex carbohydrates and disaccharides.[1218–1225]

If a person is unable to swallow or is unresponsive, subcutaneous, intramuscular, or intranasal glucagon or IV glucose should be given by a trained family member or medical personnel. There are at least 3 FDA-approved formulations of standard glucagon for reconstitution and injection. These formulations are supplied as lyophilized white powder requiring reconstitution using the liquid in an included prefilled syringe prior to injection as 1 mg per vial. The adult dose is 1 mg. For children weighing less than 44 lbs (20 kg), the dose is 0.5 mg.[1226–1229]

New, more stable formulations of glucagon have recently become available for clinical use: intranasal glucagon, dasiglucagon, and nonaqueous soluble glucagon. These new FDAeapproved formulations have demonstrated glycemic responses similar to standard glucagon formulations for the treatment of hypoglycemia but without the need of reconstitution.[1230] Three mg of intranasal glucagon (1 mg glucagon per 10 mg dry powder) appears to have maximal effect.[1231–1235] Nonaqueous glucagon and dasiglucagon can be administered via a prefilled syringe or auto-injector, reducing the steps to prepare and administer glucagon in the event of hypoglycemia.[1236,1237] Dasiglucagon is a novel stable peptide analog of human glucagon consisting of 29 amino acids with 7 amino acid substitutions relative to native glucagon. In clinical trials, the time taken to increase glucose concentration to above 70 mg/dL was 6 minutes with doses of 0.3 mg and 0.6 mg of dasiglucagon, which is comparable to standard glucagon at doses of 0.5 mg and 1 mg.[1237,1238] For all these forms of glucagon rescue, if there is no response after 15 minutes, an additional same dose may be administered subcutaneously while waiting for emergency assistance, which should be called for immediately after administering the first dose (Table 20).

As soon as the individual is awake and able to swallow, they should receive a rapidly absorbed source of carbohydrate (eg, glucose tablets or dietary sugar like fruit juice) followed by a snack or meal containing both protein and carbohydrates (eg, cheese and crackers or a peanut butter sandwich).[1216,1217,1233,1239–1241]

Hypoglycemia is the primary limiting factor in the treatment of both T1D and T2D. It remains a significant barrier in terms of treatment adherence and achievement of glycemic

goals.[1108] Long-term management of hypoglycemia depends on appropriate adjustment of therapy to prevent hypoglycemia or reduce its frequency and severity in persons prone to hypoglycemia (eg, the elderly and persons with T1D). In T2D, hypoglycemia typically occurs in association with use of exogenous insulin, SUs (especially glyburide),[1242] and glinides; symptoms may be mild, moderate, or severe. The risk of hypoglycemia may be further increased by the addition of other antihyperglycemic agents to SUs or insulin. Therefore, in adults with T2D, treatment strategies should emphasize the increased number of antihyperglycemic medication classes that are not associated with severe hypoglycemia (Table 16). Also, the role of hypoglycemia must be considered in determining ideal A1C goals for each patient.

BGM and especially CGM are important tactics to help persons prevent, identify, and document hypoglycemia, although it is essential that the glucose meter and CGM meet accuracy standards and that users are provided with education and support. CGM use is particularly important in persons with recurrent asymptomatic hypoglycemia (hypoglycemia unawareness, hypoglycemia-associated autonomic failure), recurrent hypoglycemia, and persons on regimens placing them at risk for hypoglycemia.[153,1198]

Persons with hypoglycemic unawareness are particularly susceptible to marked variations in glucose levels. Therapeutic approaches can minimize glycemic excursions and prevent hypoglycemia.[1243–1247] Also, CGM, especially when connected to insulin pumps and HCL devices, can reduce occurrence of hypoglycemia.[1248]

Question 15: How should DM be managed in the hospital?

Recommendation 15.1—All hospitalized persons should have laboratory glucose testing on admission. Persons with DM or with admission hyperglycemia >140 mg/dL should have glucose monitoring during hospitalization.

Grade B; BEL 1

Recommendation 15.2—To guide inpatient therapy and inform discharge planning, clinicians should measure A1C in all persons with DM, unless their A1C is known and was tested within the previous 3 months.

Grade B; BEL 2

Recommendation 15.3—Hospitalized persons with hyperglycemia but without known DM should have A1C measured to identify preexisting DM and inform discharge planning.

Grade B; BEL 2

Recommendation 15.4—Initiate bedside POC capillary glucose monitoring at an appropriately chosen schedule to guide therapy for hyperglycemia during hospitalization in all persons with DM, persons without prior DM who have hyperglycemia, and persons receiving therapies with a high risk of hyperglycemia, such as corticosteroids and enteral or parenteral nutrition.

Grade A; BEL 1

Recommendation 15.5—For hospitalized persons with DM eating on a regular schedule, check POC BG before each meal and at bedtime, if clinically indicated. In hospitalized persons who are not eating (eg, NPO [nothing by mouth] or continuous feeding), initially check POC BG at least every 4 to 6 hours. Additional checks may be warranted for those at higher risk of hypoglycemia. For those on IV insulin, POC BG should be obtained from every 30 minutes to every 2 hours.

Grade A; BEL 1

Recommendation 15.6—Although inpatient CGM has not received regulatory approval, CGM may be useful in inpatient settings, while complying with institutional policies and safety precautions. CGM may improve detection of severe hypoglycemic and hyperglycemic events, identify glucose trends and patterns, and improve satisfaction in persons with DM.

Grade C; BEL 2

Recommendation 15.7—CGM may be considered under special regulatory allowance during the time of COVID-19 to reduce staff exposure and use of personal protective equipment and assist with glycemic monitoring of persons in the hospital setting.

Grade C; BEL 2

Recommendation 15.8—Specialized inpatient DM teams and/or CDCES, if available, should be used to improve outcomes in hospitalized persons with DM or hyperglycemia. The use of virtual consults may be considered an alternative to support hospitals lacking these services.

Grade B; BEL 1

Recommendation 15.9—For critically ill persons, IV insulin infusion is recommended to treat persistent hyperglycemia in the ICU using validated protocols that allow adjustment of insulin dose for glycemic excursions based on prespecified glucose targets. For those receiving IV insulin, POC testing should be performed every 30 to 120 minutes.

Grade A; BEL 1

Recommendation 15.10—A glucose target of 140 to 180 mg/dL is recommended for most critically ill persons in the hospital setting. More intensive targets between 110 to 140 mg/dL may be appropriate in select populations, particularly critically ill persons postcardiothoracic or other surgeries, while minimizing the risk of hypoglycemia.

Grade A; BEL 1

Recommendation 15.11—For most noncritically ill persons in the hospital setting, a glucose target of 140 to 180 mg/dL is recommended. For hospitalized persons who are able to achieve and maintain glycemic control without hypoglycemia, a lower target range

(100 to 140 mg/dL) may be reasonable. For persons in a hospital setting with high clinical complexity, terminal illness, limited life expectancy, or high risk for hypoglycemia, less stringent targets are appropriate.

Grade B; BEL 1

Recommendation 15.12—Insulin therapy following approved protocols is recommended as the preferred therapy for managing hyperglycemia in the hospital. For noncritically ill hospitalized persons with T2D, an individualized approach is recommended for consideration of noninsulin agents alone or in combination with insulin (see also **R 15.16**).

Grade A; BEL 1

Recommendation 15.13—The insulin regimen for hospitalized persons with satisfactory meal intake should include basal, prandial, and correction doses. For those without adequate food intake, a regimen of basal, prandial, and correction doses should be used as necessary for glycemic control. Exclusive use of “sliding-scale” insulin should only be used for those whose glucoses are in the target range most of the time, and only occasionally exceed it.

Grade A; BEL 1

Recommendation 15.14—The management of hyperglycemic emergencies, including DKA and hyperosmolar state, should include fully adequate fluid resuscitation to correct fluid deficits, electrolyte replacement (potassium), and insulin therapy. Simultaneous continued infusion of insulin and dextrose solutions after correction of hyperglycemia is often required until DKA resolves to avoid hypoglycemia.

Grade A; BEL 1

Recommendation 15.15—Transition from IV insulin in the ICU to a subcutaneous insulin regimen is typically required when acidosis is resolved and a person is no longer critically ill. A proactive regimen with scheduled subcutaneous insulin therapy, with basal, nutritional/prandial, and/or correctional doses, is recommended for most persons.

Grade A; BEL 1

Recommendation 15.16—For hospitalized persons with T2D and mild admission hyperglycemia (glucose <180 mg/dL), a personalized approach is recommended for the use of noninsulin agents alone or in combination with basal insulin, aiming for the most efficacious regimen with the lowest hypoglycemic risk. For some hospitalized persons with T2D, DPP-4 inhibitors plus correction doses with rapid-acting insulin, or basal insulin plus DPP-4 inhibitors may be sufficient.

Grade A; BEL 1

Recommendation 15.17—A hospital-wide standardized plan should be in place to prevent hypoglycemia. Each hypoglycemic episode should be documented, and appropriate adjustments should be made to prevent recurrence.

Grade B; BEL 2

Recommendation 15.18—It is recommended to start discharge planning soon after hospital admission and to provide and document appropriate individualized plans for transition to an ambulatory setting and follow-up care at discharge for all persons with DM or newly diagnosed hyperglycemia.

Grade A; BEL 1

Evidence Base 15: How should DM be managed in the hospital?

DM affects up to ~10% of the US population[36] and is even more common among hospitalized persons, present in up to 20% to 40% of admissions and has been particularly high during the COVID-19 pandemic.[1249,1250] The association between inpatient hyperglycemia and increased risk for complications and mortality is well established in persons with and without previously diagnosed DM.[1251–1254] Hyperglycemia is associated with prolonged hospital stay, increased incidence of infections, greater disability after hospital discharge, and death.[91,1255,1256]

Substantial evidence indicates that correction of hyperglycemia with insulin administration reduces hospital complications and mortality in critically ill persons, as well as those who receive care for general medicine and surgery.[92,1257,1258] Several RCTs, including the real-world Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation study[95,96,104] and meta-analyses[1257,1259,1260] reported higher rates of severe hypoglycemia and increased morbidity and mortality with intensive insulin therapy (glycemic targets of 80 to 110 mg/dL) compared with more relaxed glycemic targets, demonstrating that intensive glycemic control (80 to 110 mg/dL) in critically ill persons may be difficult to achieve, with no consistent mortality benefits in all studies, and increased risk of complications in those treated intensively, compared to moderate glycemic targets.[95,96,104] However, personalized glycemic targets between 110 to 140 mg/dL may improve outcomes in selected populations, particularly critically ill persons postcardiothoracic surgery, in hospital units that have shown low rates of hypoglycemia. In addition, minimizing glycemic variability, independent of glucose levels, could result in lower rates of complications and CV mortality in critically ill persons[1261–1263] and in reduced hospital stays and mortality in non-ICU settings.[1264] Thus, glucose targets <110 mg/dL are no longer universally recommended, and the AACE/ADA consensus statement on inpatient glycemic control favors more relaxed glycemic targets in the ICU, as high as 140 to 180 mg/dL.[105]

Treatment of Hyperglycemia in Persons in the Hospitalized Setting—Persons with DM have a 3-fold greater chance of hospitalization compared to those without DM, with 30% to 40% requiring 2 or more hospitalizations in any given year.[1264–1266] It is well established that hyperglycemia in persons with or without a prior diagnosis of DM increases

both mortality and disease-specific morbidity in hospitalized persons,[91,105,1251,1267] and that goal-directed insulin therapy can improve outcomes.[92,94,101] This topic has been extensively reviewed in the AACE/ADA consensus statement on inpatient hyperglycemia,[105] 2021 ADA Standards of Medical Care in DM,[1268] and 2022 Endocrine Society clinical practice guideline titled Management of Hyperglycemia in Hospitalized Adult Patients in Noncritical Care Settings.[99]

The management of hyperglycemia in the hospital setting presents multiple challenges including variable nutritional status and altered levels of consciousness, as well as resource limitations for monitoring glycemia during these changes. Given the paramount importance of patient safety, reasonable glucose targets in the hospital setting should be set at modestly higher levels than targets for outpatients with DM. For noncritically ill persons, a premeal glucose target of <140 mg/dL and a random BG of <180 mg/dL are recommended, while avoiding hypoglycemia (BG <70 mg/dL). Additionally, glycemic targets should be modified according to clinical status. For persons who are able to achieve and maintain glycemic control without hypoglycemia, a lower target range may be reasonable. For persons with terminal illness, limited life expectancy, or high risk for hypoglycemia, higher target ranges may be reasonable.[100,1259,1269–1274] Refer to **Section 1 on Screening, Diagnosis, Glycemic Targets, and Glycemic Monitoring** for additional guidance.

We recommend to check A1C for all persons with known DM, unless the A1C level is available and had been checked within the prior 3 months. A1C levels provide an overview of prior glycemic control, can predict response to therapy in the hospital, and guide discharge therapy.[103,1275–1279]

Some studies have demonstrated that the use of specialized DM management teams can result in better hyperglycemia correction, and avoidance of hypoglycemia, with positive impacts on readmissions and costs.[1280–1283] The use of e-consults or virtual visits may be an alternative for hospitals lacking these services,[1284] or for postdischarge DM follow-up.[1285–1287]

Management of Adults with Inpatient Hyperglycemia in the ICU—Insulin therapy is the preferred method of glycemic control in most hospitalized persons. IV infusion of insulin is the preferred route of administration for persons in the ICU. In the critical care setting, a variety of CSII protocols have been shown to be effective in achieving glycemic control with a low rate of hypoglycemic events and also to improve hospital outcomes.[94,101,1288–1290]

For ICU settings, most hospitals use institutional-based, nurse-driven protocols, with several validated protocols published.[1291–1293] Automated, computerized, IV insulin protocols, including commercially available or institutional-based protocols, have improved glycemic control, with good acceptance by nursing personnel.[1294–1307] The preference will depend on local needs, support, and cost to the institution. Preference should be given to use of regular insulin for IV administration,[1308,1309] given lower cost and wide availability, and short-acting insulin analogs have shown effective glycemic control.[1308]

The management of hyperglycemic emergencies (including DKA and hyperosmolar state) should follow standardized protocols with aggressive fluid resuscitation, electrolytes replacement, and also insulin therapy.[28,1310,1311] Persons with severe DKA should typically receive IV insulin therapy, whereas mild-to-moderate crises may be managed with frequent subcutaneous insulin administration and glucose monitoring protocols.[28,1121,1310,1312] Caution is recommended in persons with advanced renal failure because standard IV fluid and insulin replacement may result in increased volume overload and hypoglycemia.[1313,1314] Prevention and correction of hypokalemia and hypoglycemia should be proactively part of any treatment protocol. Severe hypokalemia (K ≤2.5 mEq/L) and severe hypoglycemia (BG <40 mg/dL) have been associated with increased mortality.[1315]

The addition of noninsulin agents, such as DPP-4 inhibitors or GLP-1 RAs, before admission or during the perioperative period, has not reduced rates of stress hyperglycemia and may increase nausea and vomiting rates[1316–1324] among critically ill persons. While the use of these agents is safe and may result in lower glucose levels and insulin doses, we do not recommend addition of a DPP-4 inhibitor or GLP-1 RA to IV insulin therapy until efficacy is demonstrated.

Most persons with T2D and all persons with T1D in the ICU receiving IV insulin infusion will require transition to a subcutaneous insulin regimen.[105] Those who are suitable for this transition ideally have a stable infusion rate and BG levels in the target range. Several studies[1266,1325–1329] recommend starting at a daily insulin dose ~80% of the IV insulin used in the preceding 12 to 24 hours and splitting it into basal and bolus insulin.[105] Persons without DM but with stress or newly diagnosed hyperglycemia who have required an insulin rate less than 1 to 2 units/hour at the time of transition may not require a scheduled subcutaneous insulin regimen.[1330] Many of these individuals can be treated with correction insulin to determine if they will require scheduled subcutaneous insulin.

Management of Hospitalized Adults with Inpatient Hyperglycemia in the Non-ICU Setting—In the noncritically ill setting, scheduled subcutaneous insulin regimens with a combination of basal, nutritional, and correctional components is recommended. Prolonged use of “sliding scale” insulin as the sole method of glucose control is strongly discouraged. Clinicians should only consider using “sliding scale” insulin alone in persons whose glucoses are in the target range most of the time, and only occasionally exceed it (ie, with stress hyperglycemia or well-controlled DM).[1331,1332]

RCTs have shown that treatment with a basal prandial regimen using insulin analogs improved glycemic control with fewer hospital complications in general medical and surgical persons with T2D compared with sliding-scale regular insulin alone.[92,107,108,1333–1336] Persons with T1D should be treated with basal-prandial insulin regimens to avoid severe hyperglycemia and DKA. In insulin-naïve persons with T2D, a starting insulin TDD between 0.3 and 0.5 units/kg/day is effective and safe in thosewho receive care for general medicine and surgery. Persons with T2D receiving insulin therapy before admission are at risk for severe hyperglycemia in the hospital if insulin therapy is discontinued. Assessment of the need for modification of the home insulinregimenis important as requirements varyaccordingto clinical stressors and altered

caloric intake.[105,1337] Lower starting insulin TDD of 0.20 to 0.25 units/kg are recommended in persons with impaired kidney function[1338,1339] in the elderly, and in those with poor caloric intake.[1339,1340] In addition, for persons whose glucose is controlled with insulinprior to admission, reducingtheinsulin TDD by 20% to 25% is recommended for those with poor caloric intake to avoid hypoglycemia in in the hospital setting,[1340] though persons with uncontrolled DM may actually require higher doses. In a single-center RCT, the use of correctional insulin sliding scales for bedtime hyperglycemia did not improve glycemic control in persons with T2D.[1341,1342]

Several studies have compared different basal insulin formulations, including glargine U100, insulin detemir U100, glargine U300, and degludec U100, with similar glycemic control results.[92,107,1343–1346] Although some RCTs have shown similar glycemic control and lower hypoglycemia with the use of insulin analogs[1308] in low-resource settings, the use of NPH may result in similar glycemic control, with minimally increased hypoglycemia,[1347,1348] albeit with higher insulin dose and injections per day. However, the use of pre-mixed insulin formulations (ie, 70/30) have resulted in significantly higher rates of hypoglycemia during hospitalization and are not recommended.[1349]

Though effective, the basal-bolus regimen is labor intensive, requires several injections per day, and is associated with risk of hypoglycemia, affecting up to 10% to 30% of noncritically ill persons.[102,1333] Several studies have been published on the use of alternative approaches, aiming for a more personalized approach. Evidence suggests that the best regimen should be individualized to achieve glycemic targets with the lowest risk of hypoglycemia. Clinical judgment will guide the best plan, incorporating a person's comorbidities, severity and complexity of disease, life expectancy, severity of acute hyperglycemia (ie, admission glucose), prior glycemic control (ie, A1C levels), and prior antihyperglycemic regimen (insulin-naïve vs insulin-treated persons).[102,103,1266,1268]

For noncritically ill persons with T2D and mild-to-moderate hyperglycemia (ie, admission glycemia below 180 to 200 mg/dL),[1266] the use of basal insulin plus correctional insulin (basal-plus regimen),[108] or basal insulin with DPP-4 inhibitors, or DPP-4 inhibitors plus correctional insulin doses with rapid-acting insulin may provide equal glycemic control to basal-bolus insulin.[1350–1352] The basal-plus approach in an RCT resulted in similar glycemic control compared with a standard basal-bolus regime[108] and can be an effective alternative with low insulin requirements, decreased oral intake, or when undergoing surgery.[1266,1353]

Studies have assessed inpatient uses of noninsulin agents with low hypoglycemic risk (DPP-4 inhibitors or GLP-1 RAs).[1351,1352,1354–1358] These newer agents are not expected to increase risk of lactic acidosis in ill persons (ie, unlike metformin) nor enhance risk of hypoglycemia (ie, unlike SUs and similar secretagogues), or cause edema or CHF (ie, unlike TZDs). Oral DPP-4 inhibitors have been tested in RCTs in medical and surgical noncritically ill persons with mild hyperglycemia (admission glucose <180 mg/dL).[1351,1354–1357] DPP-4 inhibitors combined with low-dose basal insulin have been similarly effective to basal-bolus insulin and associated with less hypoglycemia and less treatment burden.[1351,1354–1357,1359] The use of SGLT2is have not been evaluated in

hospitalized persons. In ambulatory studies, these agents increased the risk of infections (urinary, perineal), euglycemia DKA, acute renal failure, and hyperkalemia.[974] The FDA recommends withholding SGLT2is 3 to 4 days before surgery.[1360] We do not recommend SGLT2is in the hospital until further studies prove efficacy and safety, with the hypotheses derived from ambulatory studies where SGLT2is decreased cardio-renal and HF outcomes in persons with and without DM.[974] Hence, SGLT2is added at discharge to appropriately chosen persons who are stable may decrease clinical inertia and improve long-term outcomes.

Hypoglycemia and Hospital Outcomes—Meta-analyses of RCTs have reported increased risk ratio of 6 to 7.7 times for occurrence of hypoglycemia with intensive insulin therapy vs conventional glycemic control in critically ill persons,[1259,1361] with some studies showing a risk ratio >10.[1259] Inpatient hypoglycemia has been associated with higher rates of hospital complications, longer hospital stays, higher health care resource utilization, and increased hospital mortality, creating a J-shaped relationship between glucose levels and death rates.[1362,1363] BG <50 mg/dL was associated with 22.2% mortality compared with 2.3% without hypoglycemia.[1364] Hypoglycemia is associated with adverse CV outcomes such as prolonged QT intervals, ischemic electrocardiogram changes, angina, arrhythmias, and death.[1365] Despite these epidemiologic associations between hypoglycemia and poor clinical outcomes, data demonstrating that insulin-induced hypoglycemia is the direct cause of harm in hospitalized persons are sparse. The severity of hypoglycemia and not insulin therapy, per se, is associated with increased risk of mortality in critically ill persons.[1363] Hypoglycemia resulting from severe systemic illness (spontaneous hypoglycemia), rather than insulin-induced hypoglycemia, is associated with increased risk of inpatient mortality and complications.[1366–1368] Hospitals and hospital systems should implement nurse-driven protocols for the management of hypoglycemia.[1369–1372] These protocols should include specific treatment options for different levels of hypoglycemia, with indications to repeat treatment options within 15 minutes until resolution.

SUs may be associated with prolonged hypoglycemia, especially in persons with impaired renal function. In some instances, individuals will present with hypoglycemia on admission or mild hyperglycemia that rapidly results in hypoglycemia upon initiation of insulin therapy in the hospital. With increased use of antihyperglycemic agents with prolonged half-life and duration of action up to 5 to 7 days (glargine U300, degludec, dulaglutide, semaglutide, long-acting exenatide), clinicians should be aware of potential prolonged glucose-lowering effects of these agents, particularly in the setting of decreased oral intake, prolonged fasting episodes, decreased renal function, or liver failure during hospitalization (expert recommendations). Detailed medication reconciliation should occur upon admission to avoid these situations and assist early discharge planning.

Some retrospective studies have demonstrated severe hypoglycemia inpersons with and without DMtreated with IV bolus of insulin for hyperkalemia in the emergency room or while hospitalized.[1373,1374] The majority of these cases occur in persons with advanced CKD, often requiring dialysis treatment. Rates of severe hypoglycemia events in ambulatory persons with end-stage kidney disease on dialysis are 10-fold higher than among other nondialysis persons with CKD and often associated with prolonged hypoglycemic episodes

and poor response to regular hypoglycemia treatment.[1375] The most effective treatment is prevention with modified hyperkalemia treatment protocols, using lower insulin doses (5 units vs 10 units) and coadministration of dextrose (25 to 50 g IV).[1376,1377] However, this approach has not resulted in reduced rates of hypoglycemia in all studies, concluding that frequent glucose monitoring for up to 6 hours is recommended after using IV insulin to correct hyperkalemia[1376,1377] especially in persons at higher risk: without DM, with previous use of insulin or glucose-lowering agents, with pretreatment normoglycemia or mild hyperglycemia, or undergoing hemodialysis.[1373,1374]

Recommendations after Hospital Discharge—Persons with stress or hospital-related hyperglycemia, defined as any BG concentration >140 mg/dL without evidence of previous DM, should undergo A1C testing during admission or hospital stay.[102,1276–1278] Measurement of A1C may differentiate persons with stress hyperglycemia from those with previously undiagnosed DM, as well as identifying persons with known DM who will benefit from intensified glycemic management. In the presence of hyperglycemia, an A1C >6.5% suggests the diagnosis of DM. Because up to 40% to 50% of persons admitted with stress-related hyperglycemia have confirmed DM at 1 year they should be closely monitored after discharge.[1378,1379] A systematic review of 18 studies (N = 111,078 participants) found that the prevalence of DM after discharge was 4%, 12%, and 28% for persons with inpatient normoglycemia (fasting <100 mg/dL and random <140 mg/dL), mild hyperglycemia (fasting <126 mg/dL and random <200 mg/dL), and severe hyperglycemia (fasting >126 mg/dL and random >200 mg/dL, respectively).[1279]

The transition of persons from the hospital to ambulatory or subacute settings is a high-risk period for medication errors, but also an opportunity to improve glycemic control, avoiding what is often termed clinical inertia.[102,1285,1286,1380] Persons should have careful review of all prescribed medications to be taken post discharge and ideally have any needed prescriptions filled prior to discharge. Discharge algorithms based on A1C levels provide discharge guidance for hospitalized persons.[1275] For persons with A1C <7% and no hypoglycemia, it is recommended to restart prior ambulatory antihyperglycemic regimen, unless a new clinical indication or new contraindications require other adjustment. It is recommended to decrease (50% reduction) or stop SUs, aiming to reduce the risk of hypoglycemia with a low admission A1C. For persons with admission A1C between 7% and 9%, modification or intensification of therapy is recommended, including adding basal insulin, if clinically indicated. Addition of 50% of hospital dose of basal insulin is suggested. In persons with A1C >9%, the addition of basal insulin at 80% of hospital dose is suggested.[1275] Recent evidence suggests that adding GLP-1 RAs at discharge to select persons with uncontrolled T2D may result in better glycemic control, less hypoglycemia, and weight loss compared with adding basal insulin.[1381]

With several newer antihyperglycemic agents showing benefits beyond glucose reduction such as prevention of CV events or kidney disease progression, hospital discharge may be an important opportunity to revise prior antihyperglycemic therapy. For instance, many persons with T2D and underlying CVD admitted with CV event, HF, or kidney failure may have indications to use SGLT2 inhibitors or GLP-1 RAs. However, the evidence is very limited in the setting of acute illness. Trials of SGLT2 in the hospital and at discharge are

ongoing.[1382,1383] Starting SGLT2is for hospitalized persons with HF is not recommended at this time. There are limited studies assessing its efficacy or safety in hospitalized persons.[1384] If persons are stable and ready for discharge, starting these agents at discharge and communicating with the patient's primary clinician may represent a good opportunity to avoid clinical inertia, with preliminary studies showing no adverse safety signals.[1384]

Glucose Monitoring in the Hospital—Bedside capillary POC testing is the preferred method for guiding ongoing glycemic management of hospitalized persons.[99] Some glucose meters received approval for hospital use among persons in the ICU and non-ICU setting.[1385] It is recommended that all hospitals develop procedures for maintaining and calibrating glucose meters in use.

POC testing is usually performed 4 times a day: before meals and at bedtime for persons who are eating. For those who are not able to eat, have orders for holding food before procedures or as part of therapy, or receiving continuous enteral nutrition; POC testing is recommended every 4 to 6 hours. More frequent glucose monitoring is indicated in persons treated with CSII or after a medication change that could alter glycemic control, such as corticosteroid use, abrupt discontinuation of enteral or parenteral nutrition, or frequent episodes of hypoglycemia. For inpatients with steroid-induced hyperglycemia or with posttransplant diabetes receiving daily steroids, CGM studies have demonstrated that while fasting glucose could be within range, hyperglycemia is mostly detected in the afternoon and evening.[1386]

Prospective observational studies, using the current standard of care of checking capillary glucose before meals and at bedtime, have shown that about 45% of persons experience asymptomatic hypoglycemia events.[1387,1388] Hence, current methods for monitoring hypoglycemia in hospitals often fail to detect most hypoglycemic episodes, particularly asymptomatic or nocturnal hypoglycemia, which may be the most dangerous episodes.[1389] While still investigational, consensus guidelines and experts agree that CGM may better detect and prevent hypoglycemic episodes.[1390,1391] Innovative methods, such as a "glucose telemetry system"[1392–1394] or other approaches using CGM may provide better glycemic monitoring, including predictive tools or alarms before hypoglycemia occurs enabling prevention. CGM in the hospital is not currently approved by regulatory agencies, with ongoing validation studies.[1395] Research on implementing CGM targeting approval of some devices for hospital use has been focused mostly on the ICU. Earlier devices were invasive and required capillary glucose calibration. Hence, use was not widely adapted by clinicians and hospitals, leading to lack of availability of these sensors at this time.[1390]

During the COVID-19 pandemic, hospitals faced a critical need to minimize personnel exposure and save personal protective equipment. Several hospitals implemented emergency use, particularly of newer factory-calibrated CGM not requiring capillary glucose calibrations, for persons in ICU and non-ICU medical and surgical settings.[1266,1389,1390,1396,1397] Some studies have shown potential improvements in detection of glycemic excursions and prevention of hypoglycemia, specifically with the use of glucose telemetry systems.[1392–1394] However, there are no intervention studies showing benefits of CGM to adjust therapy. While expert consensus expects CGM in hospitalized

persons to improve detection of glycemic excursion and overall glycemic control,[153,1390] CGM remains investigational in the hospital.[1398,1399]

With proper protocols in place, persons previously using CGM can be allowed to continue using their devices during hospitalization, unless clinically not appropriate.[153,1390] Given limited approval from regulatory agencies of CGM devices, adjustment of antihyperglycemic therapy should be performed with the use of hospital-calibrated glucose meters, per local hospital policies. CGM values outside the desired range, specifically hypoglycemia (BG <70 mg/dL or <54 mg/dL), should prompt nursing notification by the patient to be confirmed with hospital-calibrated glucose meters. The implications of these hospital policies are unknown when applied to SAP therapy or AID systems (eg, HCL systems, artificial pancreas devices), since the insulin pump uses glucose information received from the CGM without information from POC testing or direct interaction with a practitioner.[153]

MNT for Persons in the Hospital Setting—MNT is an essential component of inpatient glycemic management in persons with DM and hyperglycemia. The goals of inpatient MNT for persons with DM are to help optimize glycemic control, provide adequate calories to meet metabolic demands, address individual needs based on personal food preferences, and provide a discharge plan for follow-up care. Most hospitalized persons require 25 to 35 calories/kg/day; critically ill persons require between 15 and 25 calories/kg/day.[1400–1405] This translates to a diet containing approximately 1800 to 2000 calories/day or about 200 g of carbohydrate per day divided between meals. Care must be taken not to overfeed hospitalized persons because this may exacerbate hyperglycemia. No single meal-planning system is ideal for hospitalized persons. However, hospitals should provide a consistent carbohydrate DM meal-planning system.[1400,1402–1405] The carbohydrate components of breakfast, lunch, dinner, and snacks may vary, but the day-to-day carbohydrate content of specific meals and snacks should be kept constant. Persons requiring clear or full liquid diets should receive about 200 g of carbohydrate per day in equally divided amounts at meal and snack times. Persons on liquid diets, in particular during the perioperative period, do not meet these nutritional needs. Increasing evidence indicates that a person's food intake should be initiated as quickly as possible with progression from clear liquids to full liquids to solid foods as rapidly as tolerated postsurgery.[1402–1406] Early enteral feeding is safe and well tolerated and is associated with reduced wound morbidity, improved wound healing, fewer septic complications, diminished weight loss, and improved protein kinetics.[1406] Among persons in the ICU, the use diabetes-specific formulas improved glycemic control, decreased insulin requirements, and risk of infections relative to the standard formulas.[1407]

Question 16: How should DM in pregnancy be managed?

Recommendation 16.1—For women with GDM, the following treatment goals are recommended: preprandial glucose concentration ≤95 mg/dL and either a 1-hour postmeal glucose ≤140 mg/dL or a 2-hour postmeal glucose ≤120 mg/dL to decrease adverse fetal outcomes.

Grade C; BEL 4 and expert opinion of task force

Recommendation 16.2—All women with preexisting DM (T1D, T2D, or previous GDM) need access to preconception care and counseling to ensure adequate nutrition, healthy weight, and glucose control before conception, during pregnancy, and in the postpartum period.

Grade B; BEL 2

Recommendation 16.3—Rapid-acting insulin analogs (insulin-lispro, insulin-aspart) should be used to treat postprandial hyperglycemia in pregnant women.

Grade B; BEL 1

Recommendation 16.4—Options for basal insulin include long-acting insulin (eg, NPH, detemir, or glargine) or rapid-acting insulin via a CSII. Regular insulin, although not recommended as first-line therapy, is acceptable to use in managing pregnant women with DM when rapid-acting insulin analogs are not available.

Grade B; BEL 1

Recommendation 16.5—Insulin is the preferred therapeutic choice for pregnant women with GDM or T2D, but metformin has been given a category B for pregnancy with accumulating clinical evidence of metformin's safety during the first trimester and beyond. Metformin has been shown to improve pregnancy and fetal outcomes except for increased rates of infants with SGA and later onset of obesity. The prescriber should discuss the potential risks and benefits of oral agent therapy during pregnancy as well as the need for longer-term outcome studies.

Grade B; BEL 1

Evidence Base 16: How should DM in pregnancy be managed?

Abnormal glucose tolerance develops at higher rates and at younger ages among offspring of women with DM. A 2021 study examining the trends in GDM from 2011–2019 suggested that the rates of GDM have increased across all racial and ethnic subgroups.[1408] Maternal DM is one of the strongest risk factors for the development of T2D among children.[1409–1411] By the time these offspring reach childbearing age, they are very likely to be obese and have DM, thereby perpetuating a vicious cycle with significant implications for public health and health care costs.[1411] That this is not simply a genetic predisposition is inferred from the finding of lower rates of DM in offspring of women who were born before their mothers developed DM[1412]; this is true among sibling pairs whose birth dates straddle the onset of their mother's DM.[1409] Thus, all women with DM in childbearing years should have preconception care and guidance to target an A1C level of <6.5%.[75,1413–1417]

The HAPO study confirmed findings in Pima Indians[1409] that, even among offspring of women without GDM as it is currently defined, there is a linear association between maternal glucose concentration during pregnancy and newborn weight, rates of large-for-

gestational-age, and cesarean delivery.[64,1418–1421] DM during pregnancy and even maternal obesity itself[1418] set the stage for a vicious cycle with offspring of mothers with DM during pregnancy being more likely to become obese and to develop DM at younger ages.[1420] Maternal DM and obesity, although major risk factors for the metabolic health of the offspring, are not the only factors at play in the early stages of childhood that can have lasting adverse effects on offspring. Both low and high birth weight are associated with higher rates of DM.[1421] Abnormal birth weight directly affects the offspring and leads to higher rates of GDM eventually in the offspring, thereby compounding the vicious cycle. Early diagnosis and treatment of DM, careful preconception care and guidance for women with DM or at risk for GDM, and meticulous control of glucose abnormalities throughout pregnancy are currently our best hope to break this perpetuating cycle.[67,1422,1423]

Thus, women with risk factors for DM (Table 5) should be screened at the first prenatal visit for undiagnosed T2D using standard criteria (Table 4), and all pregnant women without a prior diagnosis of DM should be screened for GDM with a 2-hour OGTT using a 75-g glucose load or a 2-step 1-hour/3-hour OGTT at 24 to 28 weeks' gestation.[63,1424] Glucose criteria diagnostic for GDM are an FPG >92 mg/dL, 1-hour postglucose challenge value ≥180 mg/dL, or 2-hour value ≥153 mg/dL.[59]

For women with GDM, glucose should be managed with the following treatment goals: preprandial glucose concentration ≤95 mg/dL and either a 1-hour postmeal glucose ≤140 mg/dL or a 2-hour postmeal glucose ≤120 mg/dL to decrease fetal macrosomia. However, no controlled trials have been performed to identify ideal glycemic target beyond the outcome of macrosomia, and the majority of the studies are extrapolated from T2D in pregnancy vs GDM data.[122,1425,1426]

Maternal diet modification and control is the initial intervention for a new diagnosis of GDM. Referral for nutrition counseling or meeting with a certified diabetes educator to discuss label reading, carbohydrate counting, and meal splitting is recommended. While initial treatment of GDM involves modifying maternal diet, if medication is needed beyond diet control, split dosing with long-acting and rapid-acting insulin is recommended. First-line therapy for GDM involves using NPH, detemir, or glargine; regular insulin is considered for treatment if long-acting insulin analogs are not available.[1427–1429] Furthermore, while insulin is the recommended therapy, if not available or if unable to safely initiate, oral agents such as metformin or glyburide have not shown increased adverse pregnancy outcomes and therefore can be considered.[1430–1435] If concerns for postprandial hyperglycemia occur, rapid-acting insulin and analogs are recommended.[75,1436–1438]

In T1D, optimal care may necessitate CGM and CSII utilization (often already in use given the longevity of the disease). Rapid-acting insulin analogs for pump therapy that have been studied in pregnancy include lispro and aspart.[1439–1442] Data that detemir is safe in pregnancy are convincing.[1443–1446] Glargine is widely used; however, there are still no conclusive reports on its safety as performing an RCT in pregnant persons with T1D has its own challenges. Discussion for women with glargine should include considering maternal risks vs fetal benefits and understanding that drug studies can clearly demonstrate concern when abnormal fetal outcomes are above the baseline population risk (1% to 2%). When that

is not present, it is unclear whether documented fetal abnormalities are due to the drug or baseline population rate. Therefore, if glargine has been successful in maintaining a person with T1D in a euglycemic state, potentially changing medication in pregnancy and altering maternal blood sugar levels is riskier than fetal risk.

Insulin is the preferred treatment for women with pregnancy and DM. For those with GDM or pregestational T2D, and insulin is inaccessible, metformin and glyburide may be alternative options. The prescriber should discuss the potential risks and benefits of oral agent therapy during pregnancy as well as the need for longer-term outcome studies.[1447,1448]

Finally, women with GDM specifically need to have appropriate postpartum follow-up with a 2-hour OGTT within 6 weeks of delivery and referral to primary care for appropriate monitoring for T2D development.

Section 4: Select Additional Topics on Education, Nonpharmacologic Components of a Care Plan for Children and Adolescents, Male and Female Infertility, Secondary Diabetes, Posttransplant Diabetes, Sleep Medicine, Depression, SDOH, Virtual Health, Occupational Safety, Nutritional Supplements, Cancer Risk, and Vaccinations

Question 17: What education interventions have been shown to be most effective in management of persons with DM?

Recommendation 17—Comprehensive individualized DSMES is recommended at the time of DM diagnosis and subsequently as appropriate. Therapeutic lifestyle management must be discussed with all persons with DM or prediabetes at the time of diagnosis and throughout their lifetime. This includes MNT (with reduction and modification of caloric and fat intake to achieve weight loss in those who are overweight or obese), appropriately prescribed physical activity, avoidance of tobacco products, and adequate sleep quantity and quality. Additional topics commonly taught in DSMES programs outline principles of glycemia treatment options; BGM; insulin dosage adjustments; acute complications of DM; and prevention, recognition, and treatment of hypoglycemia.

Grade A; BEL 1

Evidence Base 17: What education interventions have been shown to be most effective in management of persons with DM?

DSMES is an ongoing educational program that imparts skills and knowledge needed for DM self-care throughout the life span.[907] In a disease that is largely self-managed, DSMES includes nutrition, physical activity, and an understanding of treatment relevant to glycemic control, knowledge regarding the natural history of DM, and measures to prevent cardiometabolic and microvascular disease outcomes. Evidence indicates that DSMES imparts enhanced knowledge of DM and self-care practices resulting in improved A1C values,[909,912,1449–1451] modest reductions in weight, better QoL,[912,1451,1452] and lower mortality risk,[1453] while at the same time leading to a reduction in health care costs.[1454,1455]

In a systematic review, patient education for those with DM has been suggested to be both cost-effective[1456,1457] as well as to reduce complications and overall mortality.[1458,1453]

A personalized educational approach to persons with DM, leveraging members of a multidisciplinary team, will lead to greater self-management skills.[1459–1463] When designing a patient education program, one should consider individual preferences and needs, social-educational status, health literacy, and learning barriers along with the types of locally available resources. The frequency and intensity of education are based on the natural history of the DM and particular situations such as pregnancy, CVD, initiation of insulin, or intensive insulin therapy incorporating pump or sensor technology. The National Institutes of Health[1464] and AACE disease state resources provide useful online resources and education.

Patient education has proven to be effective for persons with T1D and T2D[909,1465] across a variety of ages,[1466] in rural[1467,1468] and urban settings,[1469] individually or in groups,[1470] as well as across cultures and ethnicities,[225,1471–1473] particularly if cultural and psychosocial issues are addressed.[906,1474,1475]

Patient education can be successful in many formats including individual sessions, group sessions,[1476] telephone or video,[1456,1469,1477,1478] and computer-based programs.[1479,1480] Internet-based DSMES services and telemedicine approaches for DM prevention and the management of T2D management have also been shown to be effective.[1481–1484] Digital enhancement of patient education curriculum via online formats, social media, and gamification has the potential to increase access to and engagement with DSMES.[1485–1487]

Members of the DM educational team can include nurses,[1488,1489] dietitians, and pharmacists.[1490,1491] In addition, nonmedical colleagues such as patient peers[1492] or community health workers[1493–1495] may also contribute to self-efficacy of a person with DM. A CDCES, after fulfilling eligibility criteria and passing the certification exam,[1496] can be a critical member of a DM education program with their educational expertise as well as real-world knowledge of DM management. The goal is to improve a person's knowledge of DM as well as their competency in DM self-management. Efforts to continually engage persons with DM may help sustain the outcomes achieved by the initial structured educational program.[1497]

Question 18: What are the key nonpharmacological components of a comprehensive diabetes care plan for children and adolescents?

Recommendation 18.1—T1D and T2D in children and adolescents should be managed in close consultation with the patient and their family members, involving school and daycare personnel whenever possible.

Grade B; BEL 2

Recommendation 18.2—It is recommended that all children and adolescents with DM should be given age and culturally appropriate education and guidance for physical activity and lifestyle modification.

Grade A; BEL 1

Recommendation 18.3—Interventions by family and/or community are recommended to improve dietary behavior and increase physical activity in efforts to prevent childhood obesity and T2D (**Grade A**). Game-based interventions also can be incorporated to enhance healthy lifestyle habits (**Grade B**).

BEL 1

Recommendation 18.4—Routine psychological assessment with consideration of family stressors and psychosocial factors that may impact glycemic control is recommended for all youth with DM.

Grade A; BEL 1

Recommendation 18.5—With the risk of glycemic control worsening during adolescence, coordinated, individualized, planned transition from pediatric to adult DM care is recommended for all adolescents.

Grade A; BEL 1

Evidence Base 18: What are the key nonpharmacological components of a comprehensive diabetes care plan for children and adolescents?

Parental involvement in DM care and monitoring has been shown to improve adherencetotreatmentplans as wellasglycemiccontrol in childhood,[1498–1500] and parental support through adolescence has been shown to improve DM outcomes.[1501] Similarly, because many children spend large portions of their day at school or in daycare, it is essential to communicate and coordinate with school personnel and other childcare providers to optimize glycemic control.[1501,1502]

Improvement in fitness and/or diet correlate with improvement in glycemic control in youth with T2D. The largest study of youth with T2D, TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) clinical trial, demonstrated that achieving a healthy lifestyle in this age group is challenging,[1503] but when successful, it results in decreased A1C and homeostatic model assessment for insulin resistance.[1504] More data are needed to determine optimal interventions for these positive lifestyle changes. In T1D, though physical activity may not improve glycemic control, it is important for preventing obesity and building healthy habits for adulthood and is an integral part of a diabetes care plan when coupled with hypoglycemia avoidance strategies.[1502]

DM care providers for children and young adults must recognize the prevalence of mental health disorders in this population as well as the impact of psychological concerns on glycemic control.[1505] It is important that care providers understand normal cognitive and psychological development in youth as well as signs of mental illnesses such as depression/anxiety, eating disorders, and substance use disorders in children and young adults. Targeted depression-prevention programs with DM specific content have been shown to reduce DM distress and depression among youth with T1D compared with advanced DM education

alone.[1506] Mental health professionals should be included in the care team when needed for appropriate support.[1498,1507,1508]

Childhood obesity is a primary contributor to the development of T2D in children and young adults. Family-based interventions such as nutrition counseling with psychological support and more frequent family meals have been shown to be effective in obesity prevention.[1509–1513] Inadequate sleep duration is an important contributor to childhood obesity.[1514]

Physical activity improves BMI in overweight and obese children.[1515,1516] Games used to increase physical activity and increase nutritional knowledge have been effective.[1517] Exergaming interventions at home and at school have been shown to increase physical activity in children and to improve BMI z-score and cardiometabolic parameters.[1518–1520] There is evidence that community programs involving cross-age peers can be effective at delivering nutritional interventions[1521] and in reducing BMI,[1522] particularly in low-income or minority populations.

Although before and after-school interventions to increase physical activity in school-age children and adolescents have been effective in improving BMI and preventing obesity,[1523,1524] results from in-school nutrition and lifestyle education programs have been inconsistent.[1525–1531] Such interventions may be more effective when combined with family and community involvement.[1525,1532,1533]

There has been considerable interest in transitional care from pediatrics to adult care for persons with DM. Glycemic control has been shown to worsen during transition from pediatric to adult care for persons with T1D and T2D.[1534,1535] There is strong consensus that an organized, planned process is necessary to appropriately transition persons from pediatric to adult DM care. However, due to limited studies there is insufficient evidence to support a particular transitional care model.[1536–1541] Transitional care models may vary with respect to type of multidisciplinary staffing, separate vs joint clinics with pediatrician and adult physician, individual vs group education approaches and many other variables. Since no particular approach to transition has been found to be superior, more studies are needed to identify the most effective transitional care model.

Question 19.1: Should persons with infertility be screened for DM?

Recommendation 19.1—Men and women undergoing investigation for infertility and preparation for infertility interventions, including in vitro fertilization, should be screened for DM.

Grade B; BEL 2

Question 19.2: How should persons with preexisting DM and infertility be evaluated?

Recommendation 19.2—For all persons with DM and possible infertility, in addition to routine endocrine evaluation, further collaborative consultation with a reproductive specialist should be considered. For women with T2D and infertility, or those with T1D who desire to preserve or estimate their fertility, anti-Müllerian hormone and midluteal progesterone

levels may be assessed and screened for ovulatory dysfunction including anovulation. For men with DM and infertility, a standard semen analysis may be assessed, and an endocrine evaluation be initiated.

Grade B; BEL 2

Question 19.3: Should men with DM and cardiometabolic disorders be assessed for hypogonadism?

Recommendation 19.3—All men with CMD including prediabetes, metabolic syndrome, obesity, and T2D should be assessed for hypogonadism by history and physical examination; test for testosterone deficiency in persons with loss of libido and/or loss of muscle strength or mass, erectile dysfunction, osteopenia, or infertility.

Grade B; BEL 1

Evidence Base 19:

19.1 Should persons with infertility be screened for DM?

19.2 How should persons with preexisting DM and infertility be evaluated?

19.3 Should men with DM and cardiometabolic disorders be assessed for hypogonadism?

Many persons with infertility have not had appropriate evaluations for underlying medical causes. Men and women with undiagnosed, untreated, or undertreated DM may have higher rates of infertility. For those diagnosed with DM, it also is important to emphasize that appropriate glycemic control is the best way to safeguard current and future fertility, and preconception care is essential for improved pregnancy outcomes.[1542,1543] Desired outcomes of fertility treatments may be reduced in persons with undiagnosed controlled DM. Since infertility treatments are also resource intensive, it may be prudent to screen for DM universally in persons seeking evaluation for infertility.[1544]

Men with DM (T1D or T2D) have higher rates of infertility and a reduced number of offspring (T1D). [1545–1548] IGT also is present in a significant proportion of men undergoing investigation for primary infertility.[1549] The presence of metabolic syndrome components has been associated with poor sperm morphology and erectile dysfunction.[1550] Hyperglycemia has been shown to impair gamete number and competency oligoasthenospermia) as well as erectile and ejaculatory function.[1551] DM is associated with worsened sperm quality including decreased concentration, progressive motility, and sperm morphology.[1546] The molecular mechanisms that underlie these findings are not fully understood. There may be impaired sperm mitochondrial function in men with T1D and epididymal dysfunction.[1546,1552] For men with T2D, semen analysis can display findings of increased oxidative stress.[1546] Men with DM also may have lower testosterone levels due to decreased hypothalamic gonadotropin-releasing hormone drive and/or damage to the testes. Initial investigation can include semen analysis and an endocrine evaluation for secondary hypogonadism and/or secondary hypothyroidism.[1547,1553–1556]

There appears to be a higher likelihood for undiagnosed hyperglycemia in those seeking fertility.[1557] In preclinical or animal models, hyperglycemia can impact oocyte competence by known and unknown mechanisms.[1558,1559] In addition, women with DM may have higher rates of ovulatory dysfunction including hypothalamic hypogonadism.[1560] Womenwith autoimmune DM may be especially prone to accelerated oocyte atresia and early menopause,[1561] which may be one explanation for decreased numbers of offspring of women with T1D compared with controls or unaffected siblings,[1548] especially for those with earlier childhood onset. Women with T1D with hyperglycemia may also have hypothalamic-pituitary-gonadal axis dysfunction, which can contribute to oligo- or amenorrhea.[1562] Initial investigations include measurement of anti-Müllerian hormone and midluteal progesterone levels.[1563,1564] Collaboration with a reproductive specialist is recommended to discern risk factors for infertility.

There is a significant knowledge gap regarding the impact of pharmacologic treatments for DM on gamete health, fertility, and pregnancy as well as for reproductive technologies.[1565] Current data do not allow us to determine which treatments for DM could preserve or compromise fertility.

An additional consideration is that men with CMD, whether characterized by prediabetes, metabolic syndrome, obesity, or T2D, are at increased risk of hypogonadism and testosterone deficiency.[1566–1569] Testosterone may impair gonadotropin secretion and result in impaired spermatogenesis.[1570] Furthermore, testosterone replacement improves glycemia, dyslipidemia, hepatic steatosis, body composition, and CVD risk and also prevents progression from prediabetes to T2D.[1571–1574] Therefore, it is important to screen for and treat hypogonadism and testosterone deficiency in men with CMD and ABCD.

Question 20.1: How should persons at risk for secondary diabetes be assessed?

Recommendation 20.1—Persons withrisk factors for developing secondary diabetes, such as postorgan transplantation, cystic fibrosis, chronic pancreatitis/postpartial pancreatectomy, or on medication associated with hyperglycemia, should be monitored routinely for IFG, IGT, and/or overt DM.

Grade A; BEL 1

Evidence Base 20.1: How should persons at risk for secondary diabetes be assessed?

Common forms of secondary diabetes include posttransplant diabetes (PTDM), cystic fibrosiserelated diabetes (CFRD), pancreatogenic diabetes (type 3c), and diabetes associated with certain medications such as corticosteroids, protease inhibitors, and, most recently, immune checkpoint inhibitors. These conditions have unique pathophysiologic mechanisms with associated risk factors such as genetic (human leukocyte antigen typing, family history), clinical phenotypes (overweight/obese), or medication-related disruption of normal glucose metabolism. Others are related to underlying primary disease process, such as cystic fibrosis, resulting in a loss of pancreatic function. Similarly, diabetes related to chronic pancreatitis or postpartial pancreatectomy is a common complication, with one meta-analysis demonstrating an incidence of up to 77% after distal pancreatectomy.[1575]

The risk factors for PTDM are similar to those for T2D, particularly with demographics, and obesity[1576–1578] with the additive effects of immunosuppressive medications resulting in insulin deficiency as well as insulin resistance. Other more unique risk factors in this population include genetic polymorphisms, polycystic kidney disease, hepatitis C, and cytomegalovirus status.[1579–1581] Of the various immunosuppressive agents, belatacept[1582,1583] appears to be the least diabetogenic and tacrolimus having the highest risk for PTDM.[1584–1590] Electrolyte abnormalities such as hypomagnesemia may also add to the risk.[1586] It is still unclear if steroid-sparing regimens decrease the risk of PTDM with studies showing mixed results.[1591–1595] Other immunosuppressive therapy associated with a lower risk of PTDM include antithymocyte globulin and Interleukin 2 receptor antagonists.[1583,1589,1596,1597]

Early screening and diagnosis are important as PTDM is associated with increased adverse outcomes in persons with transplant.[1598,1599]

An increasing body of new literature points to the association of immune checkpoint inhibitors with new-onset hyperglycemia and DM. At this time, most of the literature is in the form of case reports demonstrating hyperglycemia, new-onset diabetes, and DKA, either with or without autoimmune markers of T1D.[1579,1600–1605] Presentation may range from mild hyperglycemia to frank DM, ranging from 1% to 6%.[1606,1607] Therefore, persons on immune checkpoint inhibitor therapy should be monitored closely for early detection and therapy for hyperglycemia and the long-term development of DM.

Corticosteroids and protease inhibitors (anti-retroviral agents) also cause insulin resistance and IGT and are strongly associated with secondary DM.[1608–1611] With all these secondary causes of hyperglycemia, a high index of suspicion is necessary to screen for both fasting and postprandial hyperglycemia to diagnose new onset of DM.

Question 20.2: What are the best treatment strategies for management of secondary diabetes, such as posttransplant diabetes, cystic fibrosis–related diabetes, and other forms of secondary diabetes?

Recommendation 20.2.1—Select treatment for secondary DM based on the underlying pathophysiology. Insulin therapy is safe and effective, but alternative glucose-lowering agents may be considered in specific patient populations.

Grade A; BEL 1

Recommendation 20.2.2—DPP-4 inhibitors can be safely used to improve glycemic control for posttransplant diabetes.

Grade A; BEL 1

Evidence Base 20.2: What are the best treatment strategies for management of secondary diabetes, such as posttransplant diabetes, cystic fibrosis–related diabetes, and other forms of secondary diabetes?

Treatment strategies vary based on the etiology of the secondary DM. Other than PTDM, clinical trials for specific therapies for the various forms of secondary DM have been limited in size and scope. In any secondary DM with obvious insulin deficiency or diabetic emergencies such as hyperosmolar hyperglycemic syndrome or DKA, insulin is the primary therapy. Insulin therapy is efficacious in all forms of secondary DM.

There is limited evidence to support any particular non-insulin therapy in secondary DM. There are several studies on PTDM and oral antihyperglycemia agents, including repaglinide, DPP-4 inhibitors, and pioglitazone.[1612] In particular, DPP-4 inhibitors have been studied the most in several RCTs of persons with kidney transplant and have been shown to be safe and efficacious.[1612–1614] The choice to use immunosuppressive agents is also a consideration in both prevention and management of PTDM. Use of antithymocyte globulin, belatacept, and minimization or elimination of tacrolimus in the immunosuppressive regimen has been shown to reduce hyperglycemia and new onset PTDM.[1590,1615,1616] SGLT2is are emerging as a potential option for PTDM and have demonstrated safety and efficacy.[1612,1617–1619]

Studies on intensive lifestyle intervention for secondary DM are limited. However, one prospective study demonstrated a beneficial role of lifestyle intervention in persons with transplant.[1620]

Studies on CFRD are small and limited. In a 24-month RCT of newly diagnosed CFRD, repaglinide was demonstrated to be equivalent to insulin.[1621] However, insulin remains the most common therapy for CFRD, particularly when corticosteroid therapy is also used for CF management.

Question 21: What is the role of sleep medicine in the care of persons with DM?

Recommendation 21.1—Health care professionals should assess persons with T2D for symptoms and signs of OSA, especially in the presence of obesity or suggestive clinical features of OSA.

Grade B; BEL 2

Recommendation 21.2—Based on resources available locally, persons suspected to have OSA should be referred to an appropriate center for diagnosis and management of OSA.

Grade B; BEL 4 and Expert Opinion of Task Force

Recommendation 21.3—Weight loss is recommended as the predominant intervention to improve both OSA and insulin sensitivity. In addition, devices that provide positive airway pressure as prescribed by a sleep specialist are effective.

Grade A; BEL 1

Evidence Base 21: What is the role of sleep medicine in the care of persons with DM?

The National Sleep Foundation[1622] recommends an average of at least 7 hours of sleep for adults ≥18 years of age. Chronic inefficient sleep duration has been reported to be associated adversely with obesity, DM,[1623] hypertension, CVD, and increased mortality. OSA is prevalent in persons with T2D (58%-77%) and even higher (86%) in those with both T2D and obesity.[1624]

The American Academy of Sleep Medicine recently emphasized the detrimental effects of sleep disorders and the importance of sleep education and routine screening for sleep disorders by health care professionals as strategies for optimizing healthy sleep.[1625] Screening in the office should assess for symptoms associated with OSA such as snoring, apnea or choking during sleep, unrefreshed sleep, excessive daytime sleepiness, or fatigue, especially in overweight or obese individuals with DM. Some clinics have supplemented clinical screening with the use of home oximetry. Clinical screening with a tool such as the STOP-Bang questionnaire can be augmented with home sleep apnea testing depending on available resources.[1626,1627]

Treatment of OSA in persons with prediabetes and DM with continuous positive airway pressure (CPAP) improves OSA symptoms.[1623,1628–1631] Weight loss whether via lifestyle intervention or pharmacologic approaches also has been shown to result in improvements of OSA.[1628–1630,1632–1636] From Sleep AHEAD study data, intensive lifestyle intervention resulting in weight loss had a greater impact on the apnea-hypopnea index and OSA remission than standard DMsupport and education, and this wassustained at 10 years.[1635]

The effects on A1C are more variable with one study suggesting that despite improvements in insulin resistance, CPAP treatment of OSA does not necessarily improve A1C.[1637] However, a 2021 meta-analysis found that in adults with T2D and OSA, treatment with CPAP resulted in significant improvement in A1C.[1638] More consistently, weight loss was independently reported to improve both sleep apnea and A1C in those with T2D.[1634]

Question 22: Should screening for depression be a routine component of clinical assessment in persons with DM?

Recommendation 22—Routine screening of adults with DM for depression and DM distress is recommended during each clinic encounter, if appropriate. Referral to mental health professionals should be made as soon as possible once depression is suspected or diagnosed.

Grade A; BEL 1

Evidence Base 22: Should screening for depression be a routine component of clinical assessment in persons with DM?

Depression is highly prevalent in those with T2D and if untreated, can be associated with poor adherence to lifestyle and medical regimens and potentially lead to more CVD and other DM-related complications.[1639,1640] DM-related distress, anxiety, subthreshold depression, having more than 3 chronic diseases and having stressful life events can predict

depression and should trigger screening with effective tools like the WHO Wellbeing Index (WHO-5), the Patient Health Questionaire-9, or the Beck Depression Inventory II.[1641–1644] For DM distress, The Problem Areas in Diabetes Scale and the Diabetes Distress Scale are available.[1643] Screening for and treatment of depression among persons with DM has been associated with reduction in DM comorbidities and better outcomes for glycemic control and DM complications.[1645–1648]

Cognitive behavioral therapy delivered by trained mental health personnel, either face to face or through virtual web-based media, is effective in reducing depression and improving self-care and DM outcomes.[1645–1647,1649,1650] Although chronic use of antidepressant medication has been associated with a modestly increased relative risk of T2D, this may reflect the association of DM with depression rather than an adverse effect of these agents.[1651,1652] Selective serotonin reuptake inhibitors (SSRIs) appear to improve glycemic outcomes independent of their effect on depression or weight.[1653] Treatment of depression with SSRIs among persons with DM has been associated with weight reduction in some reports.[1654,1655] These interventions for depression were most effective when combined with exercise and DM education in several RCTs.[1647,1656,1657]

Question 23: Is the evaluation of SDOH in persons predisposed to or with DM useful in improving health outcomes?

Recommendation 23—Clinicians should assess SDOH in persons with DM to better guide them to the most appropriate resources. Interventional trials addressing SDOH and health inequities in DM are needed to evaluate reversibility of their impact.

Grade B; BEL 1

Evidence Base 23: Is the evaluation of SDOH in persons predisposed to or with DM useful in improving health outcomes?

Considering only biologic variables of DM may result in partial understanding of the etiology of DM outcomes. In addition to assessing biologic variables of a disease, evaluation of SDOH will lead to a greater contextual understanding of the natural history of disease. SDOH are the conditions in which people are born, grow, live, work, and age. These circumstances are shaped by the distribution of money, power, and resources at global, national, and local levels. The SDOH are mostly responsible for health inequitiesdthe unfair and avoidable differences in health status seen within and between countries.[1658] The World Health Organization lists the following examples of SDOH:

1. Income and social protection
2. Level of education
3. Unemployment and job insecurity
4. Working life conditions
5. Food insecurity
6. Housing, basic amenities, and the environment

7. Early childhood development
8. Social inclusion and nondiscrimination
9. Structural conflict
10. Access to affordable health services of decent quality

Socioeconomic factors have been associated with poor lifestyle practices like physical inactivity and smoking.[1659] Research shows that social determinants can be more important than health care or lifestyle choices by themselves in influencing health outcomes. For example, numerous studies suggest that SDOH account for between 30% to 55% of health outcomes.[1660] Those persons with lower socioeconomic status have a higher risk for developing T2D, worse DM control, and more DM-related complications.[1661–1663] For example, lower socioeconomic status has been associated with increased risk of developing DKA in T1D[1664] and diabetic retinopathy in T2D.[1665] In addition, estimates show that the contribution of sectors outside health to population health outcomes exceeds the contribution from the health sector.[1666] A study looking at food insecurity among Latinos with T2D reported decreased sleep quality attributed to anxiety, depression, and DM distress from food insecurity.[1667] Job-related insecurity was associated with diabetic retinopathy in T2D.[1665] The increased prevalence of DM among Native Americans is well known and attention must be paid not only to biologic causes and medical management but also to sociocultural and environmental factors.[1668]

Various interventions with specific strategies targeting the underlying disparities resulting from social factors have been shown to be effective in reducing the burden posed by SDOH.[1669,1670] Recognition of SDOH and engaging community stakeholders and resources may result in lower-cost programs to improve metabolic health. Once disparities and adverse SDOH are apparent, connecting impacted persons with DM to appropriate community resources that address housing, nutrition, and health care access should be helpful. This should result in a public health societal approach in addition to medical-biological approaches.[1669]

There are inadequate equity-related considerations in DM trials limiting the relevance and applicability of their data to disadvantaged populations.[1671] Targeted recruitment and explicit focus on SDOH and health inequities are recommended to close this gap.[1672]

Question 24: Is telehealth/virtual care an effective care-delivery model for the management of persons with DM?

Recommendation 24—Offer telehealth, if available and appropriate, to persons with DM as part of their wholistic health care.

Grade A; BEL 1

Evidence Base 24: Is telehealth/virtual care an effective care-delivery model for the management of persons with DM?

With globally expanding access to virtual platforms, telehealth is becoming a mainstream component of health care delivery. Mobile applications, web-based interventions, virtual

coaching, and other electronic tools have been shown to improve DM self-management.[153] While DM consists of multiple complex factors, each of which could be amenable to different technological approaches, the focus of this discussion is consideration of the outcome of improved glycemic control.

With respect to glycemic control, telehealth appears noninferior (as good or superior) to traditional health care delivery for persons with T1D or T2D, particularly in those who require more interactions, are newly diagnosed, have higher A1C levels, are diagnosed with GDM, or have other comorbid conditions.[1673–1681] Telehealth may reduce the incidence of hypoglycemia.[1682] The virtual care approach appears to be effective across age or racial lines.[1683]

Telehealth also allows for integration of a multidisciplinary team, which could include nurses, pharmacists, dieticians, and other health care professionals, for an individual's health care.[1684–1686]

Telehealth appears to be cost-effective and is likely to be even more economical in the future. Incorporation of automated recommendations regarding dosing of one's insulin or antihyperglycemic medications will further enhance economies of scale.[1687–1691]

Future research is needed to determine the impact of the interplay between an individual's preference of platform and type of health care delivery (telehealth vs hybrid vs traditional models). Beyond improvement in glycemic control, there may be additional benefits of improved adherence, improvement in comorbid conditions, and reduced cost of health care per person.

For information on incorporation of DM technology into one's practice, please refer to the 2021 AACE Advanced Diabetes Technology Guideline.[153]

Question 25: Which occupations have specific public safetyerelated diabetes management considerations?

Recommendation 25—Persons with DM who are engaged in occupations with public safety implications, such as commercial drivers and pilots, have special management requirements for certification. CGM to predict hypoglycemia in real time and pharmacotherapy that minimizes hypoglycemia are recommended as effective strategies for persons with DM who work in these occupations.

Grade A; BEL 1 and expert opinion of task force

Evidence Base 25: Which occupations have specific public safetyerelated diabetes management considerations?

It is important to note that existing evidence for the association of commercial vehicle accidents and DM does not consider recent advances in nonhypoglycemic therapies and in glucose monitoring technology, both of which have potential to reduce the risk of hypoglycemia-related accidents. More studies are needed on the impact of these advances on vehicular safety. Nevertheless, the licensing and certification of two occupations in

particular, commercial vehicle drivers and airline pilots, have become more favorable in recent years. In 2018, the Department of Transportation Federal Motor Carrier Safety Administration (FMCSA) reversed the previous blanket exclusion against insulin use with a new rule for interstate commercial drivers with DM. This new rule was the first update on DM since 1970 and allows medical certification by obtaining an assessment from a treating clinician that the applicant has "properly controlled insulin-treated diabetes" and is on a "stable insulin regimen." The treating clinician determines whether a particular individual meets these criteria, which do not include a threshold A1C value. Proliferative diabetic retinopathy is a permanently disqualifying complication; treating clinicians can assess other complications on an individual basis to determine if they impair one's ability to operate a commercial vehicle driver safely. A medical examiner then determines if the individual meets the FMCSA's physical qualification standards. These individuals must also consult their state licensing agencies for their laws to reflect this new federal rule.[1692,1693]

Similarly, in 2019, the Federal Aviation Administration outlined considerations for insulin-treated T1D or T2D with a CGM option. This policy permits special issuance of medical certification to some applicants who provide medical documentation of their history of treatment, accidents, and current medical status by an endocrinologist. For first- and second-class airman certification, CGM data is a requirement, whereas third-class airmen may use non-CGM protocol.[1694]

Risk of Accidents and Potential Treatment-Associated Hypoglycemia—An area of great concern has been whether DM might lead operators of commercial vehicles (eg, bus, truck, taxi, ferry, or airplane) to lose control and have an accident, putting themselves or others at risk of injury. Eye disease associated with DM, including various forms of retinopathy and cataracts, is of course a potential cause of impaired driving ability. There is general consensus that ascertainment of the visual acuity of commercial motor vehicle drivers or airline pilots is a reasonable measure for such risk. Similarly, coronary artery disease, CVD, musculoskeletal conditions, and diabetic neuropathy might in various ways impair safe driving or piloting ability.

Hypoglycemia may impair judgment and motor ability, which could increase the likelihood of an accident during operation of a motor vehicle or airplane. The Federal Motor Carrier Safety Administration Evidence Report on Diabetes and Commercial Motor Vehicle Driver Safety addresses some key aspects of these hypoglycemia-related issues.[1695] Taken as a whole, individuals with DM do not have a significantly increased risk of motor vehicle accidents compared with drivers without DM. However, a separate analysis of studies conducted within the United States showed a 25% increase in risk of accidents, whereas studies conducted outside the United States showed no increased risk. This was particularly true when non-US and US cohorts of insulin-treated persons were compared. An analysis of 2 available US studies showed a 2.75-fold greater risk of motor vehicle accidents when insulin-treated persons were compared with individuals without DM ($P = .001$), while studies from outside the United States demonstrated no significant difference in accident risk.[1695]

A meta-analysis restricted to US studies of persons with DM not using pharmacologic treatment or using oral antihyperglycemic agents did not show a significant increase in risk of accidents. Among individual studies included in the analysis, use of SU did not significantly increase the risk of accidents.[1696–1698] However, SU treatment is associated with a greater likelihood of hypoglycemia than all other noninsulin antihyperglycemic agents (metformin, TZDs, alpha-glucosidase inhibitors, DPP-4 inhibitors, and GLP-1 RAs) and carries a nearly a 2-fold greater likelihood of hypoglycemia than basal insulin.[1699] Studies of insulin users involved mostly persons with T1D, but the use of a basal insulin analog as the sole administered insulin for T2D is associated with considerably lower hypoglycemia rates than older insulin preparations or the use of basal-bolus treatment.[1065]

With respect to pilots with DM, recent experience in Europe reported no episodes of pilot incapacitation nor worsening of glycemic control with insulin-treated DM.[1700]

Unfortunately, reliable large population studies of motor vehicle accidents involving persons with T2D treated with current approaches are not available (studies of oral antihyperglycemic agents included in the meta-analysis examined data from the late 1980s to early 1990s). Although in a post hoc analysis, one study demonstrated the potential role of CGM in predicting hypoglycemia more consistently than intermittent BGM.[1701] Advances in vehicle technology combined with reliable rtCGM should result in safer driving or flying.[1702]

Although, the diagnosis of DM has not been shown to be directly associated with increased collision risk, persons with older age and on insulin therapy tend to have a higher risk.[1703] A validated patient questionnaire may be a useful tool for clinicians to predict and reduce driving mishaps among persons with DM.[1704] Treatment efforts should focus on agents with reduced likelihood of causing hypoglycemia.

Although commercial drivers and pilots with DM are highly scrutinized, those with shift work or extended periods of work should also have customized regimens of therapeutic dosing and scheduling, nutrition variability, and glycemic monitoring. The goal is to support an individual’s productivity and safety.

Question 26: Is there a role for nutritional supplements in the management of DM and what might be the associated risks?

Recommendation 26—Nutritional supplements (ie, noncaloric oral supplements) have modest or neutral effects on glycemic control, lipids, and BP. Until proven scientifically, these supplements should not be used for managing DM or related CV risk factors among persons with DM. In view of potential harm, we recommend that persons with DM use caution and discuss with their physicians the use of unregulated nutritional supplements.

Grade A; BEL 1

Evidence Base 26: Is there a role for nutritional supplements in the management of DM and what might be the associated risks?

Nutritional supplements are a heterogenous group of substances marketed without prescription with varying effects on glycemic control and CV risk factors such as hypertension and dyslipidemia in persons with DM. They include vitamins, minerals, herbs or botanical products, and probiotics. These supplements generally are not regulated by governmental approval agencies and have inconsistent composition and quality.

Probiotics are among the most studied nutritional supplements. Several RCTs and systematic reviews/meta-analyses have noted a positive effect of probiotics on glucose, A1C, lipids, and BP.[1705–1714] The main limitation of these studies is the wide variation in methodologies including differences in the type, formulation, concentration, and duration of exposure to probiotics.

A meta-analysis reported that psyllium when taken before meals led to significant improvement in fastin BG (−37.0 mg/dL; $P < .001$) and A1C (−0.97%; $P = .048$) among persons with T2D.[1715] Zinc supplementation at 20 mg daily in persons with prediabetes in an RCT resulted in a reduction in BG, decreased insulin resistance, improved β-cell function, and reduced progression to DM compared with controls.[1716]

Other nutritional supplements, specifically resveratrol, selenium, and vitamin D, have mixed effects on glycemic control and other CV risk factors.[1705,1717–1724] Some reports suggest potential harm with the use of these agents. One systematic review found potential increase in risk for developing DM with selenium supplementation, but an RCT found no harm to b cells or insulin sensitivity.[1720,1721]

Question 27: How should potential increased cancer risk be managed in persons with obesity/T2D?

Recommendation 27.1—Clinicians should recommend age, sex, and risk-appropriate screening for common cancers, especially those associated with obesity and DM.

Grade B; BEL 2

Recommendation 27.2—With the increased risk of certain cancers in persons with obesity or DM, clinicians should educate persons regarding cancer risk and encourage a healthy lifestyle, including weight reduction.

Grade A; BEL 1

Evidence Base 27: How should potentially increased cancer risk be managed in persons with obesity/T2D?

Epidemiologic evidence suggests increased risks of cancer and cancer mortality in persons with obesity and/or DM.[1725–1730] There also may be an additive interaction of overweight or obesity with DM, further increasing cancer risk and mortality.[1731,1732]

Persons who are overweight (>25 kg/m^2) or obese (>30 kg/m^2) may have an increased risk of a variety of cancers, although risk may be modified by age, sex, race, menopausal status, duration of obesity, anthropomorphic distribution of adiposity, and the presence of additional metabolic syndrome components.[1730,1732–1738] Variably increased risk has been reported for cancers of the breast (postmenopausal) endometrium ovary gall bladder, stomach and esophagus, kidney, thyroid (papillary, follicular, and anaplastic but not medullary), colon, bladder, and pancreas.[1733,1734,1739–1752] There also is increased risk of hematologic malignancies with leukemia (acute myeloid leukemia), malignant and multiple myeloma, and non-Hodgkin and Hodgkin lymphoma.[1753,1754] Increased BMI may, however, be protective for lung cancer (in never smokers),[1755] although a large meta-analysis found increased lung cancer risk among current smokers, past smokers, and never smokers with increased abdominal obesity measured by WC.[1756] An inverse relationship between BMI and prostate cancer has been reported,[1757] but this may be dependent on racial background with increased risk in African American men.[1735] There is evidence of an association of obesity and high-grade aggressive prostate cancers.[1758] In premenopausal women, increased BMI may be protective overall for breast cancer[1759] but not with hormone receptor negative breast cancer.[1760] Although the pathophysiologic mechanisms that drive an increase in cancer risk with obesity have not been clearly elucidated, higher BMI is associated with increased systemic levels of endogenous insulin, insulin-like growth factors, adipokines, inflammatory cytokines, and angiogenic factors that have potential procancerous effects. The local interaction of adipose tissue and tumor cell microenvironments may also be important in the promotion of cancer.[1761,1762]

DM also is reported to be associated with the risk of specific cancers, although it is challenging to isolate DM-associated risk from that of comorbid obesity.[1732] Most of the available evidence is generated from T2D cohorts, possibly because it is the most prevalent DM, although increased risk of certain cancers also has been reported for persons with T1D.[1763] There also may be cancer detection bias with increased screening after diagnosis of DM,[1732] although there also is evidence that persons with DM may be underscreened for certain cancers compared to those without DM.[1764] T2D has been shown to be associated with increased risk for hepatic,[1765] bladder,[1766] pancreatic,[1767,1768] and colorectal cancers.[1769] For womenwith DM, increased risk has been reported for endometrial[1770] and breast cancer.[1771] Sex differences also are reported with women at higher risk than men for oral, gastric, colorectal, and kidney cancers as well as leukemia, but with decreased risk for liver cancer.[1772,1773] Bladder cancer risk may be higher in men.[1766] There is an inverse association between the risk of prostate cancer and DM,[1774] although the use of antihyperglycemic agents may have diminished the apparent DM-associated risk in epidemiologic studies.[1775] Importantly, elevated BG and DM are associated with increased prostate cancer mortality.[1775–1777] In addition to the obesity-related mechanisms for cancer risk that are discussed above, hyperinsulinemia and hyperglycemia may promote a microenvironment amenable to cancer cell proliferation with activation of mitogenic signaling.[1778]

With the understanding of the increased cancer risk, up-to-date age- and sex-appropriate cancer screening is imperative in persons with obesity and/or DM but is not always met.[1764] Education regarding cancer risk for persons with overweight/obesity and/or DM also may

encourage adherence to lifestyle modifications and weight loss,[1779] but a major knowledge gap is how such interventions impact risk of cancer in the long term. There are data to support a modest reduction of obesity-related cancers with weight loss (HR, 0.84; 95% CI, 0.68–1.04) in persons with DM but without a significant impact on total cancer incidence or mortality.[1780]

Pharmacologic Therapies for DM and Cancer Risk or Prognosis—To date, no definitive relationship has been established between specific antihyperglycemic agents and an increased risk of cancer or cancer-related mortality. The evidence for the effects of specific antihyperglycemic agents on cancer risk is confounded by factors such as obesity, hyperinsulinemia, glycemic control, and combination pharmacotherapy in DM.

Metformin—Metformin mayeither be neutral or modestly protective regarding cancer incidence and mortality; however, most of the available evidence was gathered from observational studies with varied designs and risk for bias.[1781–1783] A decreased risk of colorectal adenomas and colorectal carcinoma is a consistent finding with a potential for a survival benefit for colorectal carcinoma.[1784–1790] Modest survival benefits also have been reported for breast, ovarian, endometrial, prostate, lung, kidney, liver, and earlier stage pancreatic cancers.[1791–1800] There is no reported effect of metformin on the incidence or overall survival for bladder cancer.[1801] The effect of metformin on cancer outcomes (prostate, breast, lung, colorectal, pancreas) is currently being explored in multiple prospective trials, including with metformin as an adjuvant to chemotherapy. Although definitive statements regarding the benefits of metformin and cancer cannot be made, the above findings could inform the decision to initiate metformin as a treatment in persons with DM and specific cancers.

Thiazolidinediones—Large population-based cohort studies have found that pioglitazone is associated with a modestly increased risk of bladder cancer when compared with other oral DM therapies including the TZD rosiglitazone as the comparator.[1802,1803] However, evidence from a large study of over 1 million persons from several international cohorts did not find an association with cumulative exposure to pioglitazone and bladder cancer[1002] and 10 years of observation of participants fromthe PROACTIVE did not find increased risk of bladder cancer (0.8% pioglitazone vs 1.2% placebo).[1804] TZD therapy in general is not associated with other cancers and a modest reduction in overall cancer risk has been reported for pioglitazone.[1781]

Incretin Therapies—A concern about increased risk of pancreatic cancer with incretin therapies wasraised bya studyofhumanpancreata from persons with DM on incretin therapy compared to controls, which reported exocrine dysplasia and alpha-cell hyperplasia.[1805] However, a thorough review of available data conducted by the FDA and the European Medicines Agency did not uncover evidence to support a causal association.[1806] Retrospective and meta-analysis of data from large placebo-controlled clinical trials with GLP-1 RAs and DPP-4 inhibitors have not found an increased risk of pancreatic cancer.[1034,1807,1808]

An increase in thyroid C-cell hyperplasia, adenomas, and medullary thyroid carcinomas was observed in preclinical rodent studies of liraglutide, while exenatide has been shown to cause nodular C-cell lesions without medullary thyroid carcinoma, [1809,1810] leading to concerns regarding the potential for development of medullary thyroid carcinoma in persons with DM on GLP-1 RAs. From placebo-controlled clinical trial data, there is no evidence of increased calcitonin or C-cell neoplasia in humans,[1811] and meta-analyses have not uncovered increased risk for thyroid cancer with GLP-1 RAs or DPP-4 inhibitors.[1808,1812,1813] Human calcitonin-producing C-cells do not express GLP-1 RAs as do rodent C-cells. Overall, there is no evidence that incretin-based therapies increase risk for medullary thyroid carcinoma in humans.[1808,1812,1813] Nonetheless, GLP-1 RAs should not be used in individuals with a personal or family history of medullary thyroid carcinoma or in persons with multiple endocrine neoplasia syndrome type 2.

SGLT2 Inhibitors—Among the SGLT2is, more cases of bladder cancer occurred among dapagliflozin-treated than control-treated persons in clinical trials, and the product labeling indicates that this agent should not be used inpersons with active bladder cancer and should be used with caution in persons with a history of bladder cancer.[1814] Warnings regarding bladder cancer are not included in the canagliflozin or empagliflozin prescribing information.[1815,1816] There was no increased bladder cancer risk in a large meta-analysis of multiple SGLT2is,[1817] although a separate meta-analysis suggested that there could be some increased risk, but a causal relationship was inconclusive.[1818] Overall risk for all cancers is not increased with SGLT2is.[1817,1818]

Sulfonylureas—There is no evidence for increased cancer risk for SUs compared to controls in RCTs, although cancer risk may be higher compared to a metformin comparator in cohort studies.[1819]

Insulin—Contrary to preliminary cohort-level evidence suggesting that exogenous insulin may be associated with an increased cancer risk,[1820] particularly glargine, the large-scale ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial did not substantiate this risk.[1821] In ORIGIN, >6000 participants received insulin glargine over a median trial duration of 6 years with no associated increased risk of any cancer (HR, 1.0; 95% CI, 0.88–1.13) or cancer death (HR, 0.94; 95% CI, 0.77–1.15), including breast, lung, colon, and prostate cancers.[1821] A meta-analysis of data from 10 cohort studies examined insulin use and overall cancer risk found an increased risk of 28% for persons with DM using insulin compared with non-users.[1822] Given that endogenous hyperinsulinemia is one of the proposed factors for the link between cancer and obesity and DM, an improved understanding of the impact of insulin therapy on cancer risk and progression is imperative.

Question 28: Which vaccinations should be given to persons with DM?

Recommendation 28.1—AACE supports the recommendations of the CDC Advisory Committee on Immunization Practices (ACIP) that all persons with DM receive age-appropriate vaccinations according to the CDC/ACIP schedule.[1823] Immunization recommendations for adults with DM are summarized in Table 21.

Grade A; BEL 4 and expert opinion of task force

Recommendation 28.2—An annual influenza vaccine is recommended for those with DM who are ≥6 months old.

Grade A; BEL 1

Recommendation 28.3—The 15- or 20-valent pneumococcal conjugate vaccine (PCV15 or PCV20) should be administered to all adults aged 19 to 64 years who have DM. When PCV15 is used, PPSV23 should be administered at least 12 months following the dose of PCV15. A minimum interval of 8 weeks may beused for adults withimmunocompromising conditions.

Grade B; BEL 3

Recommendation 28.4—For adults over 65 who have not previously received PCV or whose vaccination history is unknown, PCV15 or PCV20 should be administered. When PCV15 is used, it should be followed by a dose of PPSV23.

Grade B; BEL 3

Recommendation 28.5—It is recommended to administer hepatitis B vaccinations to all individuals as soon after diagnosis of DM as possible up to age 59 years.

Grade A; BEL 1

Recommendation 28.6—Consider hepatitis B vaccination of adults ≥60 years based on assessment of risk and likelihood of an adequate immune response.

Grade C; BEL 4

Recommendation 28.7—Tetanus-diphtheria-pertussis (Tdap) vaccine is typically included with routine childhood vaccinations. However, all adults with DM should receive a tetanus-diphtheria (Td) booster every 10 years.

Grade C; BEL 4

Recommendation 28.8—Health care professionals may consider recommending vaccines for the following diseases for persons with T2D based on individual needs: Tdap - tetanus, diphtheria, and pertussis (whooping cough); measles/mumps/rubella; varicella (chicken pox); and polio. In addition, persons traveling to other countries may require vaccines for endemic diseases.

Grade D; BEL 4, expert opinion of task force

Recommendation 28.9—Due to the increased risk for serious complications of COVID-19, persons with DM should be vaccinated against COVID-19 according to current guidelines.

Grade B; BEL 2

Recommendation 28.10—Recombinant zoster vaccine (RZV) is recommended for adults aged ≥50 years for protection against shingles according to the CDC/ACIP vaccination schedule.

Grade A; BEL 1

Recommendation 28.11—Health care professionals should utilize interventions with demonstrated effectiveness in increasing vaccination rates to improve uptake of vaccination among persons with DM.

Grade B; BEL 2

Evidence Base 28: Which vaccinations should be given to persons with DM?

Bacterial and viral infections cause significant morbidity and mortality in persons with DM.[1824] A cohort study of adults <65 years of age with DM showed that DM increased the risk of influenza-associated hospitalizations by 6% (risk ratio, 1.06; 95% CI, 1.02–1.10; absolute risk difference 6 per 1000 adults per year), even though the rates of influenza and pneumonia were similar between diabetic and nondiabetic populations ($P = .11$).[1825] Both community-acquired and nosocomial infections with pneumococcal bacteria may also be higher among persons with DM, who may also be at greater risk of death from these diseases.[1826-1828] However, vaccines can safely and effectively reduce serious complications from influenza. A systematic review found reduction in all-cause mortality ranging between 33% and 68% among persons older than 65 years with DM and with seasonal influenza vaccination.[1829] Other systematic reviews have demonstrated effective immunogenicity of influenza vaccine with decreased risk for hospitalization and mortality among persons with DM (especially those aged >65 years) compared with healthy individuals.[1830,1831] An RCT evaluating the safety of the inactivated influenza vaccine in persons with DM compared with controls found that the vaccine was tolerated with mild-to-moderate adverse effects and with similar immune response among persons with DM compared to those without DM.[1832] CDC/ACIP recommends a yearly influenza vaccine for all individuals with DM, although live attenuated influenza vaccine should be used with caution because its safety in persons with DM has not been established.[1823] Inactivated influenza vaccine may be considered for persons with DM.[1833] The CDC also provides references and resources related to influenza.[1834]

The CDC/ACIP also recommends a single dose of PCV15 or PCV20 for adults with DM who have not previously received PCV or whose previous vaccination history is unknown). When PCV15 is used, it should be followed by a dose of PPSV23.[1835] The updated CDC recommendations are based on several trials demonstrating safety and immunogenicity of the new conjugate vaccines, PCV15 and PCV20, which were comparable to PCV13. No studies of clinical efficacy studies were included.

Hepatitis B vaccination is recommended for all persons with DM aged 59 years or younger and should be considered for persons 60 years or older with shared clinical decision-making

based on risk assessment and likelihood of an adequate immune response. A prospective, multicenter RCT found that seroprotection following hepatitis B vaccination was lower among persons with DM compared with non-DM individuals and tended to wane with older age.[1836] A 2-dose hepatitis B vaccine, HBsAg-1018, had greater seroprotection rates (90%) among persons with DM compared with the 3-dose hepatitis B vaccine (65.1%) 28 weeks after vaccination.[1837] A similar finding was reported by another RCT involving persons with DM and CKD.[1838]

Individuals with DM, when infected with COVID-19, are more likely to be hospitalized, need higher levels of care, and have higher mortality.[1839,1840] COVID-19 vaccination has demonstrated efficacy in reducing these adverse outcomes. Hence, individuals with DM should be vaccinated once eligible according to current recommendations.[1841,1842]

The CDC recommends the tetanus, diphtheria, and acellular pertussis (Tdap) vaccine as part of the child/adolescent immunization schedule and for adults every 10 years due to waning immunity.[1843] Persons with DM may be more susceptible to respiratory infections and tetanus. A meta-analysis of observational studies found an increased risk of respiratory infections in persons with DM (odds ratio, 1.35; 95% CI, 1.28–1.43).[1844] Although tetanus infections overall are rare, a surveillance study reported an increased risk of mortality in persons over age 65 (relative risk, 5.1; 95% CI, 2.1–12.2) and in persons with DM (relative risk, 2.4; 95% CI, 1.2–4.8).[1845] Tdap is also recommended for tetanus prophylaxis in wound management, which could be important for persons with DM who have foot ulcers.[1846]

The recombinant zoster vaccine (RZV) is recommended for adults 50 years of age and older according to the CDC/ACIP schedule.[1823] A large meta-analysis found that older adults who received RZV had a lower incidence of herpes zoster (relative risk, 0.08, 95% CI, 0.03–0.23) after over 3 years of follow-up compared with placebo. Following vaccination, a 2019 meta-analysis found that persons who received RZV had a mild-to-moderate systemic or injection site reaction, but no serious adverse effects or death compared with placebo.[1847] An RCT reported a 100% vaccine response rate following RZV injection given either via subcutaneous or intramuscular route.[1848] Coadministration of RZV with PPSV23 in adults aged ≥50 years in a 2018 RCT resulted in no immunologic interference or safety concerns between the 2 vaccines.[1849] The live attenuated zoster vaccine, which was found to be safe and effective in reducing herpes zoster among adults ≥50 years,[1847,1850] is no longer available for use in the United States.

Interventions with demonstrated effectiveness to increase vaccination rates include strategies that involve convenience of vaccinations, better communication with persons, enhanced vaccination systems with motivation by designated vaccination champions and the coadministration of compatible vaccines while avoiding vaccine coadministration that may decrease immune response to individual vaccines.[1851-1855] These strategies should be utilized to improve vaccination rates in the DM population. The CDC Standards for Immunization Practice support clinicians in addressing low vaccination rates (https://www.cdc.gov/vaccines/hcp/adults/for-practice/standards/index.html). The practice standards include the following key points:

- Assess immunization status of all persons with DM at every encounter.

  - Stay up to date on the latest recommendations from the CDC (https://www.cdc.gov/vaccines/schedules/index.html). Vaccination recommendations change frequently, so clinicians should always find the most recent recommendations before advising their patients.
  - Implement policies or workflow changes to facilitate review of immunizations by care team staff and to provide patient reminders.

- Strongly recommend any vaccines a person may need (see Table 21 for vaccine recommendations for adults with DM).
  - Provide a nonjudgmental environment to address any questions or concerns.
  - A strong recommendation from a clinician is the best predictor for a person choosing to get immunized.
- Administer vaccines, if stocked in practice, or refer persons with DM to local vaccine providers, which may include primary care clinicians, pharmacies, or public health offices.
- Document administered or received vaccines in the electronic health record and the state immunization registry.

Future Directions

DM is a paradoxical condition in which most clinicians are familiar with its prevalence and impact on health, but many are not fully knowledgeable about all the nuances of optimal management. Simultaneously, the advance of big data, outcome studies, and therapeutic and monitoring capabilities have shifted the paradigm of DM management.

Reflecting the evolving natural history of T2D in the United States, screening for DM should start at 35 years of age. Although the glycemic criteria for the official diagnosis of DM have not changed, it has been increasingly apparent that those with prediabetes need to have their CVD risk factors managed as aggressively as those with DM. The impact of health disparities and adverse SDOH in both developed and developing nations have been shown to affect the QoL as well as metabolic control in those with DM. However, there is need for interventional studies in these areas to demonstrate improvement in DM outcomes. Access to proper nutrition and effective medicines will continue to be a difficult challenge.

For those with prediabetes/DM and obesity, it is paramount that achieving and maintaining effective weight loss is the key to improving glycemic control as well as management of CVD risk, neuropathy, OSA, and other complications of DM. Lifestyle optimization remain the cornerstone treatment for those with DM. The arrival of new peptide therapies may approach weight loss observed with bariatric procedures should revolutionize obesity management. Avoidance of weight gain or weight loss have become key differentiators of therapeutic choices.

We have primarily classified DM into 2 types based on insulin deficiency vs insulin resistance and the presence of autoimmune destruction of the endocrine pancreas. As DM

management moves to personalized approaches in the era of precision medicine, there have been early efforts to subcategorize T2D based on phenotype and metabolic characteristics. Pharmacogenomic strategies related to prediction of drug efficacy and/or safety will be incorporated into clinical practice. Some of the subtypes of DM include monogenic forms, and genetic screening will likely become more cost-effective to inform clinicians about the most appropriate treatments and genetic counseling. Secondary forms of DM, such as posttransplant diabetes and CFRD should be screened in order to begin earlier and timely pathophysiologic-focused treatment.

Adverse outcomes that can occur in the inpatient setting or during pregnancy need to be further studied with the use of CGM technology. CGM and its metrics provide a deeper description of glycemia that should further complement the use of A1C and lead to improved clinical insights into both hyperglycemia and hypoglycemia. The safety net provided by CGM cannot be discounted, for CGM studies may provide more information about the frequency and impact of level one hypoglycemia. Select workers such as commercial drivers and pilots have been highly regulated with respect to concurrent DM. Recently, these regulations have been updated allowing persons with DM to preserve their occupation. There will be more progress toward developing an “artificial pancreas” with closed-loop insulin delivery and/or faster-acting prandial and longer-lasting basal insulins and/or delivery systems providing both insulin and glucagon as well as the potential for smart insulins and insulin delivery into the portal system.

The default aggressive management of hypertension and dyslipidemia in those with DM is universally accepted. For those with established ASCVD, options such as PCSK9 targeted therapies allow even greater reduction in LDL-C levels. The pathogenic involvement of apo B-100 in atherosclerosis is well understood; more CVOTs examining apo B-100 as a metabolic target may inform revisions of future recommendations.

The SGLT2i and the GLP-1 RA classes have CV benefit independent of glucose-lowering mechanisms. There likely will be greater utilization of these agents in persons without DM by our primary care and cardiology colleagues as well as endocrinologists.

DKD, retinopathy, and neuropathy remain prominent microvascular complications. Use of retinal photographs evaluated by artificial intelligence programs promise increased and potentially more accurate retinopathy screening. In addition, newer therapies, such as anti-VEGF intravitreal injections with or without concomitant laser therapy have revolutionized the management of macular edema and vision-threatening retinopathy while reducing adverse effects of treatment. Diabetic neuropathy, including peripheral sensorimotor loss, autonomic dysfunction, and cardiac autonomic neuropathy are not uncommon in persons with DM; earlier recognition and new, more efficacious therapies are needed.

This task force has incorporated the latest landmark CVOTs and other RCTs examining the effect of antihyperglycemic agents on CVD, HF, and CKD outcomes and has made strong recommendations for appropriate use of SGLT-2is and GLP-1 RAs in ASCVD, HF, and cerebrovascular disease. These recommendations along with development of new therapies

and further ASCVD, HF, and CKD outcome studies are likely to enhance the ability to care for those with these disorders, including some without DM.

Glycemic management will be more oriented to use of agents that do not cause hypoglycemia, that promote weight loss and those that reduce risk of cardio-renal disease. Both long-acting and rapid-acting insulin analogs have expanded options for persons who require insulin. CGM and insulin pumps with or without AID allow persons to achieve glycemic goals more safely.

Avoidance of hypoglycemia is key to achieving euglycemia safely, which is possible with newer antihyperglycemic therapies and the use of CGM. Additionally, treatment of severe hypoglycemia will be greatly improved with the advent of newer formulations of and delivery methods for glucagon and glucagon analogs. More work is needed to discover methods to restore hypoglycemic awareness.

To paraphrase Dr. Eliot Joslin, “The person with diabetes who knows the most, lives the longest.” In the 21st century, multidisciplinary education can be personalized with respect to age group, type of diabetes, language, and location. The task force reviewed hundreds of articles uncovering many innovative approaches to delivery of diabetes education. There is no single platform or approach that will benefit every individual. The key will be to find the right approach for the right patient.

Mental health is often suboptimally managed in those with DM, often due to time and resource constraints. There is need for more professional mental health expertise to address this burgeoning need. Sleep apnea ishighly prevalent buta neglectedcomorbidity inpersons with T2D; early diagnosis and future advances in management may contribute to improved DM control. Since persons with DM are more susceptible to more severe infections, validated proven vaccinations, as recommended by public health agencies, should be more consistently administered to those who would benefit from them.

We address virtual telemedicine, virtual/digital medicine, which has risen to prominence during the COVID-19 pandemic. Early evidence suggests that virtual care can be a satisfying experience for the clinician and the patient and lead to comparable outcomes. In the near future, telemedicine will become seamlessly integrated into traditional care programs, improving access to care. Patient-generated data will be incorporated into one’s medical record allowing more informed medical decisions. Artificial intelligence and machine-learning applications will lead to unexpected clinical insights.

Conclusions

A number of newer antihyperglycemic therapies have enhanced safety with reduced or very low risk for hypoglycemia, and at least two classes, SGLT2is and GLP-1 RAs, have been found to reduce the risk of CVD, HF, and/or CKD, independent of glycemic control. Medical management of obesity continues to advance with significant improvements in weight loss. Insulin formulations are available to address more individual lifestyles and medical profiles. Insulin delivery platforms and CGM technologies are improving rapidly and converging toward a closed-loop system.

Future improvements in the organization of health care delivery are critical for overall management of DM and will require coordination and cooperation from a multidisciplinary team that is patient centered and uses shared decision-making.

Despite the optimism from recent developments, access remains a significant challenge and will require, in future, greater cooperation of public and private sectors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the CPG Oversight Committee for their thoughtful reviews and insightful comments on this guideline update. We also thank Stephanie Adams, PhD, for assistance in assigning evidence levels, study types, and references; Melanie Bird, PhD, MSAM, for assistance with evidence review, document review, and references; Kendall Alexander, MPH, for assistance with document review; and Amy Ogunsulade, BS, for assistance with references.

Funding

This CPG on developing a comprehensive plan for the care of persons with diabetes mellitus was developed with financial support from the American Association of Clinical Endocrinology (AACE). All members who served on this AACE task force completed work on the manuscript electronically and met via video conferences. AACE received no outside funding for the development of this guideline. Volunteer authors on this task force received no remuneration for their participation in development of this guideline.

Abbreviations

AACE	American Association of Clinical Endocrinology
ABCD	adiposity-based chronic disease
ABPM	ambulatory BP monitoring
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin-converting enzyme
ACIP	CDC Advisory Committee on Immunization Practices
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AHA	American Heart Association
AHEI	Alternative Healthy Eating Index
aHR	adjusted hazard ratio
AID	automated insulin delivery
AKI	acute kidney injury

apo B	apolipoprotein B
ARB	angiotensin II receptor blocker
ASCVD	atherosclerotic cardiovascular disease
A1C	hemoglobin A1c
BG	blood glucose
BGM	blood glucose monitoring
BMI	body mass index
BP	blood pressure
CAN	cardiovascular autonomic neuropathy
CDC	Centers for Disease Control and Prevention
CDCES	certified diabetes care and education specialist
CFRD	cystic fibrosiserelated diabetes
CGM	continuous glucose monitoring
CHF	congestive heart failure
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology
CMD	cardiometabolic disease
CPAP	continuous positive airway pressure
CPG	clinical practice guideline
CRP	C-reactive protein
CSII	continuous subcutaneous insulin infusion
CV	cardiovascular
CVA	cerebrovascular accident
CVD	cardiovascular disease
CVOT	cardiovascular outcome trial
DASH	Dietary Approaches to Stop Hypertension
DKA	diabetic ketoacidosis
DKD	diabetic kidney disease
DM	diabetes mellitus

DPN	diabetic peripheral neuropathy
DPP-4	dipeptidyl peptidase 4
DSMES	diabetes self-management education and support
eGFR	estimated glomerular filtration rate
EL	evidence level
FDA	Food and Drug Administration
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
FPG	fasting plasma glucose
GDM	gestational diabetes mellitus
GFR	glomerular filtration rate
GI	gastrointestinal
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HAPO	Hyperglycemia and Pregnancy Outcomes
HCL	hybrid closed-loop
HDL-C	high-density lipoprotein cholesterol
HEI	Healthy Eating Index
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
HRV	heart rate variability
IC	insulin to carbohydrate
ICU	intensive care unit
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
isCGM	intermittently scanned CGM
ISF	insulin sensitivity factor
IV	intravenous
KDIGO	Kidney Disease: Improving Global Outcomes

LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular event
MDI	multiple daily injections
MI	myocardial infarction
MNT	medical nutrition therapy
MODY	maturity-onset diabetes of the young
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NPH	Neutral Protamine Hagedorn
OGTT	oral glucose tolerance test
OR	odds ratio
OSA	obstructive sleep apnea
PCSK9	proprotein convertase subtilisin/kexin type 9
PCV	pneumococcal conjugate vaccine
PG	plasma glucose
POC	point-of-care
PPG	postprandial glucose
PTDM	posttransplant diabetes
PTH	parathyroid hormone
QoL	quality of life
RAAS	renin-angiotensin-aldosterone system
RCT	randomized controlled trial
RDN	registered dietitian nutritionist
rtCGM	real-time CGM
RZV	recombinant zoster vaccine
SAP	sensor-augmented pump
SDOH	social determinants of health
SGLT2i	sodiumglucose cotransporter 2 inhibitor
SU	sulfonylurea

T1D	type 1 diabetes
T2D	type 2 diabetes
Tdap	tetanus-diphtheria-pertussis
TDD	total daily dose
TIR	time in range
TZD	thiazolidinedione
UACR	urine albumin-to-creatinine ratio
UKPDS	UK Prospective Diabetes Study
US	United States
VEGF	vascular endothelial growth factor
VLDL	very low-density lipoprotein
WC	waist circumference

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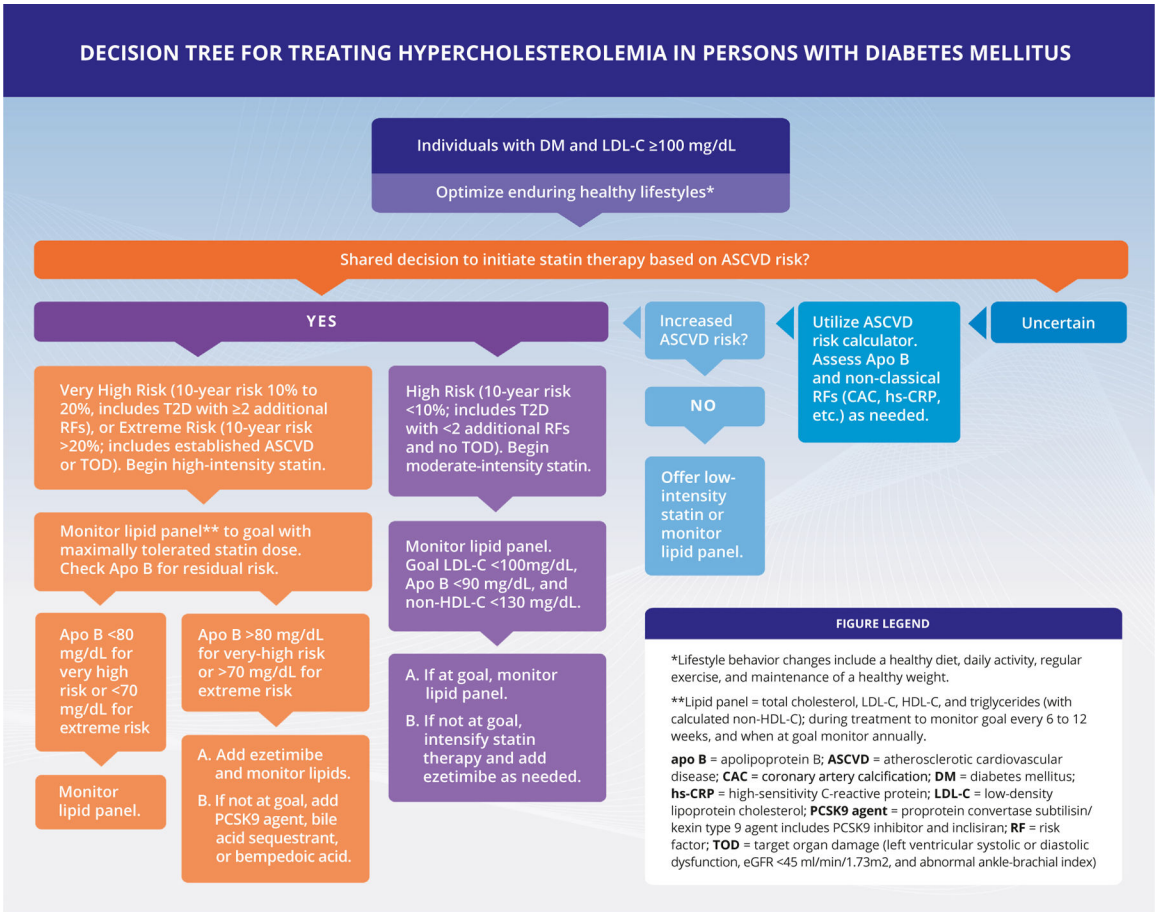


Figure 1.

Decision Tree for Treating Hypercholesterolemia in Persons with Diabetes Mellitus.

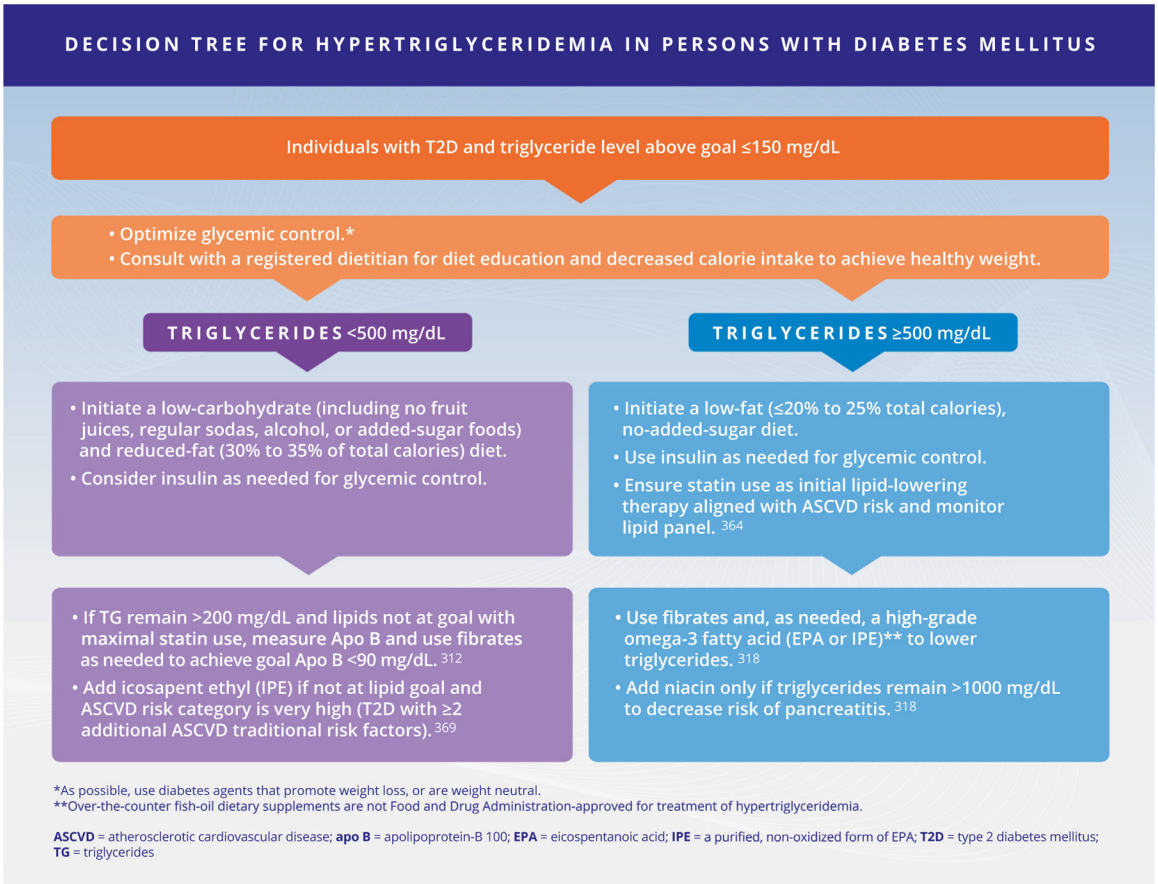
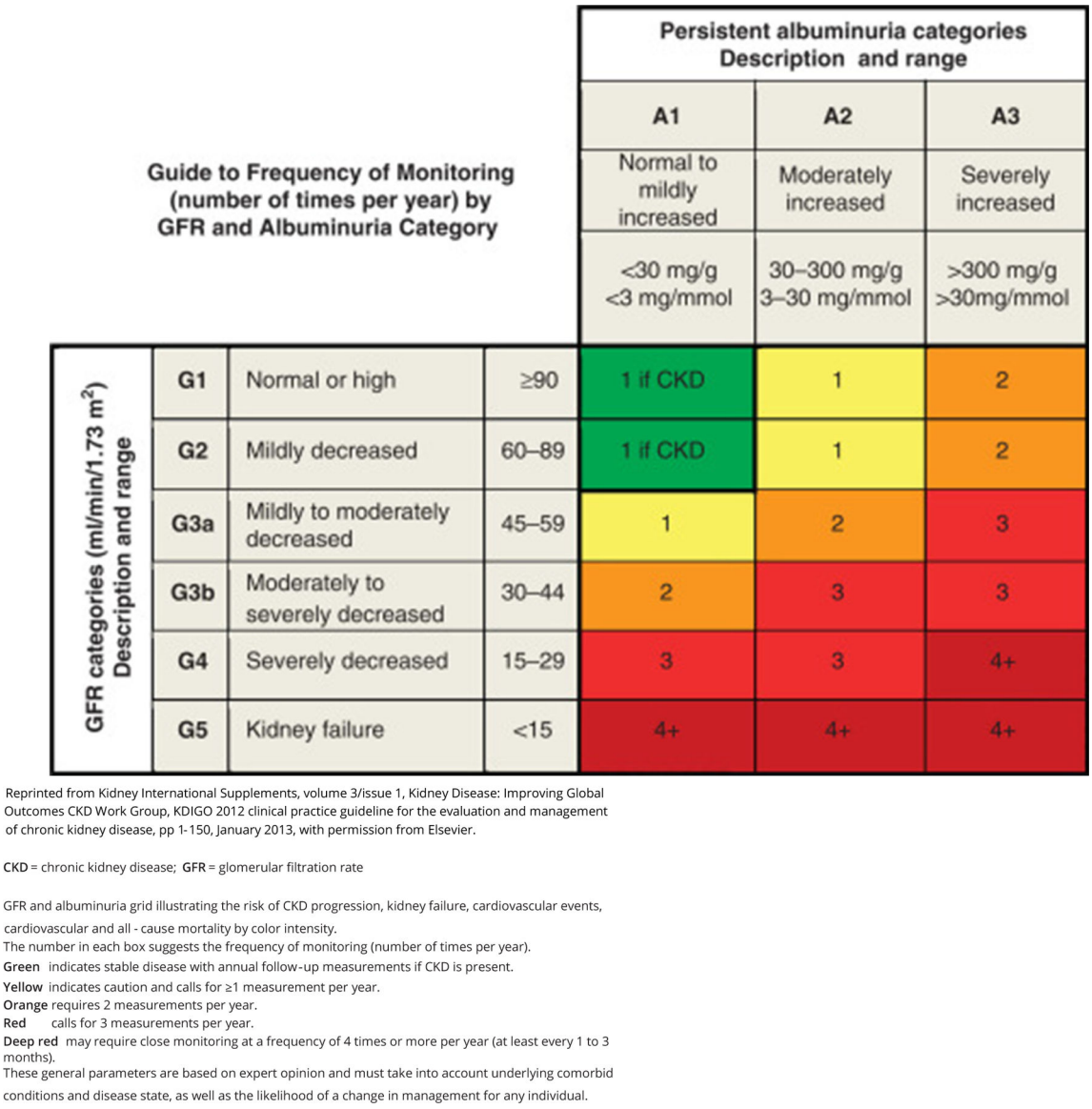


Figure 2.

Decision Tree for Hypertriglyceridemia in Persons with Diabetes Mellitus. Copyright © 2022 AACE. May not be reproduced in any form without express written permission from Elsevier on behalf of AACE. Visit https://doi.org/10.1016/j.eprac.2022.08.002 to request copyright permission.



Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30mg/mmol
	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

Reprinted from Kidney International Supplements, volume 3/issue 1, Kidney Disease: Improving Global Outcomes CKD Work Group, KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease, pp 1-150, January 2013, with permission from Elsevier.

CKD = chronic kidney disease; **GFR** = glomerular filtration rate

GFR and albuminuria grid illustrating the risk of CKD progression, kidney failure, cardiovascular events, cardiovascular and all - cause mortality by color intensity.
The number in each box suggests the frequency of monitoring (number of times per year).
Green indicates stable disease with annual follow-up measurements if CKD is present.
Yellow indicates caution and calls for ≥1 measurement per year.
Orange requires 2 measurements per year.
Red calls for 3 measurements per year.
Deep red may require close monitoring at a frequency of 4 times or more per year (at least every 1 to 3 months).
These general parameters are based on expert opinion and must take into account underlying comorbid conditions and disease state, as well as the likelihood of a change in management for any individual.

Figure 3.

Guide to Frequency of Monitoring (Number of Times per Year) by Glomerular Filtration Rate and Albuminuria Category

Reprinted from Kidney International Supplements, volume 3/issue 1, Kidney Disease: Improving Global Outcomes CKD Work Group, KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease, pp 1– 150, January 2013, with permission from Elsevier.

CKD = chronic kidney disease; **GFR** = glomerular filtration rate

GFR and albuminuria grid illustrating the risk of CKD progression, kidney failure, cardiovascular events, cardiovascular and all - cause mortality by color intensity.

The number in each box suggests the frequency of monitoring (number of times per year).

Green indicates stable disease with annual follow-up measurements if CKD is present.

Yellow indicates caution and calls for ≥1 measurement per year.

Orange requires 2 measurements per year.

Red calls for 3 measurements per year.

Deep red may require close monitoring at a frequency of 4 times or more per year (at least every 1 to 3 months).

These general parameters are based on expert opinion and must take into account underlying comorbid conditions and disease state, as well as the likelihood of a change in management for any individual.

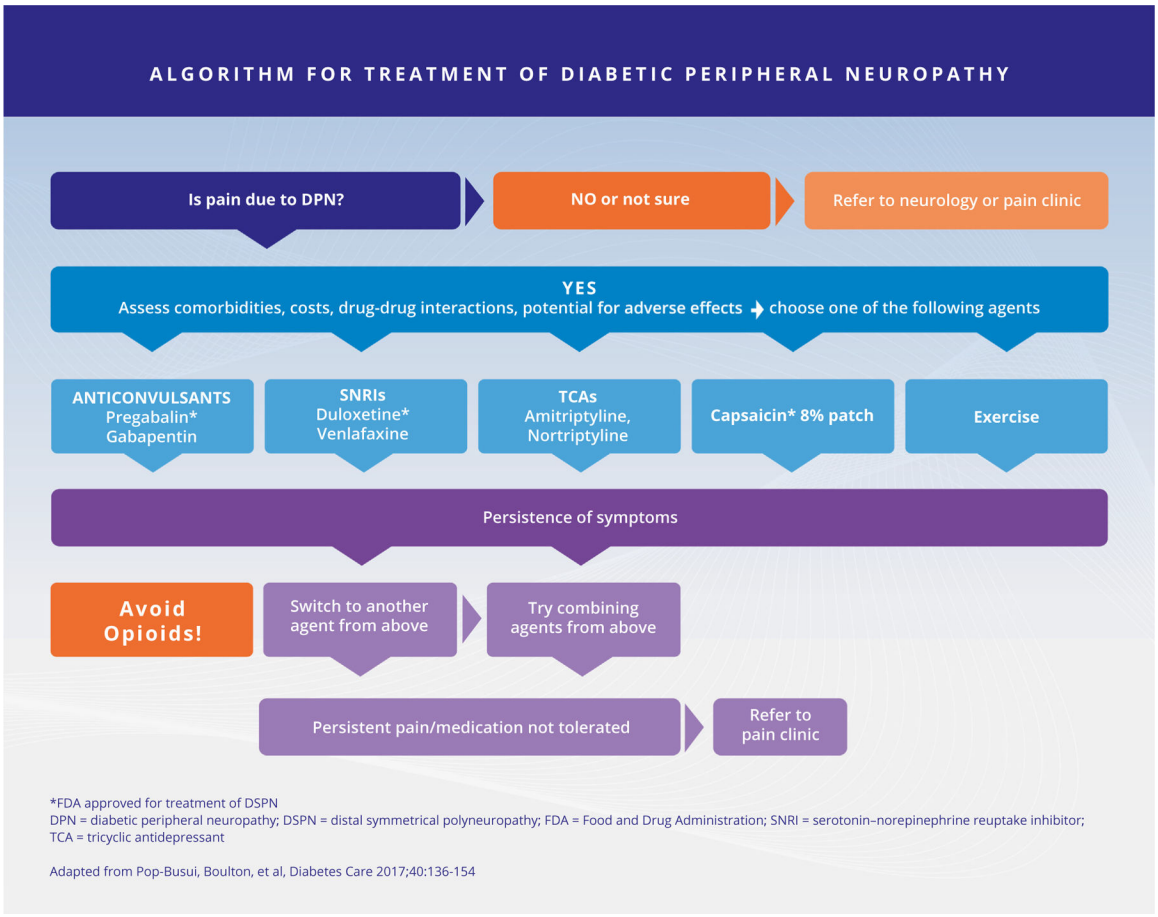


Figure 4.
Algorithm for Treatment of Diabetic Peripheral Neuropathy

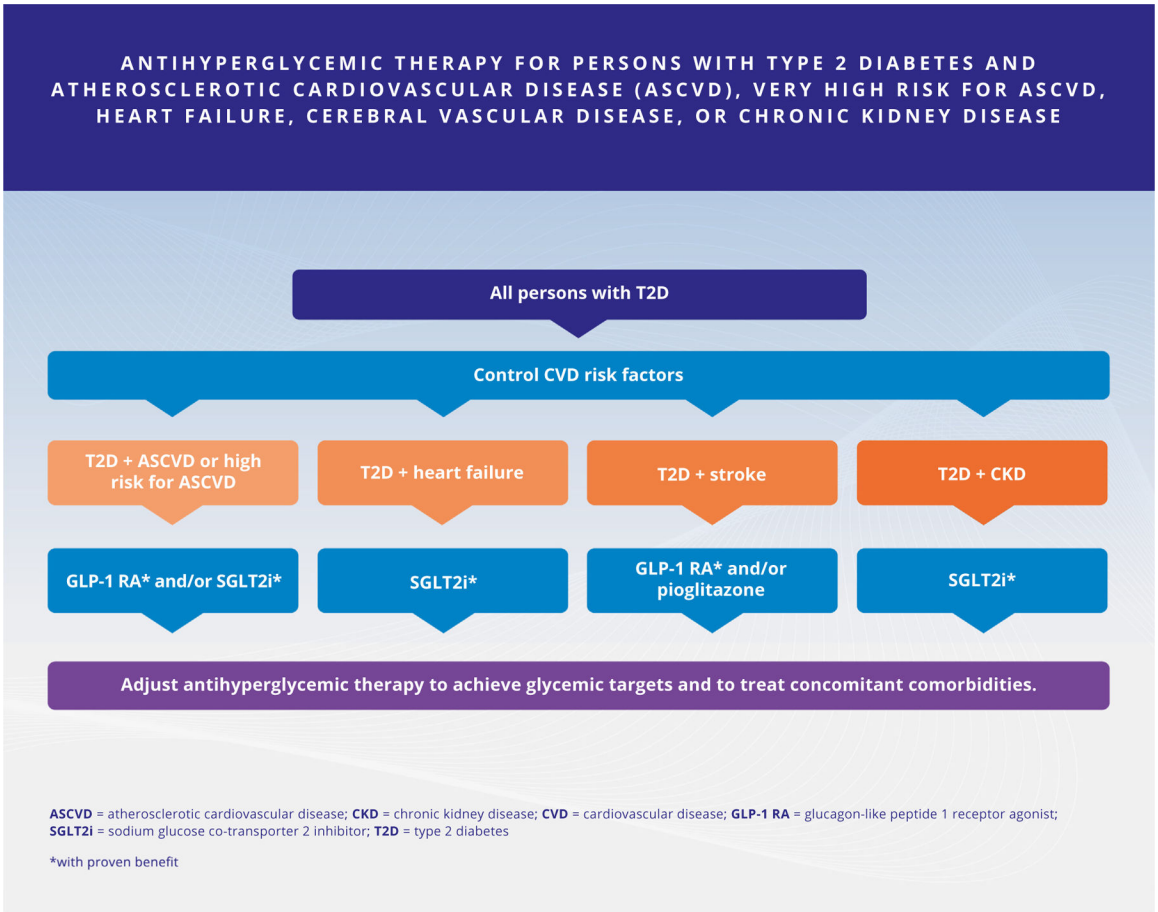


Figure 5.

Antihyperglycemic Therapy for Persons with Type 2 Diabetes and Atherosclerotic Cardiovascular Disease (ASCVD), Very High Risk for ASCVD, Heart Failure, Cerebral Vascular Disease, or Chronic Kidney Disease.

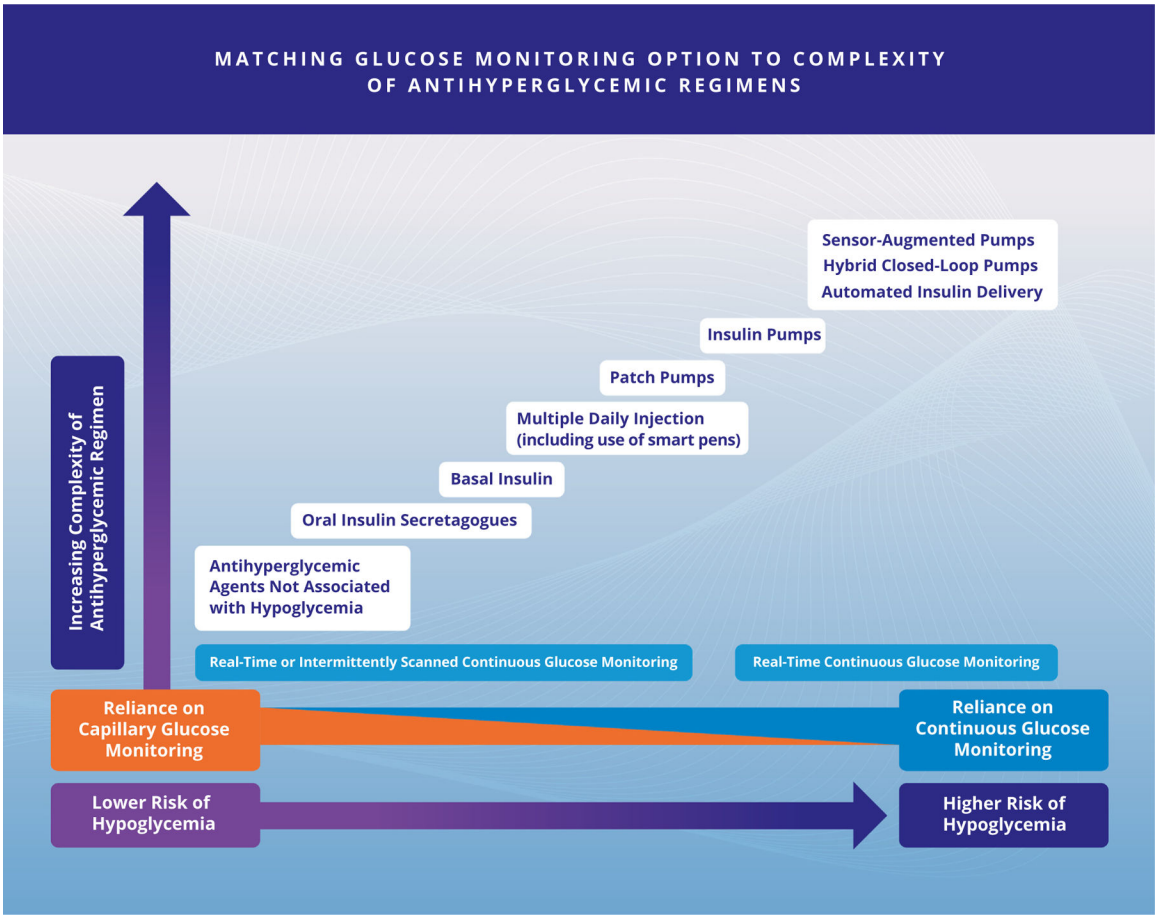


Figure 6.

Matching Glucose Monitoring Option to Complexity of Antihyperglycemic Regimens.

Table 1

Summary of Questions

Q = Question	
Section 1	**Screening, diagnosis, glycemic targets, glycemic monitoring**
Q1	How is the diagnosis of DM made and what is the current screening protocol for prediabetes and diabetes?
Q2	What are the glycemic treatment goals for persons with DM?
Q3	When and how should glucose monitoring be used?
Section 2	**Comorbidities and complications**
Q4	How should hypertension be managed in persons with DM?
Q5	How should dyslipidemia be managed in persons with DM?
Q6	How should DKD or CKD in DM be managed?
Q7	How should retinopathy be managed in persons with DM?
Q8	How should neuropathy be diagnosed and managed in persons with DM?
Q9	How should antihyperglycemic agents be prioritized in persons with T2D at high risk for/or with established CVD?
Q10	How should obesity be managed in persons with DM?
Section 3	**Management**
Q11	How should prediabetes be managed?
Q12	How can glycemic targets be achieved in persons with T2D?
Q13	How should insulin therapy be used for management of persons with T1D?
Q14	How should hypoglycemia be managed?
Q15	How should DM be managed in the hospital?
Q16	How should DM in pregnancy be managed?
Section 4	**Education and other topics**
Q17	What education interventions have been shown to be most effective in management of persons with DM?
Q18	What are the key nonpharmacological components of a comprehensive diabetes care plan in children and adolescents?
Q19.1	Should persons with infertility be screened for DM?
Q19.2	How should persons with preexisting diabetes mellitus and infertility be evaluated?
Q19.3	Should men with DM and cardiometabolic disorders be assessed for hypogonadism?
Q20.1	How should persons at risk for secondary diabetes be assessed?
Q20.2	What are the best treatment strategies for management of secondary diabetes, such as posttransplant diabetes, cystic fibrosis−related diabetes, and other forms of secondary diabetes?
Q21	What is the role of sleep medicine in the care of persons with DM?
Q22	Should screening for depression be a routine component of clinical assessment in persons with DM?

Q = Question	
Q23	Is the evaluation of SDOH in persons predisposed to or with DM useful in improving health outcomes?
Q24	Is telehealth/virtual care an effective care-delivery model for the management of persons with DM?
Q25	Which occupations have specific public safetyerelated diabetes management considerations?
Q26	Is there a role for nutritional supplements in the management of DM and what might be the associated risks?
Q27	How should potential increased cancer risk be managed in persons with obesity/T2D?
Q28	Which vaccinations should be given to adults with DM?

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; DKD, diabetic kidney disease; DM, diabetes mellitus; SDOH, social determinants of health; T1D, type 1 diabetes, T2D, type 2 diabetes.

Table 2

Summary of Recommendations

Section 1. Screening, Diagnosis, Glycemic Targets, Glycemic Monitoring	
Q 1: How is the diagnosis of diabetes mellitus made and what is the current screening protocol for prediabetes and diabetes?	
R 1.1	The diagnosis of diabetes mellitus (DM) is based on the following criteria (Table 4): • Fasting plasma glucose (FPG) concentration ≥126 mg/dL (after ≥8 h of an overnight fast), or • Plasma glucose (PG) concentration ≥200 mg/dL 2 h after ingesting a 75-g oral glucose load after an overnight fast of at least 8 h, or • Symptoms of hyperglycemia (eg, polyuria, polydipsia, polyphagia) and a random (nonfasting) PG concentration ≥200 mg/dL, or • Hemoglobin A1c (A1C) level ≥6.5% Diagnosis of DM requires 2 abnormal test results, either from the same sample or two abnormal results on samples drawn on different days. However, a glucose level ≥200 mg/dL in the presence of symptoms for DM confirms the diagnosis of DM. Grade A; BEL 2 and expert opinion of task force
R 1.2	Prediabetes is identified by the presence of impaired fasting glucose (IFG) (100 to 125 mg/dL), impaired glucose tolerance (IGT), which is a PG value of 140 to 199 mg/dL 2 h after ingesting 75 g of glucose, and/or A1C value between 5.7% and 6.4% (Table 4). A1C should be used only for screening for prediabetes. The diagnosis of prediabetes, which may manifest as either IFG or IGT, should be confirmed with glucose testing. Grade B; BEL 2
R 1.3	Type 1 diabetes (T1D) is characterized by marked insulin deficiency in the presence of hyperglycemia and positive autoantibody tests to glutamic acid decarboxylase (GAD65), pancreatic islet b cells (tyrosine phosphatase IA-2), and IA-2b zinc transporter (ZnT8), and/or insulin. The presence of immune markers and clinical presentation are needed to establish the correct diagnosis and to distinguish between T1D and type 2 diabetes (T2D) in children or adults, as well as to determine appropriate treatment. Grade A; BEL 2
R 1.4	T2D is characterized by progressive loss of b-cell insulin secretion and variable defects in insulin sensitivity. T2D is often asymptomatic and can remain undiagnosed for many years; therefore, all adults ≥35 y of age with risk factors should be screened for DM (Table 5). Grade A; BEL 1
R 1.5	Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance that begins or is first recognized during pregnancy and resolves postpartum. Pregnant women with risk factors for DM should be screened at the first prenatal visit for undiagnosed T2D using standard criteria (Table 4). Grade B; BEL 1
R 1.6	Screen all pregnant women for GDM at 24 to 28 weeks' gestation. Diagnose GDM with either the one-step or the two-step approach. • The one-step approach uses a 2-h 75-g oral glucose tolerance test (OGTT) after ≥8 h of fasting with diagnostic cutoffs of one or more FPG ≥92 mg/dL, 1-h PG ≥180 mg/dL, or 2-h PG ≥153 mg/dL. • The two-step approach uses a nonfasting 1-h 50-g glucose challenge test with 1-h PG screening threshold of 130 or 140 mg/dL. For women with a positive screening test, the 3-h 100-g OGTT is used for diagnosis with 2 or more PG tests that meet the following thresholds: FPG ≥95 mg/dL, 1-h ≥180 mg/dL, 2-h ≥155 mg/dL, 3-h ≥140 mg/dL. Grade A; BEL 1
R 1.7	Clinicians should consider evaluation for monogenic DM in any child or young adult with an atypical presentation, clinical course, or response to therapy. Monogenic DM includes neonatal diabetes and nonautoimmune diabetes of multiple genetic causes, also known as maturity-onset diabetes of the young. Most children with DM occurring under age 6 mo of age have a monogenic cause as autoimmune T1D rarely occurs before 6 mo of age. Other monogenic forms of diabetes are characterized by mutation of genes of transcription factors, genes regulating pancreatic development or atrophy, abnormal insulin genes, genes related to endoplasmic reticulum stress that impair insulin secretion or abnormal glucokinase genes that cause impaired insulin signaling. Grade B; BEL 2
Q 2: What are the glycemic treatment goals for persons with diabetes mellitus?	
2.1 Outpatient Glucose Targets for Nonpregnant Adults	
R 2.1.1	An A1C level of ≤6.5% is recommended for most nonpregnant adults, if it can be achieved safely. To achieve this target A1C level, FPG may need to be <110 mg/dL, and the 2-h postprandial glucose (PPG) may need to be <140 mg/dL (Table 6). Glucose targets should be individualized with consideration for life expectancy, disease duration, presence or absence of micro- and macrovascular complications, cardiovascular disease (CVD) risk factors, comorbid conditions, and risk for hypoglycemia, as well as a person's cognitive and psychological status. Grade A; BEL 1

Section 1. Screening, Diagnosis, Glycemic Targets, Glycemic Monitoring

Q 1: How is the diagnosis of diabetes mellitus made and what is the current screening protocol for prediabetes and diabetes?

R 2.1.2 Adopt less stringent glycemic goals (A1C 7% to 8%) in persons with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced renal disease, extensive comorbid conditions, or long-standing DM in which the A1C goal has been difficult to attain despite intensive efforts, so long as the person remains free of hyperglycemia-associated symptoms.
Grade A; BEL 1

2.2 Inpatient Glucose Targets for Nonpregnant Adults

R 2.2 For most hospitalized persons with hyperglycemia in both the intensive care unit (ICU) and non-ICU settings, a glucose range of 140 to 180 mg/dL is recommended, provided this target can be safely achieved (Table 6).
Grade A; BEL 1

2.3 Outpatient Glucose Targets for Pregnant Women

R 2.3 In women with GDM, the following glucose goals are recommended: fasting and preprandial glucose concentration ≤95 mg/dL and either a 1-h postmeal glucose value ≤140 mg/dL or a 2-h postmeal glucose value ≤120 mg/dL.
In women with preexisting T1D or T2D who become pregnant, it is recommended that glucose be controlled to meet the following goals, but only if the goals can be safely achieved: premeal, bedtime, and overnight glucose values between 60 and 95 mg/dL; a 1-h PPG value between 110 and 140 mg/dL; a 2-h glucose 100 to 120 mg/dL. A secondary target would be an A1C level of <6% if it can be accomplished without significant hypoglycemia.
Grade A; BEL 1

Q 3: When and how should glucose monitoring be used?

R 3.1 A1C should be measured at least semiannually in all persons with DM and at least quarterly in persons not at their glycemic target.
Grade B; BEL 2

R 3.2 All persons who use insulin should use continuous glucose monitoring (CGM) or perform blood glucose monitoring (BGM) a minimum of twice daily and ideally before any insulin injection. More frequent BGM may be needed by persons who are taking multiple daily injections (MDI) injections, persons not at A1C targets, or those with history of hypoglycemia. Persons who do not require insulin or insulin secretagogue therapy may often benefit from BGM, especially to provide feedback about the effects of their lifestyle choices (diet and physical activity), and to assess response to pharmacologic therapy.
Grade A; BEL 1

R 3.3 Real-time continuous glucose monitoring (rtCGM) or intermittently scanned continuous glucose monitoring (isCGM) is recommended for all persons with T1D, regardless of insulin delivery system, to improve A1C levels and to reduce the risk for hypoglycemia and DKA (see Fig. 6).
Grade A; BEL 1

R 3.4 rtCGM or isCGM is recommended for persons with T2D who are treated with insulin therapy, or who have high risk for hypoglycemia and/or with hypoglycemia unawareness (see Figure 6).
Grade A; BEL 1

Section 2. Comorbidities and Complications

Q 4: How should hypertension be managed in persons with diabetes mellitus?

R 4.1 The recommended blood pressure (BP) goal for most persons with T1D, T2D, or prediabetes is <130/80 mm Hg (Table 7).
Grade A; BEL 1

R 4.2 Therapeutic lifestyle interventions in persons with hypertension are recommended to include consultation with a registered dietitian for education about an overall healthy diet (such as the Mediterranean diet), weight management, reduced sodium intake (such as the Dietary Approaches to Stop Hypertension [DASH] diet), daily physical activity and regular exercise (several times a week), and as-needed consultation with a psychologist or certified diabetes care and education specialist (CDCES) to support long-term behavior change. (See also R 11.2 to R 11.4 and R 12.1.1 to R 12.1.5 on nutrition and lifestyle.)
Grade A; BEL 1

R 4.3 If BP goals are unattained with therapeutic lifestyle changes, use antihypertensive pharmacotherapy to achieve individual BP treatment goals.
Grade A; BEL 1

Q 1: How is the diagnosis of diabetes mellitus made and what is the current screening protocol for prediabetes and diabetes?

R 4.4 Select antihypertensive agents based on their ability to reduce BP to goal and prevent or slow the progression of micro- and macrovascular disease. Use either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) for BP control and to delay the progression of DKD or chronic kidney disease (CKD) in DM (see also R 6.1 to R 6.6 on DKD or CKD in DM).
Grade A; BEL 1

R 4.5 Intensify pharmacotherapy as needed to achieve BP goals. Antihypertensive therapy may include combinations of either an ACE inhibitor or an ARB plus any of the following agents: diuretics, calcium channel antagonists, combined alpha-beta blockers, and newer-generation beta blockers. Consider a mineralocorticoid receptor antagonist for resistant hypertension.
Grade A; BEL 1

Q 5: How should dyslipidemia be managed in persons with diabetes mellitus?

R 5.1 All persons with prediabetes, T1D over the age of 40, or T2D should have a lipid panel (fasting or nonfasting) checked at diagnosis and annually to assess cardiovascular (CV) and metabolic disease risks, and at additional intervals as needed to monitor treatment to achieve lipid goals.
Grade B; BEL 2

R 5.2 Therapeutic lifestyle interventions for dyslipidemia are recommended for all persons with prediabetes, T1D over the age of 40, or T2D, to include education with a registered dietitian about a healthy diet with emphasis on weight management, daily physical activity, and regular exercise (several times a week). Consultation with a psychologist or CDCES is recommended to support long-term behavior change.
Grade A; BEL 1

R 5.3 Persons with prediabetes or T2D without atherosclerotic cardiovascular disease (ASCVD) and with less than 2 traditional risk factors should be assessed with the aid of ASCVD risk calculators to determine initiation and intensity of lipid-lowering therapy (Fig. 1 and Table 8).
Grade A; BEL 1

R 5.4 Assess nontraditional ASCVD risk factors (Fig. 1) beyond a lipid panel to guide management when the initial shared decision is not self-evident.
Grade B; BEL 2

R 5.5 Manage persons with prediabetes and persons with T1D over the age of 40 in the same manner as those with T2D.
Grade A; BEL 1

R 5.6 In persons with high ASCVD risk, use a moderate-intensity statin regardless of DM type or status. In persons with very high ASCVD risk (T2D with 2 or more additional traditional ASCVD risk factors such as advancing age, hypertension, chronic kidney disease (CKD) stage 3a, cigarette smoking, family history of premature ASCVD in men <55 y and women <65 y, low high-density lipoprotein cholesterol (HDL-C), or high non-HDL-C), use a high-intensity statin regardless of baseline low-density lipoprotein cholesterol (LDL-C) level. For persons at extreme risk of ASCVD event (current ASCVD or target organ damage), use a high-intensity statin plus other therapies as needed to achieve lipid targets (Fig. 1 and Table 10).
Grade A; BEL 1

R 5.7 Treatment targets for persons in a high ASCVD risk category are LDL-C <100 mg/dL, apolipoprotein B (apo B) <90 mg/dL, and non-HDL-C <130 mg/dL. Treatment targets for persons in a very high risk ASCVD category are LDL-C <70 mg/dL, apo B <80 mg/dL, and non-HDL-C <100 mg/dL. Treatment targets for persons with extreme risk of ASCVD include LDL-C <55 mg/dL, apo B <70 mg/dL, and non-HDL-C <90 mg/dL (Table 9 and Fig. 1).
Grade A; BEL 1

R 5.8 Statins are recommended for the initial treatment of hypercholesterolemia. Monitor efficacy every 6 to 12 wk and increase the dose or intensity of statin as needed and tolerated to achieve LDL-C, apo B, and/or non-HDL-C goals based on individual ASCVD risk. Once lipid targets are achieved, lipid panel or apo B can be monitored less often (Fig. 1).
Grade A; BEL 1

R 5.9 Combine the cholesterol absorption inhibitor ezetimibe with statin therapy when the desired lipid targets are not achieved with a maximally tolerated statin dose. If lipid targets are not achieved on this combination, add or substitute a proprotein convertase subtilisin/kexin type 9-lowering agent. Alternatively, add bempedoic acid to the maximally tolerated statin or consider adding icosapent ethyl (in persons with triglycerides 135 to 499 mg/dL) for ASCVD risk reduction.
Grade A; BEL 1

R 5.10 Management of hypertriglyceridemia in persons with high ASCVD risk or very high ASCVD risk should begin with intensive lifestyle modification and statin therapy. In persons treated with a maximally tolerated statin who have triglyceride concentrations ≥200 mg/dL and HDL-C <40 mg/dL, add a fibrate or high-dose omega-3 fatty acid to achieve the desired apo B or non-HDL-C goal. Icosapent ethyl can be considered in persons with high or very high ASCVD risk (Fig. 2).
Grade A; BEL 1

Section 1. Screening, Diagnosis, Glycemic Targets, Glycemic Monitoring

Q 1: How is the diagnosis of diabetes mellitus made and what is the current screening protocol for prediabetes and diabetes?

Q 6: How should DKD or CKD in DM be managed?

R 6.1 Annual assessment of serum creatinine to determine the estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio is recommended to identify, stage, and monitor progression of DKD, also referred to as CKD in DM. Begin annual DKD assessment 5 y after diagnosis in persons with T1D or at diagnosis in persons with T2D.
Grade B; BEL 2

R 6.2 Advise persons with CKD in DM about optimal glycemic control, BP control, lipid control, and smoking cessation to reduce risks of development and progression of CKD and CVD. (See also R 4.1 to R 4.5 on BP control, R 5.1 to R 5.10 on lipid management, and R 12.1.1 to R 12.2.19 on glycemic control.)
Grade A; BEL 1

R 6.3 Renin-angiotensin-aldosterone system blockade with an ARB or an ACE inhibitor is recommended for persons with albuminuria (T1D or T2D) to reduce risk of DKD or CKD in DM progression (see Fig. 3 for category definitions).
Grade A; BEL 1

R 6.4 A sodium glucose cotransporter 2 inhibitor (SGLT2i) with proven benefit is recommended as foundational therapy for persons with T2D and CKD with eGFR ≥20 mL/min/1.73 m^2 to reduce progression of CKD and risk of CVD.
Grade A; BEL 1

R 6.5 A glucagon-like peptide-1 receptor agonist (GLP-1 RA) with proven benefit is recommended for persons with T2D and DKD or CKD in DM with eGFR ≥15 mL/min/1.73 m^2 for glycemic control and to reduce risk of ASCVD and progression of albuminuria.
Grade A; BEL 1

R 6.6 A non-steroidal mineralocorticoid receptor antagonist (finerenone) with proven kidney and CVD benefit is recommended for persons with T2D, an eGFR ≥25 mL/min/1.73 m^2, normal serum potassium concentration, and albuminuria (ACR ≥30 mg/g) despite a maximum tolerated dose of a renin-angiotensin-system inhibitor.
Grade A; BEL 1

Q 7: How should retinopathy be managed in persons with diabetes mellitus?

R 7.1 It is recommended that persons with T2D or adult-onset T1D should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of diagnosis or shortly after diagnosis. Individualized subsequent screening can be based on type and duration of DM, A1C or mean blood glucose (BG), BP, and the presence and grade of retinopathy.
Grade A; BEL 2 and expert opinion of task force

R 7.2 In persons with T1D, an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist should be performed within 5 y of diagnosis in children and adolescents.
Grade B; BEL 4 and expert opinion of task force

R 7.3 Women who are pregnant and have preexisting T1D or T2D should be monitored with eye examinations every trimester during pregnancy and in the postpartum period as determined by the severity of retinopathy during pregnancy.
Grade B; BEL 2

R 7.4 Persons with greater than mild nonproliferative retinopathy should have examinations at least once a year and more frequently as advised by their eyecare specialist.
Grade B; BEL 4 and expert opinion of task force

R 7.5 Follow-up with eyecare specialists typically should occur on an annual basis, but persons with T1D or T2D who have had a normal ocular examination may be screened every 2 to 3 y.
Grade B; BEL 2 and expert opinion of task force

R 7.6 Optimal glucose, BP, weight, and lipid control should be implemented to slow the progression of retinopathy.
Grade B; BEL 1

R 7.7 Artificial intelligence systems, authorized by the US Food and Drug Administration (FDA) for detecting greater than mild diabetic retinopathy, can be used as an alternative to traditional screening approaches. These systems can facilitate diagnosis of vision-threatening retinopathy and identification of persons who require ophthalmologic visits for treatment.
Grade B; BEL 1

Q 8: How should neuropathy be diagnosed and managed in persons with diabetes mellitus?

Section 1. Screening, Diagnosis, Glycemic Targets, Glycemic Monitoring

Q 1: How is the diagnosis of diabetes mellitus made and what is the current screening protocol for prediabetes and diabetes?

R 8.1 Diabetic peripheral neuropathy (DPN) is a clinical diagnosis. A comprehensive differential diagnosis should be considered to rule out nondiabetic neuropathies.
Grade B; BEL 2

R 8.2 Screening for DPN should be done at diagnosis of T2D, within 5 y of the diagnosis of T1D, and subsequently annually or whenever symptoms occur, by performing a clinical history and physical exam.
Grade B; BEL 2

R 8.3 Assessments for DPN should include a careful history to assess target symptoms, and a combination of at least two of the following: vibration sensation using a 128-Hz tuning fork, pinprick sensation, temperature discrimination, 10-g monofilament testing on the dorsal aspect of the great toe bilaterally, and ankle reflexes. All these assessments should follow the typical DPN pattern, starting distally (the dorsal aspect of the hallux) on both sides and move proximally until a sensory threshold is identified.
Grade A; BEL 2, upgraded by expert opinion of task force

R 8.4 Screening for cardiovascular autonomic neuropathy (CAN) should be considered at diagnosis of T2D and at 5 y after the diagnosis of T1D, including youth. Screening for CAN should also be considered in the presence of DPN, DKD, 2 or more CV risk factors, hypoglycemia unawareness, high glucose variability, in persons with heart failure (HF), perioperatively, or in individuals presenting with autonomic symptoms. A careful differential to exclude other comorbidities or drug effects/interactions that could mimic CAN should be performed.
Grade B; BEL 2

R 8.5 CV reflex tests (deep breathing, Valsalva, supine to standing) remain the gold standard and are recommended for assessment of CAN. Indices of heart rate variability derived from electrocardiogram recordings could also be used as an easier alternative for screening for CAN.
Grade A; BEL 2, upgraded by expert opinion of task force

R 8.6 Diabetic foot exams should be performed at every visit (in person or virtual) to identify deformities and to identify those at risk for late complications such as ulcerations and amputations.
Grade A; BEL 1

R 8.7 Intensive glucose control applied as early as possible is recommended to prevent the onset of DPN and CAN in T1D. Achieving optimal control of glucose, BP, and lipid levels along with lifestyle interventions, including weight loss and exercise, are recommended to prevent DPN and CAN in T2D. Lifestyle interventions are effective for DPN and CAN prevention in persons with prediabetes/metabolic syndrome.
Grade A; BEL 2, upgraded by expert opinion of task force

R 8.8 Pregabalin, duloxetine, and capsaicin 8% patch are recommended for the treatment of neuropathic pain due to DM and have received regulatory approval in the United States. Current evidence shows that these agents are effective in reaching 30% to 50% reduction in pain in many individuals (Grade A; BEL 1). However, gabapentin and some tricyclic antidepressants may be as effective to achieve a clinically meaningful reduction in diabetic neuropathic pain (Grade B; BEL 1). Combining two or more agents from different classes may have enhanced benefits with lower adverse effects and risks than maximizing the dose of one medication or using opioids. The use of opioids, including tapentadol or tramadol, is NOT RECOMMENDED due to high risk of addiction and other complications.
Grade A; BEL 1

R 8.9 Lifestyle interventions including a combination of regular aerobic, strengthening, and balance exercises, reduction of sedentary behavior, and dietary modification aimed at reducing calorie intake and increasing plant-based and polyunsaturated fats are recommended. Neuromodulatory techniques such as high-frequency spinal cord stimulation and combining pharmacological with nonpharmacological approaches should be considered in those with refractory painful DPN.
Grade B; BEL 1

Q 9: How should antihyperglycemic agents be prioritized in persons with type 2 diabetes at high risk for or with established cardiovascular disease?

R 9.1 In persons with T2D and established ASCVD or at high risk for ASCVD, use GLP-1 RAs with proven CV benefits to reduce the risk of myocardial infarction, stroke, or CV death regardless of other glucose-lowering or CV therapies and independent of A1C.
Grade A; BEL 1

R 9.2 In persons with T2D and established ASCVD or very high ASCVD risk, use SGLT2is with proven CV benefits to reduce the risk of hospitalization for HF, major adverse CV events, or CV death regardless of background glucose-lowering therapy, cardiovascular therapy, or A1C.
Grade A; BEL 1

R 9.3 In persons with T2D and established HF (regardless of ejection fraction, background glucose-lowering or HF therapies, or A1C), use SGLT2is with proven HF benefits to reduce the risk of hospitalization for HF or CV death, and to improve HFerelated symptoms.
Grade A; BEL 1

Section 1. Screening, Diagnosis, Glycemic Targets, Glycemic Monitoring

Q 1: How is the diagnosis of diabetes mellitus made and what is the current screening protocol for prediabetes and diabetes?

R 9.4 In persons with T2D and ASCVD or at high risk for ASCVD, use GLP-1 RAs with proven benefit for reduction in the risk of stroke. In persons with insulin resistance, prediabetes, or T2D and a prior transient ischemic attack or stroke, pioglitazone should be considered to reduce the risk of recurrent stroke.
Grade A; BEL 1

Q 10: How should obesity be managed in persons with diabetes mellitus?

R 10.1 Persons with prediabetes, T1D or T2D, and obesity/adiposity-based chronic disease (ABCD) have 2 diseases, and each should be treated effectively with the goal of optimizing their respective outcomes.
Grade B; BEL 2 and expert opinion of task force

R 10.2 The diagnosis and evaluation of ABCD in persons with prediabetes, T1D, or T2D should include both anthropometric and clinical components. The anthropometric evaluation should include body mass index (BMI), confirmed by physical examination that excludes excess muscle mass, edema, or sarcopenia. Waist circumference (WC) should be measured as a marker of cardiometabolic disease (CMD) risk.
Grade B; BEL 2 and expert opinion of task force

R 10.3 For most adults, BMI values that indicate excess body weight are 25 to 29.9 kg/m^2 for overweight and ≥30 kg/m^2 for obesity, and WC threshold values ≥102 cm for men and ≥88 cm for women.
Grade B; BEL 4 and expert opinion of task force

R 10.4 The clinical evaluation of persons with both prediabetes, T1D, or T2D and ABCD should assess the presence and severity of weight-related complications including cardiometabolic complications such as dyslipidemia, hypertension, nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH), CVD, HF, and CKD; biomechanical complications such as obstructive sleep apnea (OSA), osteoarthritis, gastroesophageal reflux disease, and urinary incontinence; abnormalities involving sex steroids, such as infertility, polycystic ovary syndrome, and hypogonadism; as well as impact on psychological disorders and quality of life (QoL).
Grade B; BEL 2 and expert opinion of task force

R 10.5 Persons with T2D and ABCD should be treated with weight-loss interventions which will both improve glycemic control and prevent or treat ABCD complications. The target for weight loss should be >5% to ≥10% of baseline body weight.
Grade A; BEL 1

R 10.6 Persons with T2D and ABCD should be instructed and supported in therapeutic lifestyle interventions that include a reduced-calorie healthy diet generally designed to produce a ≥500 kilocalorie daily energy deficit, daily physical activity, regular exercise (several times a week), and behavioral health practices.
Grade A; BEL 1

R 10.7 The Mediterranean, low-fat, low-carbohydrate, very lowecarbohydrate, vegetarian, vegan, and DASH diets are recommended, safe, and effective for short-term (1–2 y) weight loss, though evidence of long-term risk reduction for CVD events and mortality exists only for the Mediterranean diet.
Grade A; BEL 1

R 10.8 Persons with T2D and obesity/ABCD with BMI ≥27 kg/m^2 should be treated with DM medications associated with weight loss (GLP-1 RAs, SGLT2is). In addition, for persons with prediabetes, T1D, or T2D who have obesity/ABCD, consider FDAeapproved weight-loss medications as an adjunct to lifestyle intervention to achieve lowering of A1C, reduction of CVD risk factors, treatment or prevention of other ABCD complications, and improvement in QoL.
Grade A; BEL 1

R 10.9 Persons with a BMI ≥35 kg/m^2 and one or more severe obesity-related complications remediable by weight loss, including T2D, high risk for T2D (insulin resistance, prediabetes, and/or metabolic syndrome), poorly controlled hypertension, NAFLD/NASH, OSA, osteoarthritis of the knee or hip, and urinary stress incontinence, should be considered for a bariatric procedure (668).
Grade C; BEL 3

R 10.10 Persons with BMI 30 to 34.9 kg/m^2 and T2D with inadequate glycemic control despite optimal lifestyle and medical therapy should be considered for a bariatric procedure (668).
Grade B; BEL 2

Section 3. Management

Q 11: How should prediabetes be managed?

Section 1. Screening, Diagnosis, Glycemic Targets, Glycemic Monitoring

Q 1: How is the diagnosis of diabetes mellitus made and what is the current screening protocol for prediabetes and diabetes?

R 11.1 Prediabetes is a metabolic and vascular disorder, and clinicians should actively treat people with prediabetes in order to prevent or at least delay progression to T2D and development of CVD complications.
Grade A; BEL 1

R 11.2 In persons with prediabetes and/or metabolic syndrome or identified to be at high risk of T2D based on validated risk-staging instruments, the prevention of T2D can be addressed by lifestyle modifications that include a healthy meal plan, regular physical activity, and behavioral health practices and weight loss in persons with ABCD. The Mediterranean diet should be considered to reduce progression to T2D and risk of CVD. Low-fat, vegetarian, and DASH meal patterns can also be considered for prevention of T2D.
Grade A, BEL 1

R 11.3 Clinicians should manage and monitor CVD risk factors in prediabetes and metabolic syndrome, including elevated BP, dyslipidemia, and excessive weight, with the same targets as for a person with T2D.
Grade B; BEL 2

R 11.4 Lifestyle intervention should include aerobic and resistance physical activity in all persons with prediabetes and/or metabolic syndrome. The initial aerobic prescription may require a progressive increase in the volume and intensity of exercise, and the ultimate goal should be ≥150 min/week of moderate exercise performed during 3 to 5 sessions per week (Grade A; BEL 1). Resistance exercise should consist of single-set exercises that use the major muscle groups 2 to 3 times per week (Grade A; BEL 1). An increase in nonexercise and active leisure activity should be encouraged to reduce sedentary behavior (Grade B; BEL 2).

R 11.5 Obesity medications, namely phentermine/topiramate ER, liraglutide 3 mg, or weekly semaglutide 2.4 mg, in conjunction with lifestyle therapy should be considered in persons with prediabetes and/or metabolic syndrome with ABCD, whether overweight (BMI 27 to 29.9 kg/m^2) or with obesity (BMI ≥30 kg/m^2), when needed to achieve and sustain 7% to 10% weight loss for prevention of T2D.
Grade A; BEL 1

R 11.6 Although no medications have been approved for the treatment of prediabetes, diabetes medications including metformin, acarbose, pioglitazone, or GLP-1 RA can be considered in persons with prediabetes or in persons who also have ABCD and remain glucose-intolerant following weight loss using lifestyle and/or weight-loss medications.
Grade A; BEL 1

Q 12: How can glycemic targets be achieved in persons with type 2 diabetes?

12.1 Therapeutic Lifestyle Changes

R 12.1.1 All persons with prediabetes or DM should be prescribed, instructed, and supported in lifestyle interventions that include a healthy meal plan, regular physical activity, and healthful behavior practices. Individualized medical nutrition therapy (MNT) should be provided at the time of diagnosis (with intermittent re-education as needed during continued care) via evaluation and counseling by a trained registered dietitian, certified nutritionist, or a clinician knowledgeable in nutrition.
Grade A, BEL 1

R 12.1.2 MNT should consider the overall treatment plan including medications, DM complications, physical activity, body weight goals, and avoidance of hypoglycemia, as well as personal and cultural preferences, health literacy and numeracy, psychological factors, readiness for change, social determinants of health (SDOH), and support systems. For people on insulin therapy, insulin dosage adjustments should match carbohydrate intake (eg, with use of carbohydrate counting).
Grade A; BEL 1

R 12.1.3 The meal plan should contribute to therapeutic goals for control of glycemia, BP, lipids, CVD risk factors, and the prevention of DM complications. In selecting optimal meal patterns, certain Mediterranean diets should be considered which, over the long term, can protect against CVD events and premature mortality. Although there is a lack of long-term studies addressing CVD outcomes, multiple other meal plans have been shown to be safe and can achieve short-term benefits (1–2 y) regarding glycemia, BP, lipids, and CVD risk factors. These meal plans include low-fat, low-carbohydrate, very low-carbohydrate, vegetarian, vegan, and DASH diets.
Grade A, BEL 1

R 12.1.4 Given the variety of meal plans demonstrated to be beneficial in management of DM, nutritional recommendations should consider personal and cultural dietary preferences. Until there is conclusive evidence comparing the benefits of different meal patterns and the availability of long-term safety data, health care professionals should emphasize foods and nutrients that contribute to high “diet quality” scores as assessed by the Healthy Eating Index (HEI); high HEI is associated with reduced risks of DM, CVD, and mortality and includes fruits, nonstarchy vegetables, whole grains, nuts, legumes, and fish, with limited consumption of added sugars, refined grains, red meat, and processed meats.
Grade B; BEL 1

R 12.1.5 Lifestyle intervention in persons with DM should include an individualized prescription for physical activity involving aerobic and resistance exercise and reduction in sedentary behavior. The initial prescription for aerobic physical activity may require a progressive increase in the volume and intensity of exercise, and the ultimate goal should be ≥150 min/week of moderate

Q 1: How is the diagnosis of diabetes mellitus made and what is the current screening protocol for prediabetes and diabetes?

exercise performed during 3 to 5 sessions per week. (Grade A; BEL 1). Moderate exercise is considered to be activity that achieves a heart rate that is 50% to 60% higher than one's basal heart rate. The physical activity prescription also should include resistance exercise that use the major muscle groups 2 to 3 times per week (Grade A; BEL 1). Individuals should also incorporate flexibility and range-of-motion training. An increase in nonexercise and/or active leisure activity should be encouraged to reduce sedentary behavior (Grade A; BEL 1).

12.2 Antihyperglycemic Pharmacotherapy for Persons with Type 2 Diabetes

R 12.2.1 Individualized pharmacotherapy for persons with T2D should be prescribed based on evidence for benefit that includes glucose lowering, avoidance of hypoglycemia and weight gain, and reduction of cardio-renal risk.
Grade A; BEL 1

R 12.2.2 Persons with T2D and their health care professionals should use patient-centered shared decision-making to agree on therapy targets and treatments as well as a regimen for glucose monitoring (i.e., BGM, structured BGM, or CGM).
Grade B; BEL 2

R 12.2.3 Glycemic targets include A1C, BGM, and, for those using CGM, achievement of CGM targets such as time in range (TIR), percentage in low and very low range, time above range, and glycemic variability (Table 6). Nonglycemic targets include avoidance of hypoglycemia, control of BP, lipids, other CVD risk factors, and achieving and maintaining a healthy body weight.
Grade B; BEL 4

R 12.2.4 Independent of glycemic control, targets, or treatment, if there is established or high risk for ASCVD, HF, and/or CKD, clinicians should prescribe a GLP-1 RA or an SGLT2i with proven efficacy for the specific condition(s) of the person with T2D being treated (see also R 6.1 to R 6.6 on DKD or CKD in DM and R 9.1 to R 9.4 on ASCVD and HF).
Grade A; BEL 1

R 12.2.5 DM therapy should be individualized based on level of glycemia and the presence of comorbidities, complications, and access. Metformin is often the preferred initial therapy. Other agents may be appropriate as first line or in addition to metformin to reduce BG and/or to address specific comorbidities (such as ASCVD, HF, CKD, obesity, NAFLD), independent of glucose-lowering effects.
Grade A; BEL 1

R 12.2.6 For some recently diagnosed individuals with T2D and more severe hyperglycemia (A1C ≥7.5%), unlikely to attain the A1C target with a single agent, early combination pharmacotherapy should be considered, usually to include metformin plus another agent that does not cause hypoglycemia, especially a GLP-1 RA, SGLT2i, or dipeptidyl peptidase 4 (DPP-4) inhibitor.
Grade A; BEL 1

R 12.2.7 For newly diagnosed persons with T2D and an entry A1C >9.0% and/or ≥1.5% above target, one should initiate, along with lifestyle modifications, dual- or possibly triple-combination pharmacotherapy usually including metformin. Basal insulin along with noninsulin therapy is recommended if there are significant signs or symptoms of hyperglycemia, especially including catabolism (eg, weight loss) or a very high A1C >10% (86 mmol/mol) or BG levels (≥300 mg/dL [16.7 mmol/L]).
Grade A; BEL 1

R 12.2.8 Clinicians should discuss with persons with T2D the likelihood that most persons with T2D ultimately require a combination of multiple complementary antihyperglycemic agents, in addition to lifestyle interventions, to attain and maintain optimal glycemic control.
Grade B; BEL 2

R 12.2.9 The DM care team should assess medication adherence and safety and glycemic control in persons with T2D quarterly or more frequently as needed. Subsequent visits will depend upon the metabolic targets achieved and the stability of metabolic control.
Grade D; BEL 4

R 12.2.10 Persons with T2D who start on metformin should continue it unless intolerance or contraindications occur. When intensification of antihyperglycemic treatment is needed, other agents should be added to metformin.
Grade B; BEL 2

R 12.2.11 Most persons with T2D who require intensification of antihyperglycemic therapy with a GLP-1 RA or insulin should initially be prescribed a GLP-1 RA. If further intensification is required, one should prescribe a basal insulin or a switch to a fixed-ratio combination of a basal insulin and a GLP-1 RA (insulin glargine U100 + lixisenatide [GlarLixi] or insulin degludec + liraglutide [IdegLira]).
Grade A BEL 1

R 12.2.12 Insulin should be prescribed for persons with T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a person has symptomatic hyperglycemia.
Grade A; BEL 1

Section 1. Screening, Diagnosis, Glycemic Targets, Glycemic Monitoring

Q 1: How is the diagnosis of diabetes mellitus made and what is the current screening protocol for prediabetes and diabetes?

R 12.2.13	Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), degludec (U100 or U200), or detemir are preferred over intermediate-acting Neutral Protamine Hagedorn (NPH) insulin because analog insulins have demonstrated less hypoglycemia in some studies. Glargine U300 and degludec can be associated with less hypoglycemia than glargine U100 or detemir. Grade A; BEL 1
R 12.2.14	Many persons with T2D receiving basal insulin and not at goal A1C can have significantly improved glycemia by the addition of a GLP-1 RA or being switched to a fixed-ratio combination basal insulineGLP-1 RA (GlarLixi or IdegLira). One of these changes should be considered before adding a meal-time insulin for postprandial glycemic control. Grade A; BEL 1
R 12.2.15	When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or the rapid-acting inhaled human insulin powder) over regular human insulin (see Table 18). The former have a more consistent and a more rapid onset and offset of action with less risk of hypoglycemia. Grade A; BEL 1
R 12.2.16	Ultra-rapid-acting insulins (faster-acting insulin aspart, lispro aabc, and [human insulin] inhalation powder) may allow a decrease in the time between insulin administration and food intake and reduce the postprandial peak of PG as compared with rapid-acting insulins. The significance of this on long-term complications is unknown. Grade A; BEL 1
R 12.2.17	Basal-bolus insulin regimens or continuous subcutaneous insulin infusion (CSII) (ie, insulin pump) allow for adjustment of insulin doses according to carbohydrate intake and activity levels and are recommended for intensive insulin therapy in persons with T2D. Grade C; BEL 1
R 12.2.18	Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for persons with T2D who have consistent dietary and exercise patterns and in whom adherence to more intensive insulin regimens is problematic. However, these preparations have reduced dosage flexibility and may increase the risk of hypoglycemia compared with basal insulin or basal-bolus regimens. Grade A; BEL 1
R 12.2.19	In persons with T2D who are treated with basal-bolus insulin therapy, adding a GLP-1 RA, or switching to a fixed-ratio combination of a GLP-1 RA and a basal insulin, or adding an SGLT2i or pramlintide (less commonly used) may be able to reduce postprandial hyperglycemia, A1C, and weight. GLP-1 RAs may also allow reduction or discontinuation of bolus insulin in some individuals. Grade A; BEL 1

Q 13: How should insulin therapy be used for management of persons with type 1 diabetes?

R 13.1	Insulin must be used to treat all persons with T1D. Grade A; BEL 1
R 13.2	Physiologic insulin replacement regimens, which provide both basal and prandial (meal-related or bolus) insulin, are recommended for most persons with T1D. Grade A; BEL 1
R 13.3	Achievement of glucose targets using either MDI of insulin or CSII, is needed to prevent development of life-threatening crises, such as acute hyperglycemic crises (DKA and hyperglycemic hyperosmolar state) and catabolic state. Grade A; BEL 1
R 13.4	A multi-component self-management DM education program is recommended for persons with T1D. Ideally, this is provided by a professional with expertise (ie, CDCES) in the topics of healthy lifestyle, insulin technique including prandial insulin dosing guided by carbohydrate counting and diet adjustments for special situations, such as physical activity and prolonged fasting. Instruction is also needed in how to deal with sick days and prevention of DKA and hypoglycemia, and other relevant issues. Due to changes in DM self-management practices and each individual's medical history, personal and cultural background, and educational needs, specific education topics may need to be repeated at regular intervals. Grade A; BEL 1
R 13.5	The ideal insulin regimen should be personalized to an individual's needs and glycemic targets, attempting to better emulate physiological insulin replacement to maintain near normoglycemia, to prevent the development and progression of DM complications, while minimizing hypoglycemia and providing flexibility for specific daily life situations/scenarios such as: exercise, sleep, acute illness, psychological stress, etc. Grade A; BEL 1

Q 1: How is the diagnosis of diabetes mellitus made and what is the current screening protocol for prediabetes and diabetes?

R 13.6 Insulin regimens usually should involve the use of insulin analogs for most persons with T1D and include the following approaches:
a. MDI, which usually involve 1 to 2 subcutaneous injections daily of basal insulin to suppress ketogenesis and gluconeogenesis and to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or use of inhaled insulin before each meal to control meal-related glycemic excursions. CGM is the preferred method of glucose monitoring for all individuals with T1D.
Grade A; BEL 1
b. Insulin pump therapy (CSII) provides constant/continuous infusion of fast-acting insulin driven by mechanical force and delivered via a cannula inserted under the skin. CSII can improve (or enhance) glycemic control and should be an option for insulin delivery for appropriate persons with DM. Ideally, these individuals should also use CGM as stated in R13.6.a.
Grade B; BEL 1
c. Automated insulin delivery systems (AIDs), which include an insulin pump, an integrated CGM, and computer software algorithm, aim to better emulate physiological insulin replacement and achieve glycemic targets. This technology is recommended for many persons with T1D since its use has been shown to increase TIR while often reducing hypoglycemia or at least without causing increased hypoglycemia.
Grade A; BEL 1
d. Open-loop (use of a pump and sensor which do not communicate) and sensor-augmented pump (SAP) systems: (CGM communicates with pump facilitating needed adjustments to basal rate; temporary interruption of insulin delivery when glucose levels are low or forecast to be low within 30 min). Insulin pump with a CGM or an SAP is recommended to manage persons with DM treated with intensive insulin management who prefer not to use AIDs or have no access to them.
Grade D; BEL 4

Q 14: How should hypoglycemia be managed?

R 14.1 Oral intake of rapidly absorbed glucose (eg, glucose tablets or dietary sugar like fruit juice) followed by a snack or meal containing both protein and carbohydrates (eg, cheese and crackers or a peanut butter sandwich) should be used to treat hypoglycemia (measured glucose <70 mg/dL [3.9 mmol/L]) if a person is able to safely swallow.
Grade A; BEL 1

R 14.2 Glucagon, in one of the currently available forms: intranasal, prefilled liquid stable nonaqueous formulation, prefilled aqueous liquid stable glucagon analogue or with reconstitution from powder, should be used to correct hypoglycemia if individuals are unable or unwilling to ingest carbohydrates orally. If there is no response after 15 min, an additional same dose may be administered. As soon as the individual is awake and able to swallow, they should receivea rapidly absorbed source of carbohydrate.
Grade A; BEL 1

R 14.3 Persons with severe hypoglycemia with altered mental status or with prolonged hypoglycemia need to be hospitalized. If an individual has hypoglycemic unawareness and hypoglycemia-associated autonomic failure, several weeks of hypoglycemia avoidance may at least partially reverse hypoglycemia unawareness and may reduce the risk or prevent recurrence of severe hypoglycemia. Adjustment of an individual's long-term antihyperglycemic regimen may be necessary to further avoid recurrence of hypoglycemia.
Grade B; BEL 1

R 14.4 In persons with T2D who develop hypoglycemia and are being treated with alpha-glucosidase inhibitors or with pancreatic diabetes, oral glucose or lactose-containing foods (dairy products) must be given because alpha-glucosidase inhibitors inhibit the breakdown and absorption of complex carbohydrates and disaccharides (eg, table sugars or starches).
Grade A; BEL 1

R 14.5 Persons at risk for hypoglycemia should perform frequent BGM or preferably use CGM devices (see R 3.1 to R 3.4 on monitoring).
Grade B; BEL 4 and expert opinion of task force

Q 15: How should diabetes mellitus be managed in the hospital?

R 15.1 All hospitalized persons should have laboratory glucose testing on admission. Persons with DM or with admission hyperglycemia >140 mg/dL should have glucose monitoring during hospitalization.
Grade B; BEL 1

R 15.2 To guide inpatient therapy and inform discharge planning, clinicians should measure A1C in all persons with DM, unless their A1C is known and was tested within the previous 3 mo.
Grade B; BEL 2

R 15.3 Hospitalized persons with hyperglycemia but without known DM should have A1C measured to identify preexisting DM and inform discharge planning.
Grade B; BEL 2

Q 1: How is the diagnosis of diabetes mellitus made and what is the current screening protocol for prediabetes and diabetes?

R 15.4 Initiate bedside point-of-care (POC) capillary glucose monitoring at an appropriately chosen schedule to guide therapy for hyperglycemia during hospitalization in all persons with DM, persons without prior DM who have hyperglycemia, and persons receiving therapies with a high risk of hyperglycemia, such as corticosteroids and enteral or parenteral nutrition.
Grade A; BEL 1

R 15.5 For hospitalized persons with DM eating on a regular schedule, check POC BG before each meal and at bedtime, if clinically indicated. In hospitalized persons who are not eating (eg, NPO [nothing by mouth] or continuous feeding), initially check POC BG at least every 4 to 6 h. Additional checks may be warranted for those at higher risk of hypoglycemia. For those on intravenous (IV) insulin, POC BG should be obtained from every 30 min to every 2 h.
Grade A; BEL 1

R 15.6 Although inpatient CGM has not received regulatory approval, CGM may be useful in inpatient settings, while complying with institutional policies and safety precautions. CGM may improve detection of severe hypoglycemic and hyperglycemic events, identify glucose trends and patterns, and improve satisfaction in persons with DM.
Grade C; BEL 2

R 15.7 CGM may be considered under special regulatory allowance during the time of coronavirus disease 2019 (COVID-19) to reduce staff exposure and use of personal protective equipment and assist with glycemic monitoring of persons in the hospital setting.
Grade C; BEL 2

R 15.8 Specialized inpatient DM teams and/or CDCES, if available, should be used to improve outcomes in hospitalized persons with DM or hyperglycemia. The use of virtual consults may be considered an alternative to support hospitals lacking these services.
Grade B; BEL 1

R 15.9 For critically ill persons, IV insulin infusion is recommended to treat persistent hyperglycemia in the ICU using validated protocols that allow adjustment of insulin dose for glycemic excursions based on prespecified glucose targets. For those receiving IV insulin, POC testing should be performed every 30 to 120 min.
Grade A; BEL 1

R 15.10 A glucose target of 140 to 180 mg/dL is recommended for most critically ill persons in the hospital setting. More intensive targets between 110 to 140 mg/dL may be appropriate in select populations, particularly critically ill persons postcardiothoracic or other surgeries, while minimizing the risk of hypoglycemia.
Grade A; BEL 1

R 15.11 For most noncritically ill persons in the hospital setting, a glucose target of 140 to 180 mg/dL is recommended. For hospitalized persons who are able to achieve and maintain glycemic control without hypoglycemia, a lower target range (100 to 140 mg/dL) may be reasonable. For persons in a hospital setting with high clinical complexity, terminal illness, limited life expectancy, or high risk for hypoglycemia, less stringent targets are appropriate.
Grade B; BEL 1

R 15.12 Insulin therapy following approved protocols is recommended as the preferred therapy for managing hyperglycemia in the hospital. For noncritically ill hospitalized persons with T2D, an individualized approach is recommended for consideration of noninsulin agents alone or in combination with insulin (see also **R 15.16**).
Grade A; BEL 1

R 15.13 The insulin regimen for hospitalized persons with satisfactory meal intake should include basal, prandial, and correction doses. For those without adequate food intake, a regimen of basal, prandial, and correction doses should be used as necessary for glycemic control. Exclusive use of “sliding-scale” insulin should only be used for those whose glucoses are in the target range most of the time, and only occasionally exceed it.
Grade A; BEL 1

R 15.14 The management of hyperglycemic emergencies, including DKA and hyperosmolar state, should include fully adequate fluid resuscitation to correct fluid deficits, electrolyte replacement (potassium), and insulin therapy. Simultaneous continued infusion of insulin and dextrose solutions after correction of hyperglycemia is often required until DKA resolves to avoid hypoglycemia.
Grade A; BEL 1

R 15.15 Transition from IV insulin in the ICU to a subcutaneous insulin regimen is typically required when acidosis is resolved, and a person is no longer critically ill. A proactive regimen with scheduled subcutaneous insulin therapy, with basal, nutritional/prandial, and/or correctional doses, is recommended for most persons.
Grade A; BEL 1

R 15.16 For hospitalized persons with T2D and mild admission hyperglycemia (glucose <180 mg/dL), a personalized approach is recommended for the use of noninsulin agents alone or in combination with basal insulin, aiming for the most efficacious regimen with the lowest hypoglycemic risk. For some hospitalized persons with T2D, DPP-4 inhibitors plus correction doses

Section 1. Screening, Diagnosis, Glycemic Targets, Glycemic Monitoring

Q 1: How is the diagnosis of diabetes mellitus made and what is the current screening protocol for prediabetes and diabetes?

with rapid-acting insulin, or basal insulin plus DPP-4 inhibitors may be sufficient.
Grade A; BEL 1

R 15.17 A hospital-wide standardized plan should be in place to prevent hypoglycemia. Each hypoglycemic episode should be documented, and appropriate adjustments should be made to prevent recurrence.
Grade B; BEL 2

R 15.18 It is recommended to start discharge planning soon after hospital admission and to provide and document appropriate individualized plans for transition to an ambulatory setting and follow-up care at discharge for all persons with DM or newly diagnosed hyperglycemia.
Grade A; BEL 1

Q 16: How should diabetes mellitus in pregnancy be managed?

R 16.1 For women with GDM, the following treatment goals are recommended: preprandial glucose concentration ≤95 mg/dL and either a 1-h postmeal glucose ≤140 mg/dL or a 2-h postmeal glucose ≤120 mg/dL to decrease adverse fetal outcomes.
Grade C; BEL 4 and expert opinion of task force

R 16.2 All women with preexisting DM (T1D, T2D, or previous GDM) need access to preconception care and counseling to ensure adequate nutrition, healthy weight, and glucose control before conception, during pregnancy, and in the postpartum period.
Grade B; BEL 2

R 16.3 Rapid-acting insulin analogs (insulin-lispro, insulin-aspart) should be used to treat postprandial hyperglycemia in pregnant women.
Grade B; BEL 1

R 16.4 Options for basal insulin include long-acting insulin (eg, NPH, detemir, or glargine) or rapid-acting insulin via a CSII. Regular insulin, although not recommended as first-line therapy, is acceptable to use in managing pregnant women with DM when rapid-acting insulin analogs are not available.
Grade B; BEL 1

R 16.5 Insulin is the preferred therapeutic choice for pregnant women with GDM or T2D, but metformin has been given a category B for pregnancy with accumulating clinical evidence of metformin's safety during the first trimester and beyond. Metformin has been shown to improve pregnancy and fetal outcomes except for increased rates of infants with SGA and later onset of obesity. The prescriber should discuss the potential risks and benefits of oral agent therapy during pregnancy as well as the need for longer-term outcome studies.
Grade B; BEL 1

Section 4. Education and Other Topics

Q 17: What education interventions have been shown to be most effective in management of persons with diabetes mellitus?

R 17 Comprehensive individualized DSMES is recommended at the time of DM diagnosis and subsequently as appropriate. Therapeutic lifestyle management must be discussed with all persons with DM or prediabetes at the time of diagnosis and throughout their lifetime. This includes MNT (with reduction and modification of caloric and fat intake to achieve weight loss in those who are overweight or obese), appropriately prescribed physical activity, avoidance of tobacco products, and adequate sleep quantity and quality. Additional topics commonly taught in DSMES programs outline principles of glycemia treatment options; BGM; insulin dosage adjustments; acute complications of DM; and prevention, recognition, and treatment of hypoglycemia.
Grade A; BEL 1

Q 18: What are the key nonpharmacological components of a comprehensive diabetes care plan for children and adolescents?

R 18.1 T1D and T2D in children and adolescents should be managed in close consultation with the patient and their family members, involving school and daycare personnel whenever possible.
Grade B; BEL 2

R 18.2 It is recommended that all children and adolescents with DM should be given age and culturally appropriate education and guidance for physical activity and lifestyle modification.
Grade A; BEL 1

R 18.3 Interventions by family and/or community are recommended to improve dietary behavior and increase physical activity in efforts to prevent childhood obesity and T2D (Grade A). Game-based interventions also can be incorporated to enhance healthy lifestyle habits (Grade B).
BEL 1

Section 1. Screening, Diagnosis, Glycemic Targets, Glycemic Monitoring

Q 1: How is the diagnosis of diabetes mellitus made and what is the current screening protocol for prediabetes and diabetes?

R 18.4 Routine psychological assessment with consideration of family stressors and psychosocial factors that may impact glycemic control is recommended for all youth with DM.
Grade A; BEL 1

R 18.5 With the risk of glycemic control worsening during adolescence, coordinated, individualized, planned transition from pediatric to adult DM care is recommended for all adolescents.
Grade A; BEL 1

Q 19.1: Should persons with infertility be screened for diabetes mellitus?

R 19.1 Men and women undergoing investigation for infertility and preparation for infertility interventions, including in vitro fertilization, should be screened for DM.
Grade B; BEL 2

Q 19.2: How should persons with preexisting diabetes mellitus and infertility be evaluated?

R 19.2 For all persons with DM and possible infertility, in addition to routine endocrine evaluation, further collaborative consultation with a reproductive specialist should be considered. For women with T2D and infertility, or those with T1D who desire to preserve or estimate their fertility, anti-Müllerian hormone and midluteal progesterone levels may be assessed and screened for ovulatory dysfunction including anovulation. For men with DM and infertility, a standard semen analysis may be assessed, and an endocrine evaluation be initiated.
Grade B; BEL 2

Q 19.3: Should men with diabetes mellitus and cardiometabolic disorders be assessed for hypogonadism?

R 19.3 All men with CMD including prediabetes, metabolic syndrome, obesity, and T2D should be assessed for hypogonadism by history and physical examination; test for testosterone deficiency in persons with loss of libido and/or loss of muscle strength or mass, erectile dysfunction, osteopenia, or infertility.
Grade B; BEL 1

Q 20.1: How should persons at risk for secondary diabetes be assessed?

R 20.1 Persons with risk factors for developing secondary DM, such as postorgan transplantation, cystic fibrosis, chronic pancreatitis/postpartial pancreatectomy, or on medication associated with hyperglycemia, should be monitored routinely for IFG, IGT, and/or overt DM.
Grade A; BEL 1

Q 20.2: What are the best treatment strategies for management of secondary diabetes, such as posttransplant diabetes, cystic fibrosis–related diabetes, and other forms of secondary diabetes?

R 20.2.1 Select treatment for secondary DM based on the underlying pathophysiology. Insulin therapy is safe and effective, but alternative glucose-lowering agents may be considered in specific patient populations.
Grade A; BEL 1

R 20.2.2 DPP-4 inhibitors can be safely used to improve glycemic control for posttransplant diabetes.
Grade A; BEL 1

Q 21: What is the role of sleep medicine in the care of persons with diabetes?

R 21.1 Health care professionals should assess persons with T2D for symptoms and signs of OSA, especially in the presence of obesity or suggestive clinical features of OSA.
Grade B; BEL 2

R 21.2 Based on resources available locally, persons suspected to have OSA should be referred to an appropriate center for diagnosis and management of OSA. Grade B; BEL 4 and Expert Opinion of Task Force

R 21.3 Weight loss is recommended as the predominant intervention to improve both OSA and insulin sensitivity. In addition, devices that provide positive airway pressure as prescribed by a sleep specialist are effective.
Grade A; BEL 1

Q 22: Should screening for depression be a routine component of clinical assessment in persons with diabetes mellitus?

Section 1. Screening, Diagnosis, Glycemic Targets, Glycemic Monitoring

Q 1: How is the diagnosis of diabetes mellitus made and what is the current screening protocol for prediabetes and diabetes?

R 22 Routine screening of adults with DM for depression and DM distress is recommended during each clinic encounter, if appropriate. Referral to mental health professionals should be made as soon as possible once depression is suspected or diagnosed.
Grade A; BEL 1

Q 23: Is the evaluation of social determinants of health in persons predisposed to or with diabetes mellitus useful in improving health outcomes?

R 23 Clinicians should assess the SDOH in persons with DM to better guide them to the most appropriate resources. Interventional trials addressing SDOH and health inequities in DM are needed to evaluate reversibility of their impact.
Grade B; BEL 1

Q 24: Is telehealth/virtual care an effective care-delivery model for the management of persons with diabetes mellitus?

R 24 Offer telehealth, if available and appropriate, to persons with DM as part of their wholistic health care.
Grade A; BEL 1

Q 25: Which occupations have specific public safetyerelated diabetes management considerations?

R 25 Persons with DM who are engaged in occupations with public safety implications, such as commercial drivers and pilots, have special management requirements for certification. CGM to predict hypoglycemia in real time and pharmacotherapy that minimizes hypoglycemia are recommended as effective strategies for persons with DM who work in these occupations.
Grade A; BEL 1 and expert opinion of task force

Q 26: Is there a role for nutritional supplements in the management of diabetes and what might be the associated risks?

R 26 Nutritional supplements (ie, noncaloric oral supplements) have modest or neutral effects on glycemic control, lipids, and BP. Until proven scientifically, these supplements should not be used for managing DM or related CV risk factors among persons with DM. In view of potential harm, we recommend that persons with DM use caution and discuss with their physicians the use of unregulated nutritional supplements.
Grade A; BEL 1

Q 27: How should potential increased cancer risk be managed in persons with obesity/type 2 diabetes?

R 27.1 Clinicians should recommend age, sex, and risk-appropriate screening for common cancers, especially those associated with obesity and DM.
Grade B; BEL 2

R 27.2 With the increased risk of certain cancers in persons with obesity or DM, clinicians should educate persons regarding cancer risk and encourage a healthy lifestyle, including weight reduction.
Grade A; BEL 1

Q 28: Which vaccinations should be given to persons with diabetes mellitus?

R 28.1 AACE supports the recommendations of the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) that all persons with DM receive age-appropriate vaccinations according to the CDC/ACIP schedule (7). Immunization recommendations for adults with DM are summarized in Table 21.
Grade A; BEL 4 and expert opinion of task force

R 28.2 An annual influenza vaccine is recommended for those with DM who are ≥6 mo old.
Grade A; BEL 1

R 28.3 The 15- or 20-valent pneumococcal conjugate vaccine (PCV15 or PCV20) should be administered to all adults aged 19 to 64 y who have DM. When PCV15 is used, PPSV23 should be administered at least 12 mo following the dose of PCV15. A minimum interval of 8 wk may be used for adults with immunocompromising conditions.
Grade B; BEL 3

R 28.4 For adults over 65 who have not previously received PCV or whose vaccination history is unknown, PCV15 or PCV20 should be administered. When PCV15 is used, it should be followed by a dose of PPSV23.
Grade B; BEL 3

Section 1. Screening, Diagnosis, Glycemic Targets, Glycemic Monitoring

Q 1: How is the diagnosis of diabetes mellitus made and what is the current screening protocol for prediabetes and diabetes?	
R 28.5	It is recommended to administer hepatitis B vaccinations to all individuals as soon after diagnosis of DM as possible up to age 59 y. Grade A; BEL 1
R 28.6	Consider hepatitis B vaccination of adults ≥60 y based on assessment of risk and likelihood of an adequate immune response. Grade C; BEL 4
R 28.7	Tetanus-diphtheria-pertussis (Tdap) vaccine is typically included with routine childhood vaccinations. However, all adults with DM should receive a tetanus-diphtheria (Td) booster every 10 y. Grade C; BEL 4
R 28.8	Health care professionals may consider recommending vaccines for the following diseases for persons with T2D based on individual needs: Tdap - tetanus, diphtheria, and pertussis (whooping cough); measles/mumps/rubella; varicella (chicken pox); and polio. In addition, persons traveling to other countries may require vaccines for endemic diseases. Grade D; BEL 4, expert opinion of task force
R 28.9	Due to the increased risk for serious complications of COVID-19, persons with DM should be vaccinated against COVID-19 according to current guidelines. Grade B; BEL 2
R 28.10	Recombinant zoster vaccine is recommended for adults ≥50 y for protection against shingles according to the CDC/ACIP vaccination schedule. Grade A; BEL 1
R 28.11	Health care professionals should utilize interventions with demonstrated effectiveness in increasing vaccination rates to improve uptake of vaccination among persons with DM. Grade B; BEL 2

Table 3

Summary of Tables and Figures

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Table 2	Summary of Recommendations
Table 3	Summary of Tables and Figures
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Table 5	Risk Factors for Prediabetes and Type 2 Diabetes: Criteria for Testing for Diabetes in Asymptomatic Adults
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Table 14	Food and Drug Administrationdapproved Pharmacotherapy for Weight Loss in Persons with Adiposity-based Chronic Disease
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Supplementary	**Titles of Tables from AACE Protocol for Standardized Production of Clinical Practice Guidelines, Algorithms, and Checklists e 2017 Update Tables**
Supplementary Table 1	Table 5: Revised Logical Ranking of Scientific Methodologies (Step I: Evidence Rating)
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Endocr Pract. Author manuscript; available in PMC 2023 May 21.

Table 4

Glucose Testing and Hemoglobin A1C Interpretation

Normal	Prediabetes	Diabetes
FPG <100 mg/dL	IFG FPG ≥100 to 125 mg/dL	FPG ≥126 mg/dL
2-h PG <140 mg/dL	IGT 2-h PG ≥140 to 199 mg/dL	2-h PG ≥200 mg/dL Random PG ≥200 mg/dL + symptoms
A1C <5.5%	5.7% to 6.4% For screening of prediabetes[a]	≥6.5% Secondary[b]

Abbreviations: A1C = hemoglobin A1c; FPG = fasting plasma glucose; h = hour; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; PG = plasma glucose

[a]A1C should be used only for screening prediabetes. The diagnosis of prediabetes, which may manifest as either IFG or IGT, should be con rmed with glucose testing.

[b]Glucose criteria (ie, FPG or 2-h glucose after a 75-g oral glucose load) are preferred for the diagnosis of diabetes mellitus (DM). The same testdPG or A1C measurementd—should be repeated on a different day to confirm the diagnosis of DM. Two abnormal test results from the same sample confirm the diagnosis of DM. A glucose level ≥200 mg/dL in the presence of DM symptoms does not need to be confirmed.

Table 5

Risk Factors for Prediabetes and Type 2 Diabetes: Criteria for Testing for Diabetes Mellitus in Asymptomatic Adults[a]

Age ≥35 ywithout other risk factors
First-degree relative with diabetes
History of CVD
Overweight or obese[b]
Sedentary lifestyle
Member of an at-risk racial or ethnic group: Asian, African American, Hispanic, Native American (Alaska Natives and American Indians), or Pacific Islander
HDL-C <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
IGT, IFG, and/or metabolic syndrome
PCOS
Acanthosis nigricans
NAFLD
Hypertension (BP >140/90 mm Hg) or on therapy for hypertension
History of gestational diabetes mellitus or delivery of a baby weighing more than 4 kg (9 lb)
Antipsychotic therapy for schizophrenia and/or severe bipolar disease
Sleep disorders including OSA, chronic sleep deprivation, and night-shift occupation

Abbreviations: A1C = hemoglobin A1c; BP = blood pressure; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NAFLD = nonalcoholic fatty liver disease; OSA = obstructive sleep apnea; PCOS = polycystic ovary syndrome

[a]Source: US Preventive Services Task Force, Davidson KW, Barry MJ, et al. Screening for prediabetes and type 2 diabetes: Us preventive services task force recommendation statement. Jama. 2021;326(8):736–743. https://doi.org/10.1001/jama.2021.12531 [EL 4; NE].

[b]Testing should be considered in all adults who are obese (body mass index [BMI] ≥30 kg/m^2), and those who are overweight (BMI 25 to <30 kg/m^2 or >23 kg/m^2 in Asian Americans) and have additional risk factors.

Table 6

Glycemic Targets for Persons with Diabetes Mellitus

Parameter	Treatment goal	
Glucose		
A1C, %	Individualize on the basis of age, comorbid conditions, duration of disease; in general, ≤6.5 for most; closer to normal for healthy; less stringent for those at greater risk for hypoglycemia and/or adverse consequences from hypoglycemia; longer duration of diabetes; shorter life expectancy; comorbidities especially established vascular complications	
FPG, mg/dL	<110	
2-h PPG, mg/dL	<140	
Inpatient hyperglycemia: glucose, mg/dL	140 to 180	
Weight		
Weight loss	Reduce weight by >5% to ≥10%; avoid weight gain	
Diabetes type	**Glucose range**[a,179]	**Recommendations (% of readings)**
T1D and T2D	<54 mg/dL (<3.0 mmol/L)	<1%
	<70 mg/dL (<3.9 mmol/L)	<4%
	70 to 180 mg/dL (3.9 to 10.0 mmol/L)	>70%
	>180 mg/dL (>10.0 mmol/L)	<25%
	>250 mg/dL (>13.9 mmol/L)	<5%
Pregnancy with T1D	<54 mg/dL (<3.0 mmol/L)	<1%
	<63 mg/dL (<3.5 mmol/L)	<4%
	63 to 140 mg/dL (3.5 to 7.8 mmol/L)	>70%
	>140 mg/dL (>7.8 mmol/L)	<25%
Pregnancy with gestational or T2D	63 to 140 mg/dL (3.5 to 7.8 mmol/L)	>90%

Abbreviations: A1C = hemoglobin A1c; FPG = fasting plasma glucose; PPG = postprandial glucose; T1D = type 1 diabetes; T2D = type 2 diabetes

[a]Downloaded from CGM preferably, or other devices if CGM not available.

Table 7

Individualized Blood Pressure Goals for Persons with Type 1 or Type 2 Diabetes

Blood pressure (BP) <130/80 mm Hg is the recommended goal for persons with diabetes - BP control has a significant impact on morbidity and mortality. - BP goal may be set higher in persons with autonomic neuropathy, orthostatic hypotension, acute coronary syndrome, frailty, and medication intolerance. BP <120/70 mm Hg may be considered to limit progression of micro- and macrovascular disease in persons with the following: - Micro- or macroalbuminuria - Documented coronary heart disease (CHD) - Moderate-to-high risk for CHD - Peripheral vascular disease - Retinopathy

Table 8

Atherosclerotic Cardiovascular Disease Risk Calculators

ASCVD risk calculators (date)	Atherosclerotic cardiovascular disease risk factors											ASCVD end points*
	Age	Sex	Family history	Current tobacco use	T2D	SBP		Lipid profile (mg/dL)			Other CVD RFs	
						mmHg	Rx	TC	HDL-C	Rx[a]		
Reynolds CVD Risk Score (2007–2008)[290,291]	X	X	X	X	X[b]	X		X	X		hs-CRP	1,2,5,7
Framingham CVD Risk Score (2008–2009)[292,293]	X	X		X	X	X	X	X	X			1,2,3,4,6,7,8,9,10
ACC/AHA Pooled Cohort CVD Risk Calculator (2013)[294,295]	X[c]	X		X	X	X	X	X	X			1,2,7,8
MESA Risk Score (2015)[296]	X[d]	X	X[e]	X	X	X	X	X	X	X	CAC score	1,2,5[f]

Abbreviations: ACC/AHA = American College of Cardiology/American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcification; CHD = coronary heart disease; CVD = cardiovascular disease; hs-CRP = high-sensitivity C-reactive protein; HDL-C = high-density lipoprotein cholesterol; mm Hg = millimeters mercury; MI = myocardial infarction; RF = risk factor; Rx = treatment; SBP = systolic blood pressure; T2D = type 2 diabetes; TC = total cholesterol

*Endpoints: (1) CHD death, (2) nonfatal MI, (3) unstable angina, (4) stable angina, (5) coronary revascularization, (6) heart failure, (7) nonfatal stroke, (8) fatal stroke, (9) transient ischemic attack, (10) claudication

[a]Use of lipid-lowering therapy.

[b]Assessed by A1C value for women only, not for men.

[c]Validated for adults 40–79 years of age.

[d]Included non-Hispanic White, Hispanic, African American, and Chinese American ethnic groups.

[e]Family history of MI at any age.

[f]Also included resuscitated cardiac arrest.

Table 9

Atherosclerotic Cardiovascular Disease Risk Categories, Characteristics, Lipid Targets, and Therapy[a]

Risk categories	Risk characteristics	Approximate 10-y risk	Lipid targets	Therapy
High risk	T2D duration <10 y, T1D duration <20 y with <2 additional ASCVD risk factors; no TOD	<10%	LDL-C <100 mg/dL; apo B <90 mg/dL; non-HDL-C <130 mg/dL	Moderate-intensity statin to start, intensify as needed
Very high risk	T2D duration >10 y or T1D >20 y and age >40 y without ASCVD or severe TOD; ≥2 additional traditional ASCVD risk factors	10% to 20%	LDL-C <70 mg/dL; apo B <80 mg/dL; non-HDL-C <100 mg/dL	High-intensity statin, addition of ezetimibe or bempedoic acid to reach lipid targets
Extreme risk	T2D or T1D with established ASCVD or severe TOD: eGFR <45 mL/min/1.73 m^2; UACR >300 mg/g; ABI <0.9; left ventricular systolic or diastolic dysfunction	>20%	LDL-C <55 mg/dL; apo B <70 mg/dL; non-HDL-C <90 mg/dL	High-intensity statin, addition of ezetimibe, bempedoic acid, and/or PCSK9 agent to reach lipid targets

Abbreviations: ABI = ankle-brachial index; apo B = apolipoprotein B-100; ASCVD = atherosclerotic cardiovascular disease; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; T1D = type 1 diabetes; T2D = type 2 diabetes; TOD = target organ damage (left ventricular systolic or diastolic dysfunction, eGFR <45 mL/min/1.73 m^2, and abnormal ankle-brachial index); UACR = urine albumin-to-creatinine ratio

[a]Task force expert opinion

Table 10

Drug-Effectiveness for Low-Density Lipoprotein CholesteroleLowering Therapy

Drug	Dose			% LDL-C lowering [318,324],*	Mechanism	Potential adverse effects
Statins	Dose intensity (mg/d; po)					
	Low	Mod	High	Typical LDL-C decline basedon statin and dose intensity: Low <30% Mod 30% to 45% High ≥50%	Inhibits HMG-CoA reductase, alters intracellular cholesterol metabolism resulting in LDL-R upregulation	Myalgias, fatigue, diabetogenic effect for both new onset T2D and increase in A1C,[327,328] rare rhabdomyolysis (1–4/10,000 per year)
Simvastatin	10	20 to 40				
Pravastatin	10 to 20	40 to 80				
Lovastatin	20	40				
Fluvastatin	20 to 40	80[b]				
Pitavastatin		2 to 4 mg				
Atorvastatin		10 to 20	40 to 80			
Rosuvastatin		5 to 10	20 to 40			
Cholesterol absorption inhibitor						
Ezetimibe[329,330]	10 mg orally every day			12% to 25% as mono-Rx[(329–332)]; 25% when added to statin[330,331]	Inhibits intestinal and biliary cholesterol absorption, decreasing hepatic stores and increasing LDL-R upregulation	Myalgias, fatigue, URI symptoms, GI symptoms
Bile acid sequestrants						
Colesevelam	625 mg/tab; 3 tabs bid			8% to 16% as mono-Rx	Efficient binding of bile acids, lowering hepatic cholesterol, promoting LDL-R upregulation	GI symptoms, constipation, can bind other drugs; avoid if TG >300mg
Colestipol	1 g/tab; 2 to 6 g/d					
Cholestyramine	4 g/packet; 8 to 16 g/d					
PCSK9i	Initial dose		Max dose			
Alirocumab	75 mg sc every 2 weeks		300 mg sc every 4 weeks	48% to 58%[c]	Decreases PCSK9 levels, leading to reduced hepatic LDL-R degradation and increased expression	
Evolocumab	140 mg sc every 2 weeks		420 mg sc every 4 weeks	63% to 71%[c]		
ACL inhibitor						
Bempedoic acid[a]	180 mg orally every day			17% to 18% as mono-Rx. Further lowering when added to statin (+22%)[(333)] or ezetimibe (+13%)[(329)]	Inhibits ACLY, an upstream enzyme of HMG-CoA reductase	Myalgias, fatigue, URI symptoms, uric acid increase

Drug	Dose	% LDL-C lowering [318,324],*	Mechanism	Potential adverse effects
PCSK9 siRNA				
Inclisiran[a,334]	284 mg every 6 months sc X2, then 284 mg every 6 months sc	38% to 52%	small interfering	RNA directs breakdown of PCSK9 mRNA

Abbreviations: A1C = hemoglobin A1c; ACLY = adenosine triphosphate (ATP) citrate lyase; bid = twice a day; d = day; g = grams; GI = gastrointestinal; HMG-CoA = 3-hydroxy 3-methylglutaryl coenzyme A; IV = intravenous; LDL-C = low-density lipoprotein cholesterol; LDL-R = LDL receptor; Max = maximal; mg = milligrams; Mod = moderate; mono-Rx = monotherapy; mRNA = messenger RNA; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; RNA = ribonucleic acid; sc = subcutaneous; siRNA = small interfering RNA; T2D = type 2 diabetes; TG = triglyceride; tab = tablet; URI = upper respiratory infection

*Additional sources: Casula M, Mozzanica F, Scotti L, et al. Statin use and risk of new-onset diabetes: A meta-analysis of observational studies. *Nutr Metab Cardiovasc Dis.* 2017;27(5):396–406. doi: 10.1016/j.numecd.2017.03.001 [EL 2; MNRCT]; Mansi IA, Chansard M, Lingvay I, Zhang S, Halm EA, Alvarez CA. Association of statin therapy initiation with diabetes progression: A retrospective matched-cohort study. *JAMA Intern Med.* 2021;181(12):1562–1574. doi: 10.1001/jamainternmed.2021.5714 [EL 2; CS]; Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *Eur J Prev Cardiol.* 2020;27(6):593–603. doi: 10.1177/2047487319864671 [EL 1; RCT]; Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med.* 2015;372(25):2387–2397. doi: 10.1056/NEJMoa1410489 [EL 1; RCT]; Wu NQ, Guo YL, Zhu CG, et al. Comparison of statin plus ezetimibe with double-dose statin on lipid profiles and inflammation markers. *Lipids Health Dis.* 2018;17(1):265. doi: 10.1186/s12944–018-0909-z [EL 1; RCT]; Ouchi Y, Sasaki J, Arai H, et al. Ezetimibe lipid-lowering trial on prevention of atherosclerotic cardiovascular disease in 75 or older (ewtopia 75): A randomized, controlled trial. *Circulation.* 2019;140(12):992–1003. doi: 10.1161/circulationaha.118.039415 [EL 1; RCT]; Lalwani ND, Hanselman JC, MacDougall DE, Sterling LR, Cramer CT. Complementary low-density lipoprotein-cholesterol lowering and pharmacokinetics of adding bempedoic acid (ETC-1002) to high-dose atorvastatin background therapy in hypercholesterolemic patients: A randomized placebo-controlled trial. *J Clin Lipidol.* 2019;13(4):568–579. doi: 10.1016/j.jacl.2019.05.003 [EL 1; RCT]; US Food & Drug Administration (FDA). Inclisiran prescribing information/package insert. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214012lbl.pdf Accessed February 19, 2022.[EL 4; NE].

[a]Food and Drug Administration-approved for use in persons with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease who are taking maximally tolerated statin dose and require additional LDL-C lowering.

[b]40 mg bid or XL-80 mg

[c]In combination with statin therapy

Table 11

Relationship Among Categories for Albuminuria and Proteinuria (KDIGO Work Group 2013 [EL 4; NE])[a,b]

Categories			
Measure	**Normal to mildly increased (A1)**	**Moderately increased (A2)**	**Severely increased (A3)**
AER (mg/24 h)	<30	30–300	>300
PER (mg/24 h)	<150	150–500	>500
ACR (mg/mmol) (mg/g)	<3 <30	3–30 30–300	>30 >300
PCR (mg/mmol) (mg/g)	<15 <150	15–50 150–500	>50 >500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

Abbreviations: ACR = albumin-to-creatinine ratio; AER = albumin excretion rate; PCR = protein-to-creatinine ratio; PER = protein excretion rate.

[a]Reprinted with permission from Macmillan Publishers Ltd: Kidney Disease: Improving Global Outcomes CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013;3:1–150. [EL 4; NE]

[b]Albuminuria and proteinuria can be measured using excretion rates in timed urine collections, ratio of concentrations to creatinine concentration in spot urine samples and using reagent strips in spot urine samples. Relationships among measurement methods within a category are not exact. For example, the relationships between AER and ACR and between PER and PCR are based on the assumption that average creatinine excretion rate is approximately 1.0 g/d or 10 mmol/d. The conversions are rounded for pragmatic reasons. (For an exact conversion from mg/g of creatinine to mg/mmol of creatinine, multiply by 0.113.) Creatinine excretion varies with age, sex, race, and diet; therefore, the relationship among these categories is approximate only. ACR <10 mg/g (<1 mg/mmol) is considered “normal”; ACR 10 to 30 mg/g (1 to 3 mg/mmol) is considered “high normal.” ACR >2200 mg/g (>220 mg/mmol) is considered “nephrotic range.” The relationship between urine reagent strip results and other measures depends on urine concentration.

Table 12

Mitigation of Side Effects for Newer Agents to Treat Diabetic Kidney Disease

Side effects	Mitigation strategies
SGLT2 inhibitors	
Genital mycotic infections Volume depletion	○ Hygiene, topical antifungals ○ Proactive dose reduction of diuretics in persons at risk for hypovolemia ○ Hold SGLT2is during GI illness (nausea, vomiting, diarrhea) ○ Improve glucose control to reduce glucosuria
Ketoacidosis	○ Educate persons with DM on early recognition ○ “STOP DKA” protocol (stop SGLT2i, test for ketones, maintain fluid and carbohydrate intake, use maintenance and supplemental insulin)
Hypoglycemia	○ Adjustment of background antihyperglycemic agents
GLP-1 receptor agonists	
Nausea/vomiting/diarrhea	○ Patient education on tolerability and symptom recognition ○ Start at lowest dose and titrate slowly
Hypoglycemia	○ Adjustment of background antihyperglycemic agents
Finerenone	
Hyperkalemia	○ Dietary restriction of potassium ○ Thiazide or loop diuretics ○ SGLT2i ○ Potassium-binding agents (patiromer or sodium zirconium cyclosilicate)

Abbreviations: DM = diabetes mellitus; GI = gastrointestinal; GLP-1 = glucagon-like peptide 1; SGLT2i = sodium-glucose cotransporter 2 inhibitor

Table 13

Clinical Symptoms and Signs of Diabetic Peripheral Neuropathy

	Large myelinated nerve fibers	Small nerve fibers
Symptoms	Numbness Tingling Poor balance	Pain: Burning Electric shocks Stabbing pain Hyperalgesia Allodynia
Function	Pressure, balance	Nociception; protective sensation
Examination (clinically diagnostic)[a]	Ankle reflexes Reduced Abolished Vibration perception[a] Reduced Absent 10-g monofilament[a] Reduced Absent Proprioception impaired	Thermal (cold/hot) discrimination[a] Reduced Absent Pinprick sensation[a] Reduced Absent

[a]Document impairment/loss in symmetrical, distal to proximal pattern

Table 14

Food and Drug Administrationeapproved Pharmacotherapy for Weight Loss in Persons with Adiposity-based Chronic Disease

Weight-loss medication	Dose; escalate as tolerated	Mechanism	Potential side effects	Warnings and contraindications[a]
Approved for short-term therapy (≤3 mo)				
Phentermine	Low-dose 15 mg every day; maximum dose 37.5 mg every day (by mouth)[b]	Sympathomimetic amine (decreases appetite); stimulates CNS activity	Restlessness, insomnia, headache, dry mouth, tachycardia, BP elevation	Pregnancy, active coronary artery disease, uncontrolled hypertension, hyperthyroidism, agitated states
Approved for chronic management of obesity				
Orlistat	Treatment dose 120 mg three times a day (by mouth with meals)	Gastrointestinal lipase inhibitor (decreased fat absorption)	Fat malabsorption, flatulence, fecal urgency, oily stools	Pregnancy, fat-soluble vitamin and drug malabsorption (do not use in organ transplant), renal oxalate stones, cholestasis
Phentermine/ Topiramate-ER	Starting dose 3.75 mg/23 mg every day; treatment dose 7.5 mg/46 mg every day; maximum dose 15 mg/92 mg every day (by mouth)	Sympathomimetic amine (decreases appetite)/anticonvulsant, carbonic anhydrase inhibitor, gabaminergic (increases satiety)	Restlessness, insomnia, headache, dry mouth, tachycardia, BP elevation, paresthesia, dysgeusia, mood changes, mental clouding, blurred vision	Pregnancy, glaucoma, hyperthyroidism, metabolic acidosis, urolithiasis
Naltrexone-ER/ Bupropion-ER	8 mg/90 mg tablets; starting dose one tablet every day; treatment dose 2 tablets twice a day (by mouth)	Opioid receptor antagonist (decreases cravings)/dopamine-norepinephrine reuptake inhibitor (decreases appetite)	Nausea, vomiting, diarrhea, constipation, headache, fatigue, insomnia, agitation, mood changes, dry mouth, blurred vison	Pregnancy, seizure risk, uncontrolled hypertension, chronic opioid use
Liraglutide 3 mg	Starting dose 0.6 mg/d; maximum dose 3 mg/d (subcutaneous injection)	Glucagon-like peptide-1 receptor agonist (decreases appetite and delays gastric emptying)	Nausea, vomiting, diarrhea, constipation, headache, fatigue	Pregnancy, medullary thyroid cancer, MEN type 2, tachycardia, acute pancreatitis, acute gallbladder disease
Semaglutide 2.4 mg	Starting dose 0.25 mg/wk; maximum dose 2.4 mg/wk (subcutaneous injection)	Glucagon-like peptide-1 receptor agonist (decreases appetite and delays gastric emptying)	Nausea, vomiting, diarrhea, constipation, headache, fatigue	Pregnancy, medullary thyroid cancer, MEN type 2, tachycardia, acute pancreatitis, acute gallbladder disease, diabetic retinopathy

Abbreviations: BP = blood pressure; CNS = central nervous system; ER = extended release; MEN = multiple endocrine neoplasia.

[a]Weight-loss drugs should not be used during pregnancy, if planning to become pregnant, and during breastfeeding.

[b]15 mg / 30 mg / 37.5 mg phentermine hydrochloride = 12 mg / 24 mg / 30 mg phentermine resin, respectively.

Table 15

Recommended Meal Patterns for Persons with Diabetes Mellitus

Meal pattern	Macronutrient characteristics	Outcome evidence in diabetes (see text)	Comments
Mediterranean[694,695,697–700,724–726,814,815,821,925,926]	Uses olive oil as the principal source of dietary fat; fish and other seafood; vegetables, nuts, fruits, beans; whole grains; moderate dairy products; red meat on occasion; wine with meals; limited sweets	Reduces risk of DM; lowers A1C, BP, and triglycerides; improves hepatic steatosis; primary and secondary prevention of major CVD events and mortality	Only meal pattern with RCTs showing long-term benefits regarding CVD events and mortality
Low fat[678,690,701–704,827,927,928]	Emphasizes vegetables, fruits, starches (eg, breads, pasta, whole grains, starchy vegetables), lean protein sources, and low-fat dairy products. Defined here as total fat intake ≤30% of total calories and saturated fat intake ≤10%	As part of a structured lifestyle intervention, reduces risk of DM and reduces A1C, BP, triglycerides in T2D	No long-term safety data
Low carbohydrate[702–704,707–714,926,929,930]	Often defined as a reduction in carbohydrates to 26% to 45% of total calories. Emphasizes (i) vegetables low in carbohydrate content, (ii) meat, poultry, fish, shellfish, eggs, cheese, nuts, (iii) oils, butter, and avocado. Avoids foods high in starch and sugars such as pasta, rice, potatoes, bread, and some fruits	Reduces A1C, body weight, BP, and triglycerides, and increases HDL-C in T2D	No long-term safety data. When compared with low-fat diet, there are greater benefits early (3–6 mo) followed by equilibration at 1–2 y.
Very low carbohydrate[705,706]	Often defined as limiting nonfiber carbohydrate to 20 to 50 grams/d in order to induce ketosis, resulting in > 50% of calories from fat. Otherwise, similar to low carbohydrate		
Vegetarian/vegan[722–726,837,839,937,938]	Vegetarian: plant-based diets devoid of all flesh foods but including egg (ovo) and/or dairy (lactose) products. Vegan: eliminates all flesh foods and animal-derived products.	Reduces risk of DM; lowers A1C; weight loss; lowers LDL-C and non–HDL-C	No long-term safety data; may require supplementation of vitamins and minerals
Dietary Approaches to Stop Hypertension (DASH)[727–729]	Limitations in sodium and adequate potassium; whole grains, vegetables, fruits; low-fat dairy products; poultry, fish; limits on saturated fat, red meat; limit sweets, and sugar-containing beverages.	Reduces risk of DM; reduces glycemia, BP, and lipids in DM	No long-term safety data

Abbreviations: A1C = hemoglobin A1c; BP = blood pressure; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; RCT = randomized controlled trial; T2D = type 2 diabetes

Table 16

Profiles of Antihyperglycemic Medications

	Antihyperglycemic efficacy (as monotherapy)[c]	Hypoglycemia (as monotherapy)[e]	Weight	ASCVD events	HF	Effect on CKD worsening/other issues in presence of CKD	GI S/S
METFORMIN	++	Low risk	Neutral/ slight loss	Neutral/slight benefit	Neutral	Neutral/contraindicated if eGFR <30 mL/min/ 1.73 m^2; should not be initiated if eGFR <45 mL/min/1.73 m^2. But once started, can continue to be used if stable eGFR >30 mL/min/ 1.73 m^2, although reduction in dose is prudent if eGFR between 30 and 45 mL/min/1.73 m^2.	Moderate
GLP-1 RA	+++	Low risk	Loss	Demonstrated benefit reducing risk of MACE (dulaglutide; liraglutide; semaglutide SQ); Demonstrated reduced risk for stroke with semaglutide and dulaglutide	Neutral	Renal benefit demonstrated in CVOTs (dulaglutide, liraglutide, SQ semaglutide) largely due to decreased albuminuria; Worsening kidney function or AKI can occur in presence of volume depletion due to severe adverse GI S/S. Exenatide not recommended if eGFR below 45 mL/min/1.73 m^2 or ESKD or if CrCl <30 mL/min	Moderate
DUAL GIP/GLP-1 RA	+++	Low risk	Loss	CVOT being conducted	Neutral	One exploratory analysis showed slowing of eGFR decline in those with T2D and increased CV risk; Worsening kidney function or AKI can occur in presence of volume depletion due to severe adverse GI S/S	Moderate
SGLT2i	++	Low risk	Loss	Demonstrated benefit reducing risk of MACE (empagliflozin; canagliflozin); empagliflozin demonstrated benefit reducing risk of CV death and all-cause mortality	Demonstrated benefit reducing risk of HHF (see legend[a])	Demonstrated benefit reducing risk for CKD progression (see legend[b])	Neutral
DPP-4i	+	Low risk	Neutral	Noninferior to placebo	CVOT showed increased risk for HHF with saxagliptin; alogliptin should be used with caution in patients with CHF of NYHA	Neutral/all but linagliptin require dose adjustment if decreased kidney function.	Neutral

	Antihyperglycemic efficacy (as monotherapy)[c]	Hypoglycemia (as monotherapy)[e]	Weight	ASCVD events	HF	Effect on CKD worsening/other issues in presence of CKD	GI S/S
					functional classes III and IV.		
AGI	+	Low risk	Neutral	Neutral	Neutral	Neutral/not recommended if serum creatinine >2.0 mg/dL	Moderate
TZD	++	Low risk	Gain	Potential reduced risk of MACE/stroke (pioglitazone)	Increased risk secondary to fluid retention[d]	Neutral/potential for increased fluid accumulation	Neutral
SU/GLINIDE	++/+	Moderate-to-severe/ mild-to-moderate increased risk for both with CKD	Gain	Neutral	Neutral	Neutral/increased risk of hypoglycemia	Neutral
COLSVL	+	Low risk	Neutral	Lowers LDL-C; Can increase TG levels; Contraindicated if serum TG >500 mg/dL or if history of hypertriglyceridemia-induced pancreatitis	Neutral	Neutral	Mild to Moderate
BCR-QR	+	Low risk	Neutral	No increased risk	Neutral	Neutral	Moderate
INSULIN (basal/ basal bolus)	+++/++++	Moderate-to-severe increased risk with CKD	Gain	Neutral	Monitor for fluid retention	Neutral/increased risk of hypoglycemia	Neutral
PRAMLINTIDE	+	Increased risk because indicated in those with T1D and T2D using mealtime insulin	Modest loss	Neutral	Neutral	Neutral	Moderate

Abbreviations: AGI = alpha-glucosidase inhibitors; AKI = acute kidney injury; ASCVD = atherosclerotic cardiovascular disease; BCR-QR = bromocriptine quick release; CHF = congestive heart failure; CKD = chronic kidney disease; COLSVL = colesevelam; CrCl = creatinine clearance; CV = cardiovascular; CVD = CV disease; CVOT = CV outcome trial; DPP-4i = dipeptidyl peptidase 4 inhibitor; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; GFR = glomerular filtration rate; GI = gastrointestinal; GIP = glucose-dependent insulinotropic polypeptides; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HDL-C = high-density lipoprotein cholesterol; HF = heart failure; HHF = hospitalization for heart failure; HFrEF = heart failure with reduced ejection fraction; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; S/S = signs & symptoms; SGLT2i = sodium glucose cotransporter 2 inhibitor; SU = sulfonylurea; T1D = type 1 diabetes; T2D = type 2 diabetes; TG = triglyceride; TZD = thiazolidinedione Disclaimer: The designated row of a medication class does not imply or indicate any preference or hierarchy. In addition, prescribers should always refer to the most recent published prescribing information for medications as well as consideration of local resources and individual patient circumstances. The evidence base content in the guideline has much more comprehensive information about antihyperglycemic medications including potential adverse events and how to reduce their risk and/or treat them.

[a]Decreased HHF was seen in CVOTs with canagliflozin, empagliflozin, dapagliflozin, and ertugliflozin. Some subsequent studies had HF as primary outcomes and led to dapagliflozin receiving an indication to reduce risk of HHF in adults with T2D and either established CVD or multiple CV risk factors AND to reduce risk of CV death and HHF in adults (with or without T2D) with HFrEF

(NYHA classes II-IV). Empagliflozin has indication to reduce the risk of CV death in adult patients with T2D and established CV disease AND to reduce the risk of CV death and HHF in adults (with or without T2D) with HF (not limited to HFrEF). Because of recent publication of the Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER) trial,[1054a] it is likely that the dapagliflozin HF indication will lose the limitation to HFrEF.

[b]Canagliflozin has indication to reduce risk of ESKD, doubling of serum creatinine, CV death, in adults with T2D and diabetic nephropathy with albuminuria; HHF in those with a history of HF. Dapagliflozin has indication to reduce the risk of sustained eGFR decline, ESKD, CV death, in adults with CKD at risk of progression and HHF in those with history of HF. The EMPA-KIDNEY trial has been stopped early due to evidence of efficacy.

[c]Efficacy dependent on baseline A1C and duration of diabetes.

[d]TZDs are contraindicated in persons with NYHA Class III/IV CHF.

[e]Agents with “low risk” for hypoglycemia may have that risk increased when combined with antihyperglycemic agents that themselves can cause hypoglycemia. The latter agents may need to have a lower dose in order to reduce hypoglycemia risk.

Table 17

Recommended Steps for the Addition of Insulin to Antihyperglycemic Therapy

Glucose value	Total daily dose	Notes/caveats
Step 1. Start basal (long-acting insulin)		
A1C <8%	0.1 to 0.2 units/kg	Consider discontinuing SU therapy; basal analogs preferred over NPH; bedtime dose preferred
A1C >8%	0.2 to 0.3 units/kg	
Step 2. Titrate basal insulin every 2–3 d to reach glycemic goals [a]		
Fixed regimen	Increase by 2 units/d	
Adjustable regimen		
FBG >180 mg/dL	Add 4 units	
FBG 140 to 180 mg/dL	Add 2 units	
FBG 110 to 139 mg/dL	Add 1 unit	
Step 3. Monitor for hypoglycemia		
BG <70 mg/dL	Reduce by 10% to 20%	
BG <40 mg/dL	Reduce by 20% to 40%	

Abbreviations: A1C = hemoglobin A1c; BG = blood glucose; d = day; FBG = fasting blood glucose; NPH = Neutral Protamine Hagedorn; SU = sulfonylurea.

[a]For most persons with T2D taking insulin, glucose goals are A1C <7% and fasting and premeal blood glucose <110 mg/dL in the absence of hypoglycemia. A1C and FBG targets may be adjusted based on a person's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk.

Table 18

Recommended Steps for the Intensification of Insulin Therapy When Prandial Control Is Needed

Therapeutic option	Insulin dose	Notes/caveats
Step 1. Add prandial therapy: Begin with Step 1A for T2D and Step 1B for T1D		
Step 1A: GLP-1 RA, SGLT2 inhibitor, or DPP-4 inhibitor		If glucose goals remain unmet, add prandial insulin
Step 1B: Prandial insulin	TDD 0.3 to 0.5 units/kg (50% basal; 50% prandial)	Basal + prandial insulin analogs preferred over (NPH + regular insulin) or premixed insulin
Step 2. Monitor for hyperglycemia; Titrate insulin every 2–3 days to reach glycemic goals[a]		
Fixed regimen	Increase TDD by 2 units/d	
Adjustable regimen		
Elevated fasting BG	Increase HS basal doses	Increase dose by 10% to 20% depending on severity of BG elevation
Elevated premidday meal BG	Increase breakfast prandial insulin doses	
Elevated pre-evening meal BG	Increase midday prandial insulin dose	
Elevated bedtime BG	Increase dinner prandial insulin dose	
Premixed insulin		
FBG/premeal BG >180 mg/dL	Increase AM or PM dose depending on times of BG elevation	Increase dose by 10% to 20% depending on severity of BG elevation
Step 3. Monitor for hypoglycemia		
Adjustable regimen		
Low fasting BG	Reduce HS basal dose	Decrease dose by 10% to 20% depending on severity of hypoglycemia
Low premidday meal BG	Reduce breakfast prandial dose	
Low pre-evening meal BG	Reduce midday prandial dose	
Low bedtime BG	Reduce evening prandial dose	
Premixed insulin		
Low BGs in AM or PM	Reduce AM or PM dose depending on times of BG elevation	Reduce dose by 10% to 20% depending on severity of BG elevation

Abbreviations: A1C = hemoglobin A1c; AM = morning; BG = blood glucose; DPP-4 = dipeptidyl peptidase 4; FBG = fasting blood glucose; GLP-1 RA = glucagon-like peptide 1 receptor agonist; HS = at bedtime; NPH = Neutral Protamine Hagedorn; PM = evening; PPG = postprandial glucose; SGLT2 = sodium glucose cotransporter 2; T1D = type 1 diabetes; T2D = type 2 diabetes; TDD = total daily dose

[a]For most persons with T2D taking insulin, glucose goals are A1C <7% and fasting and premeal blood glucose <110 mg/dL in the absence of hypoglycemia. A1C and FBG targets may be adjusted based on a person's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk.

Table 19

Types of Insulin

	Onset	Peak	Duration
Basal insulins			
Intermediate-acting human (cloudy)			
Neutral Protamine Hagedorn (human)	1–3 h	5–8 h	Up to 18 h
Long-acting (clear) analogs			
Detemir	1.5 h	near peakless	16–24 h
Glargine U100[a]	1.5–2 h	near peakless	24 h
Glargine U300	6 h	peakless	>30 h
Degludec U100	1 h	peakless	42 h
Degludec U200	1 h	peakless	42 h
Prandial insulins			
Short-acting human			
Regular	30–60 min	2–4 h	5–8 h
Rapid-acting analogs			
Aspart	15 min	1–1.5 h	3–5 h
Glulisine	12–30 min	1–1.5 h	3.5–5 h
Lispro[b] (U100 and U200)	15–30 min	1–2 h	3–4.75 h
Faster-acting analogs			
Faster aspart	4 min	0.5–1.5 h	3–5 h
Lispro aabc	15–17 min	≈ 2 h	4.6–7.3 h
Inhaled technosphere insulin	≈ 12 min	0.5–1 h	1.5–3 h
Premixed Insulins (cloudy)			
70/30 NPH/Regular 70/30, 60/40, 50/50 N/R 70/30 aspart protamine/ aspart	These insulins contain a fixed ratio of intermediate-acting insulin and short- or rapid-acting insulin. These suspensions must be resuspended uniformly for more consistent glucose lowering. The timing and adjustment of these insulins depend on glucose levels and the individual kinetics of the insulin components.		

	Onset	Peak	Duration
75/25 lispro protamine/ lispro			
50/50 lispro protamine/ lispro			

Biosimilars are follow-on biologics which have been approved via the Public Health Service Act. Biosimilar designation allows the drugs to be interchangeable with the reference drug and are approved by the US Food and Drug Administration (FDA) to allow pharmacists to substitute without the need for an authorized prescription.

Clinicians should refer to the FDAdapproved prescribing information for the most current official product information on any of the insulins.

Degludec

Flexible dosing with at least 8 to 40 hours between injections was not associated with increased hypo- or hyperglycemia. Source: Mathieu C, Hollander P, Miranda-Palma B, et al. NN1250–3770 (BEGIN: Flex T1) Trial Investigators. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. J Clin Endocrinol Metab. 2013;98(3):1154–1162 [EL 1; RCT].

Similar glycemic variability parameters, but better continuous glucose monitoring metrics (time in range, time above range, time below range) compared with glargine U300.[1148]

Detemir

Up to 40% to 50% of persons may require twice daily dosing (with 12 hours after the morning dose). Sources: Dornhorst A, Lüddeke HJ, Sreenan S, Koenen C, Hansen JB, Tsur A, Landstedt-Hallin L, et al. Safety and efficacy of insulin detemir in clinical practice: 14-week follow-up data from type 1 and type 2 diabetes patients in the PREDICTIVE European cohort. Int J Clin Pract. 2007;61(3):523–528 [EL 2; PCS]; and Heller S, Koenen C, Bode B, et al. Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial. Clin Ther. 2009;31(10):2086–2097 [EL 1; RCT].

Glargine U300

Persons with type 1 diabetes may require ~15% to 30% higher dose compared with glargine U100. Source: Porcellati F, Bolli GB, Fanelli CG. Pharmacokinetics and pharmacodynamics of basal insulins. Diabetes Technol Ther. 2011;13 Suppl 1:S15–S24 [EL 4; NE].

Prandial insulins

Based on onset of action, insulin should be taken at appropriate time to match the postprandial glucose absorption. All can be used in insulin pumps with preference given to rapid-acting insulins. Source: Bode B, Weinstein R, Bell D, McGill J, Nadeau D, Raskin P, Davidson J, Henry R, Huang WC, Reinhardt RR. Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: A randomized study in type 1 diabetes. Diabetes Care. 2002;25(3):439–444 [EL 1; RCT].

[a] Glargine available as branded, U100 biosimilar (2 preparations) or U100 follow-on biologic (single preparation)

[b] Lispro available as branded, or a follow-on biologic (U-100)

Table 20

Glucagon Preparations for Treatment of Severe Hypoglycemia

	Ready to use	Nasal	Injection	Stability
Glucagon nasal powder	✓	✓		Can be stored at temperature up to 86 °F
Dasiglucagon	✓		✓	0.6 mg e shelf life is 12 mo at room temperature from date of removal from refrigeration *
Glucagon prefilled syringe (Pen)	✓		✓	1 mg ** e 30 mo at room temperature 20–25 °C
Glucagon emergency kit	Reconstitution required		✓ 4 manufacturers	Can be stored at room temperature from 18 to 36 mo, depending on manufacturer

The most common side effects of glucagon administration are nausea; vomiting; headache; runny nose; discomfort in nose; stuffy nose; redness in eyes; itchy nose, throat, and eyes; watery eyes

Refer to the full prescribing information for any prescribed glucagon formulation for the most current, US Food and Drug Administrationeapproved information.

* Do not return product to refrigerator after storing at room temperature.

** Dose for pediatric patients aged 2 to under 12 years of age who weigh <45 kg is 0.5 mg.

Table 21

Vaccine Recommendations for Adults with Diabetes Mellitus[a]

Vaccine	Recommendation	Grade and best evidence level
Age-appropriate vaccines	All persons should receive according to the CDC/ACIP immunization schedules: https://www.cdc.gov/vaccines/schedules/index.html.	A 4
Influenza IIV4 or RIV4 or LAIV	Annually	A 1
Pneumococcal PCV15 and PCV20 Age, 19–64 y	PCV15 or PCV20 for all adults aged 19 to 64 y who have underlying medical conditions, including DM. When PCV15 is used, PPSV23 should be administered at least 12 months following the dose of PCV15. A minimum interval of 8 weeks may be used for adults with immunocompromising conditions.	B 3
Pneumococcal PCV15 and PCV20 Ages ≥65 y	For adults over age 65 y who have not previously received PCV or whose vaccination history is unknown, PCV15 or PCV20 should be administered. When PCV15 is used, it should be followed by a dose of PPSV23.	B 3
Hepatitis B	All adults aged ≤59 y	A 1
HepB	Based on risk and quality of immune response for adults aged ≥60 y	C4
Tetanus, diphtheria, acellular pertussis Tdap	Every 10 y following completion of the primary series	C 4
COVID-19	All persons per FDA approval or emergency use authorization	B 2
Varicella RZV	All adults aged ≥50 y	A 1

Abbreviations: ACIP = Advisory Committee on Immunization Practices; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; DM = diabetes mellitus; FDA = Food and Drug Administration; IIV4 = quadrivalent inactivated influenza vaccine; LAIV = live, attenuated influenza vaccine; PCV15 and PCV20 = pneumococcal conjugate vaccines; PPSV23 = pneumococcal polysaccharide vaccine; RIV4 = quadrivalent recombinant influenza vaccine; RZV = recombinant zoster vaccine.

[a]For child/adolescent specic immunization recommendations, refer to the CDC Immunization Schedules: https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html