AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY – CLINICAL PRACTICE GUIDELINES FOR DEVELOPING A DIABETES MELLITUS COMPREHENSIVE CARE PLAN – 2015

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The American Association of Clinical Endocrinologists/American College of Endocrinology Medical Guidelines for Clinical Practice are systematically developed statements to assist healthcare professionals in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

AACE TASK FORCE FOR DEVELOPING A DIABETES COMPREHENSIVE CARE PLAN WRITING COMMITTEE

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Abbreviations:
A1C = hemoglobin A1c; **AACE** = American Association of Clinical Endocrinologists; **ACCORD** = Action to Control Cardiovascular Risk in Diabetes; **ACE** = angiotensin-converting enzyme; **ADA** = American Diabetes Association; **ADVANCE** = Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; **AER** = albumin excretion rate; **ApoB** = apolipoprotein B; **ARB** = angiotensin II receptor blocker; **ASCVD** = atherosclerotic cardiovascular disease; **BEL** = best evidence level; **BMI** = body mass index; **CDC** = Centers for Disease Control and Prevention; **CDE** = certified diabetes educator; **CGM** = continuous glucose monitoring; **CKD** = chronic kidney disease; **CPAP** = continuous positive airway pressure; **CPG** = clinical practice guideline; **CSII** = continuous subcutaneous insulin infusion; **CVD** = cardiovascular disease; **DCCT** = Diabetes Control and Complications; **DKA** = diabetic ketoacidosis; **DM** = diabetes mellitus; **DPP** = Diabetes Prevention Program; **DPP-4** = dipeptidyl peptidase 4; **DSME** = diabetes self-management education; **DSPN** = distal symmetric polyneuropathy; **EL** = evidence level; **ESRD** = end-stage renal disease; **FDA** = U.S. Food and Drug Administration; **FPG** = fasting plasma glucose; **GDM** = gestational diabetes mellitus; **GFR** = glomerular filtration rate; **GI** = gastrointestinal; **GLP-1** = glucagon-like peptide 1; **HBV** = hepatitis B virus; **HDL-C** = high-density lipoprotein cholesterol; **HR** = hazard ratio; **ICU** = intensive care unit; **IFG** = impaired fasting glucose; **IGT** = impaired glucose tolerance; **ISF** = insulin sensitivity factor; **LDL-C** = low-density lipoprotein cholesterol; **LDL-P** = low-density lipoprotein particles; **Look AHEAD** = Look Action for Health in Diabetes; **MDI** = multiple daily injections; **MNT** = medical nutrition therapy; **NPH** = neutral protamine Hagedorn; **OGTT** = oral glucose tolerance test; **OSA** = obstructive sleep apnea; **PG** = plasma glucose; **POC** = point-of-care; **PPG** = postprandial glucose; **PTH** = parathyroid hormone; **Q** = clinical question; **R** = recommendation; **RAAS** = renin-angiotensin-aldosterone system; **RCT** = randomized controlled trial; **SFN** = small-fiber neuropathy; **SGLT2** = sodium glucose cotransporter 2; **SMBG** = self-monitoring of blood glucose; **T1D** = type 1 diabetes; **T2D** = type 2 diabetes; **TZD** = thiazolidinedione; **UKPDS** = United Kingdom Prospective Diabetes Study; **VADT** = Veterans Affairs Diabetes Trial

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1. INTRODUCTION

These 2015 clinical practice guidelines (CPGs) for developing a diabetes mellitus (DM) comprehensive care plan are an update of the 2011 American Association of Clinical Endocrinologists (AACE) Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (1 [EL 4; NE]). The mandate for this CPG is to provide a practical guide for comprehensive care that incorporates an integrated consideration of

micro- and macrovascular risk (including cardiovascular risk factors such as lipids, hypertension, and coagulation) rather than an isolated approach focusing merely on glycemic control. In addition to topics covered in the 2011 CPG, this update offers new and expanded information on vaccinations; cancer risk; and management of obesity, sleep disorders, and depression among persons with DM, as well as medical management of commercial vehicle operators and others with occupations that put them at increased risks of obesity and DM or in which hypoglycemia might endanger other individuals. In addition, discussions of hypertension management, nephropathy management, hypoglycemia, and antihyperglycemic therapy have been substantially revised and updated. The 2015 treatment goals emphasize individualized targets for weight loss, glucose, lipid, and hypertension management. In addition, the 2015 Guidelines promote personalized management plans with a special focus on safety beyond efficacy.

When a routine consultation is made for DM management, these new guidelines advocate taking a comprehensive approach and suggest that the clinician should move beyond a simple focus on glycemic control. This comprehensive approach is based on the evidence that although glycemic control parameters (hemoglobin A1c [A1C], postprandial glucose [PPG] excursions, fasting plasma glucose [FPG], glycemic variability) have an impact on the risk of microvascular complications and cardiovascular disease (CVD), mortality, and quality of life, other factors also affect clinical outcomes in persons with DM.

The objectives of this CPG are to provide the following:

- An education resource for the development of a comprehensive care plan for clinical endocrinologists and other clinicians who care for patients with DM.
- An evidence-based resource addressing specific problems in DM care.
- A document that can eventually be electronically implemented in clinical practices to assist with decision-making for patients with DM.

To achieve these goals, this CPG includes an executive summary consisting of 67 clinical practice recommendations organized within 24 questions covering the spectrum of DM management. The recommendations provide brief, accurate answers to each question, and an extensively referenced appendix organized according to the same list of questions provides supporting evidence for each recommendation. The format is concise and does not attempt to present an encyclopedic citation of all pertinent primary references, which would create redundancy and overlap with other published CPGs and evidence-based reports related to DM. Therefore, although many highest evidence level (EL) studies—consisting of randomized controlled trials (RCTs) and meta-analyses of these trials (EL 1)—are cited in this CPG, in the interest of conciseness, there is also a deliberate, preferential, and frequent citation of derivative EL 4 publications that include many primary evidence citations (EL 1, EL 2, and EL 3). Thus, this CPG is not intended to serve as a DM textbook but rather to complement existing texts as well as other DM CPGs available in the literature including previously published AACE DM CPGs.

2. METHODS

The AACE Board of Directors mandated an update of the 2011 AACE DM CPG (1 [EL 4; NE]), which expired in 2014. Selection of the cochairs, primary writers, and reviewers, as well as the logistics for creating this evidence-based CPG were conducted in strict adherence with the AACE Protocol for Standardized Production of Clinical Practice Guidelines—2010 and 2014 Updates (2 [EL 4; CPG NE; see Fig. 1; Tables 1-4]; 3 [EL 4; CPG NE; see Tables 1-4]).

All primary writers are AACE members and credentialed experts in the field of DM care. This CPG has been reviewed and approved by the primary writers, other invited experts, the AACE Publications Committee, and the AACE Board of Directors before submission for peer review by *Endocrine Practice*. All primary writers made disclosures regarding multiplicities of interests and attested that they are not employed by industry.

Reference citations in the text of this document include the reference number, numerical descriptor (e.g., EL 1, 2, 3, or 4), and semantic descriptor (Table 1). Recommendations are based on the quality of supporting evidence (Table 2), all of which have also been rated (Table 3). This CPG is organized into specific and relevant clinical questions labeled "Q."

Recommendations (numerically labeled "R1, R2, etc.") are based on importance and evidence (Grades A, B, and C) or expert opinion when there is a lack of conclusive clinical evidence (Grade D). The best EL (BEL), which corresponds to the best conclusive evidence found in the Appendix to follow, accompanies the recommendation grade in this Executive Summary; definitions of evidence levels are provided in Figure 1 and Table 1 (2 [EL 4; CPG NE; see Fig. 1; Table 1-4]). Comments may be appended to the recommendation grade and BEL regarding any relevant subjective factors that may have influenced the grading process (Table 4). Details regarding each recommendation may be found in the corresponding section of the Appendix. Thus, the process leading to a final recommendation and grade is not rigid; rather, it incorporates a complex expert integration of objective and subjective factors meant to reflect optimal real-life clinical decision-making and enhance patient care. Where appropriate, multiple recommendations are provided so that the reader has management options. This document is only intended to

serve as a guideline. Individual patient circumstances and presentations differ, and the ultimate clinical management is based on what is in the best interest of the individual patient, involving patient input and reasonable clinical judgment by the treating clinicians.

3. EXECUTIVE SUMMARY

To guide readers, DM comprehensive management recommendations are organized into the following questions:

- Q1. How is diabetes screened and diagnosed?
- Q2. How is prediabetes managed?
- Q3. What are the glycemic treatment goals of DM?
- Q4. How are glycemic targets achieved for type 2 diabetes (T2D)?
- Q5. How should glycemia in type 1 diabetes (T1D) be managed?
- Q6. How is hypoglycemia managed?
- Q7. How is hypertension managed in patients with diabetes?
- Q8. How is dyslipidemia managed in patients with diabetes?
- Q9. How is nephropathy managed in patients with diabetes?
- Q10. How is retinopathy managed in patients with diabetes?
- Q11. How is neuropathy diagnosed and managed in patients with diabetes?
- Q12. How is CVD managed in patients with diabetes?
- Q13. How is obesity managed in patients with diabetes?
- Q14. What is the role of sleep medicine in the care of the patient with diabetes?
- Q15. How is diabetes managed in the hospital?
- Q16. How is a comprehensive diabetes care plan established in children and adolescents?
- Q17. How should diabetes in pregnancy be managed?
- Q18. When and how should glucose monitoring be used?
- Q19. When and how should insulin pump therapy be used?
- Q20. What is the imperative for education and team approach in DM management?
- Q21. Which vaccinations should be given to patients with diabetes?
- Q22. How should depression be managed in the context of diabetes?
- Q23. What is the association between diabetes and cancer?
- Q24. Which occupations have specific diabetes management requirements?

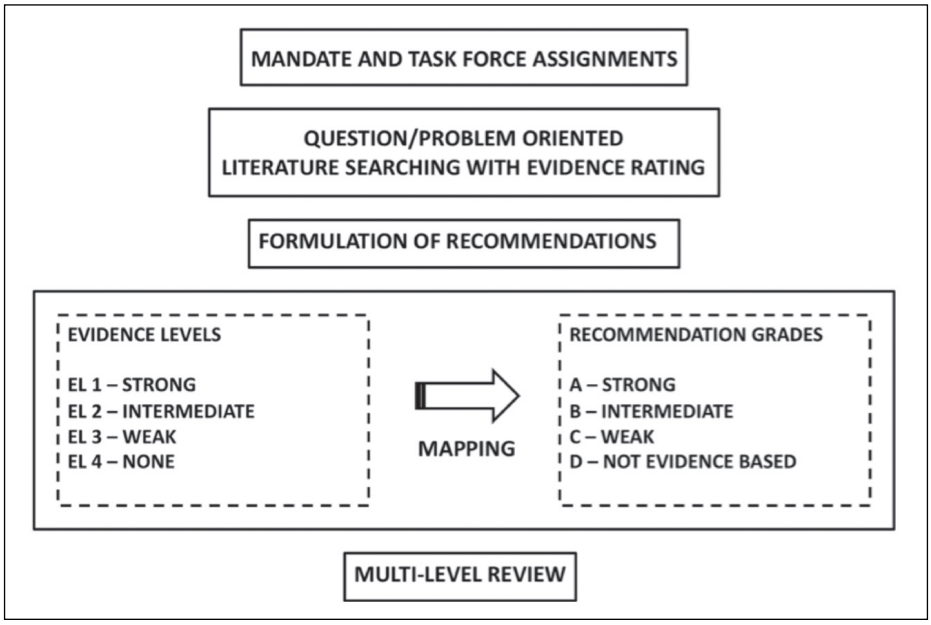

Fig. 1. 2010 American Association of Clinical Endocrinologists (AACE) Clinical Practice Guideline (CPG) methodology. Current AACE CPGs have a problem-oriented focus that results in a shortened production time line, middle-range literature searching, emphasis on patient-oriented evidence that matters, greater transparency of intuitive evidence rating and qualifications, incorporation of subjective factors into evidence-recommendation mapping, cascades of alternative approaches, and an expedited multilevel review mechanism.

Readers are referred to the Appendix (section 4) for more detail and supporting evidence for each question.

3.Q1. How is Diabetes Screened and Diagnosed?

- **R1.** There is a continuum of risk for poor health outcomes in the progression from normal glucose tolerance to overt T2D. Screening should be considered in the presence of risk factors for DM (Table 5) (**Grade C; BEL 3**). Individuals at risk for DM whose glucose values are in the normal range should be screened every 3 years; clinicians may consider annual screening for patients with 2 or more risk factors (**Grade C; BEL 3**).
- **R2.** The following criteria may be used to diagnose DM (Table 6) (**Grade B; BEL 3):**
  - FPG concentration (after 8 or more hours of no caloric intake) ≥126 mg/dL, *or*
  - Plasma glucose concentration ≥200 mg/dL 2 hours after ingesting a 75-g oral glucose load in the morning after an overnight fast of at least 8 hours, *or*
  - Symptoms of hyperglycemia (e.g., polyuria, polydipsia, polyphagia) and a random (casual, nonfasting) plasma glucose concentration ≥200 mg/dL, *or*
  - A1C level ≥6.5%

  Glucose criteria (i.e., FPG or 2-h glucose after a 75-g oral glucose load) are preferred for the diagnosis of DM. The same test—plasma glucose or A1C measurement—should be repeated on a different day to confirm the diagnosis of DM. However, a glucose level ≥200 mg/dL in the presence of DM symptoms does not need to be confirmed (**Grade B; BEL 3**).
- **R3.** Prediabetes may be identified by the presence of impaired glucose tolerance (IGT), which is a plasma glucose value of 140 to 199 mg/dL 2 hours after ingesting 75 g of glucose, and/or impaired fasting glucose (IFG), which is a fasting glucose value of 100 to 125 mg/dL (Table 6) (**Grade B; BEL 2).** A1C values between 5.5 and 6.4% inclusive should be a signal to do more specific glucose testing (**Grade D; BEL 4).** For prediabetes, A1C testing should be used only as a screening tool; FPG measurement or an oral glucose tolerance test (OGTT) should be used for definitive diagnosis (**Grade B; BEL 2).** Metabolic syndrome based on National Cholesterol Education Program IV Adult Treatment Panel III criteria should be considered a prediabetes equivalent (**Grade C; BEL 3).**
- **R4.** Pregnant females with DM risk factors should be screened at the first prenatal visit for undiagnosed T2D using standard criteria (**Grade D; BEL 4**). At 24 to 28 weeks' gestation, all pregnant subjects should be screened for gestational

Table 1
2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step I: Evidence Rating[a]

Numerical descriptor (evidence level)[b]	Semantic descriptor (reference methodology)
1	Meta-analysis of randomized controlled trials (MRCT)
1	Randomized controlled trials (RCT)
2	Meta-analysis of nonrandomized prospective or case-controlled trials (MNRCT)
2	Nonrandomized controlled trial (NRCT)
2	Prospective cohort study (PCS)
2	Retrospective case-control study (RCCS)
3	Cross-sectional study (CSS)
3	Surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modeling of database) (SS)
3	Consecutive case series (CCS)
3	Single case reports (SCR)
4	No evidence (theory, opinion, consensus, review, or preclinical study) (NE)

[a] Adapted from (1): *Endocr Pract*. 2010;16:270-283.
[b] 1, strong evidence; 2, intermediate evidence; 3, weak evidence; and 4, no evidence.

DM (GDM) with a 2-hour OGTT using a 75-g glucose load. GDM may be diagnosed using the following plasma glucose criteria: FPG >92 mg/dL, 1-hour post-glucose challenge value ≥180 mg/dL, or 2-hour value ≥153 mg/dL (**Grade C; BEL 3**).

- **R5.** DM represents a group of heterogeneous metabolic disorders that develop when insulin secretion is insufficient to maintain normal plasma glucose levels. T2D is the most common form of DM, accounting for more than 90% of cases, and is typically identified in patients who are overweight or obese and/or have a family history of DM, a history of GDM, or meet the criteria for metabolic syndrome. Once DM glucose criteria have been satisfied, T2D should be diagnosed based on patient history, phenotype, and lack of autoantibodies characteristic of T1D (**Grade A; BEL 1)**. Most persons with T2D have evidence of insulin resistance (such as elevated fasting or postprandial plasma insulin and/or elevated C-peptide concentrations), high triglycerides, and/or low high-density lipoprotein cholesterol [HDL-C]).
- **R6.** T1D is usually characterized by absolute insulin deficiency and should be confirmed by the presence of autoantibodies to glutamic acid decarboxylase, pancreatic islet β cells (tyrosine phosphatase IA-2), zinc transporter (ZnT8), and/or insulin (**Grade A; BEL 1).** Some forms of T1D have no evidence of autoimmunity and have been termed idiopathic. T1D can also occur in people who are overweight or obese. Therefore, documenting the levels of insulin and C-peptide and the presence or absence of immune markers in addition to the clinical presentation may help establish the correct diagnosis to distinguish between T1D and T2D in children or adults and determine appropriate treatment (**Grade B; BEL 2**).
- **R7.** Any child or young adult with an atypical presentation, course, or response to therapy may be evaluated for monogenic DM (formerly maturity-onset diabetes of the young); diagnostic likelihood is strengthened by a family history over 3 generations, suggesting autosomal dominant inheritance (**Grade C; BEL 3**).

3.Q2. How is Prediabetes Managed?

- **R8.** T2D can be prevented or at least delayed by intervening in persons who have prediabetes (see Table 6 for glucose criteria) (**Grade A, BEL 1)**. Frequent measurement of FPG and/or an OGTT may be used to assess the glycemic status of patients with prediabetes (**Grade C; BEL 3**). The clinician should manage CVD risk factors (especially elevated blood pressure and/or dyslipidemia) and excessive weight, and monitor these risks at regular intervals (**Grade C; BEL 3**).
- **R9.** Persons with prediabetes should modify their lifestyle, including initial attempts to lose 5 to 10% of body weight if overweight or obese and participate in moderate physical activity (e.g., walking) at least 150 minutes per week (**Grade B; BEL 3**). Physicians should recommend patients participate in organized lifestyle change programs with follow-up, where available, because behavioral support will benefit weight-loss efforts (**Grade B; BEL 3**).
- **R10.** In addition to lifestyle modification, medications including metformin, acarbose, or

Table 2
2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step II: Evidence Analysis and Subjective Factors[a]

Study design	Data analysis	Interpretation of results
Premise correctness	Intent-to-treat	Generalizability
Allocation concealment (randomization)	Appropriate statistics	Logical
Selection bias		Incompleteness
Appropriate blinding		Validity
Using surrogate end points (especially in "first-in-its-class" intervention)		
Sample size (beta error)		
Null hypothesis vs. Bayesian statistics		

[a] Reprinted from (1): *Endocr Pract*. 2010;16:270-283.

Table 3
2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step III: Grading of Recommendations; How Different Evidence Levels can be Mapped to the Same Recommendation Grade[a,b]

Best evidence level	Subjective factor impact	Two-thirds consensus	Mapping	Recommendation grade
1	None	Yes	Direct	A
2	Positive	Yes	Adjust up	A
2	None	Yes	Direct	B
1	Negative	Yes	Adjust down	B
3	Positive	Yes	Adjust up	B
3	None	Yes	Direct	C
2	Negative	Yes	Adjust down	C
4	Positive	Yes	Adjust up	C
4	None	Yes	Direct	D
3	Negative	Yes	Adjust down	D
1, 2, 3, 4	NA	No	Adjust down	D

[a] Starting with the left column, best evidence levels (BELs), subjective factors, and consensus map to recommendation grades in the right column. When subjective factors have little or no impact ("none"), then the BEL is directly mapped to recommendation grades. When subjective factors have a strong impact, then recommendation grades may be adjusted up ("positive" impact) or down ("negative" impact). If a two-thirds consensus cannot be reached, then the recommendation grade is D. NA, not applicable (regardless of the presence or absence of strong subjective factors, the absence of a two-thirds consensus mandates a recommendation grade D).
[b] Reprinted from (1): *Endocr Pract*. 2010;16:270-283.

thiazolidinediones (TZDs) should be considered for patients who are at moderate-to-high risk for developing DM, such as those with a first-degree relative with DM (**Grade A; BEL 1**).

3.Q3. What are the Glycemic Treatment Goals of DM?

3.Q3.1. Outpatient Glucose Targets for Nonpregnant Adults

- **R11.** Glucose targets should be individualized and take into account life expectancy, disease duration, presence or absence of micro- and macrovascular complications, CVD risk factors, comorbid conditions, and risk for hypoglycemia, as well as the patient's psychological status (**Grade A; BEL 1**). In general, the goal of therapy should be an A1C level ≤6.5% for most nonpregnant adults, if it can be achieved safely (Table 7) (**Grade D; BEL 4**). 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 7) (**Grade B, BEL 2**).

In adults with recent onset of T2D and no clinically significant CVD, glycemic control aimed at normal (or near-normal) glycemia should be considered, with the aim of preventing the development of micro- and macrovascular complications over a lifetime, if it can be achieved without substantial hypoglycemia or other unacceptable adverse consequences (**Grade A; BEL 1**). Although it is uncertain that the clinical course of established CVD is

improved by strict glycemic control, the progression of microvascular complications clearly is delayed. A less stringent glucose goal should be considered (A1C 7 to 8%) in patients with history of severe hypoglycemia, limited life expectancy, advanced renal disease or macrovascular complications, extensive comorbid conditions, or long-standing DM in which the A1C goal has been difficult to attain despite intensive efforts, so long as the patient remains free of polydipsia, polyuria, polyphagia, and other hyperglycemia-associated symptoms (**Grade A; BEL 1**).

3.Q3.2. Inpatient Glucose Targets for Nonpregnant Adults

- **R12.** For most hospitalized persons with hyperglycemia in the intensive care unit (ICU), a glucose range of 140 to 180 mg/dL is recommended, provided this target can be safely achieved (Table 7) (**Grade D; BEL 4**). For general medicine and surgery patients in non-ICU settings, a premeal glucose target <140 mg/dL and a random blood glucose <180 mg/dL are recommended (**Grade C; BEL 3**).

3.Q3.3. Outpatient Glucose Targets for Pregnant Subjects

- **R13.** For females with GDM, the following glucose goals should be considered: preprandial glucose 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 (**Grade D; BEL 4**). For females with pre-existing T1D or T2D who become pregnant, glucose should be controlled to meet the following goals (but only if they can be safely achieved): premeal, bedtime, and overnight glucose values between 60 and 99 mg/dL; a peak PPG value between 100 and 129 mg/dL; and an A1C value ≤6.0% (**Grade D; BEL 4**).

3.Q4. How are Glycemic Targets Achieved for T2D?

3.Q4.1. Therapeutic Lifestyle Changes

- **R14.** Medical nutrition therapy (MNT) is recommended for all people with prediabetes or DM, including T1D, T2D, GDM, and other less common forms of DM. MNT must be individualized, generally via evaluation and teaching by a trained nutritionist or registered dietitian or a physician knowledgeable in nutrition (**Grade D; BEL 4**). The goals of MNT are to improve overall health by teaching patients to eat a diet containing a variety of foods in appropriate amounts to help manage body weight, glucose, lipids, and blood pressure (Table 8). Nutritional recommendations should take into account personal and cultural preferences, as well as the individual's knowledge of nutrition, willingness to change eating habits, and barriers to change. For people on insulin therapy, insulin dosage adjustments should match carbohydrate intake (e.g., with use of carbohydrate counting).
- **R15.** Patients should engage in at least 150 minutes per week of moderate-intensity exercise such as brisk walking (15- to 20-minute mile) or its equivalent **(Grade B; BEL 2)**. Persons with T2D should also incorporate flexibility and strength-training exercises **(Grade B; BEL 2)**. Patients must be evaluated initially for contraindications and/or limitations to physical activity, and then an exercise prescription should be developed for each patient according to both goals and activity limitations. Physical activity programs should begin slowly and build up gradually (**Grade D; BEL 4**). Patients with T1D should also exercise regularly; however, individuals requiring insulin therapy should be educated about the acute and chronic effects of exercise on blood glucose levels and learn how to adjust insulin dosages and food intake to maintain good glucose control before, during, and after exercise to avoid significant hypo- or hyperglycemia (**Grade D; BEL 4**).

3.Q4.2. Antihyperglycemic Pharmacotherapy for T2D

- **R16.** Pharmacotherapy for T2D should be prescribed based on suitability for the individual patient's characteristics **(Grade D; BEL 4)**. As shown in Table 9, antihyperglycemic agents vary in their impact on FPG, PPG, weight, and insulin

Table 4
2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step IV: Examples of Qualifiers[a]

Cost-effectiveness
Risk-benefit analysis
Evidence gaps
Alternative physician preferences (dissenting opinions)
Alternative recommendations ("cascades")
Resource availability
Cultural factors
Relevance (patient-oriented evidence that matters)

[a] Reprinted from (1): *Endocr Pract*. 2010;16:270-283.

Table 5
Risk Factors for Prediabetes and T2D: Criteria for Testing for Diabetes in Asymptomatic Adults

Age ≥45 years without other risk factors
CVD or family history of T2D
Overweight or obese[a]
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 or delivery of a baby weighing more than 4 kg (9 lb)
Antipsychotic therapy for schizophrenia and/or severe bipolar disease
Chronic glucocorticoid exposure
Sleep disorders in the presence of glucose intolerance (A1C >5.7%, IGT, or IFG on previous testing), 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] Testing should be considered in all adults who are obese (BMI ≥30 kg/m^2), and those who are overweight (BMI 25 to <30 kg/m^2) and have additional risk factors. At-risk BMI may be lower in some ethnic groups, in whom parameters such as waist circumference and other factors may be used.

secretion or sensitivity, as well as the potential for hypoglycemia and other adverse effects. The initial choice of an agent involves comprehensive patient assessment including a glycemic profile obtained by self-monitoring of blood glucose (SMBG) and the patient's A1C, weight, and presence of comorbidities. Minimizing the risks of hypoglycemia and weight gain are priorities.

- **R17.** Details about the effects of and rationale for available antihyperglycemic agents can be found in the 2015 AACE Comprehensive Diabetes Management Algorithm Consensus Statement (4). The AACE recommends initiating therapy with metformin, a glucagon-like peptide 1 (GLP-1) receptor agonist, a dipeptidyl peptidase 4 (DPP-4) inhibitor, a sodium glucose cotransporter 2 (SGLT2) inhibitor, or an α-glucosidase inhibitor for patients with an entry A1C <7.5% **(Grade C; BEL 3)**. A TZD, sulfonylurea, or glinide may be considered as alternative therapies but should be used with caution due to side-effect profiles **(Grade C; BEL 3)**. For patients with entry A1C levels >7.5%, the AACE recommends initiating treatment with metformin (unless contraindicated) plus a second agent, with preference given to agents with a low potential for hypoglycemia that are weight neutral or associated with weight loss **(Grade C; BEL 3)**. This includes GLP-1 receptor agonists, SGLT2 inhibitors, or DPP-4 inhibitors as the preferred second agents; TZDs and basal insulin may be considered as alternatives. Colesevelam, bromocriptine, or an α-glucosidase inhibitor have limited glucose-lowering potential but also carry a low risk of adverse effects and may be useful for glycemic control in some situations **(Grade C; BEL 3)**. Sulfonylureas and glinides are considered the least desirable alternatives due to the risk of hypoglycemia **(Grade B; BEL 2)**. For patients with an entry A1C >9.0% who have symptoms of hyperglycemia, insulin therapy alone or in combination with metformin or other oral agents is recommended **(Grade A; BEL 1)**. Pramlintide and the GLP-1 receptor agonists can be used as adjuncts to prandial insulin therapy to reduce postprandial hyperglycemia, A1C, and weight (**Grade B; BEL 2**). The long-acting GLP-1 receptor agonists also reduce fasting glucose.
- **R18**. Insulin should be considered for T2D when noninsulin antihyperglycemic therapy

fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia (**Grade A; BEL 1**). Therapy with long-acting basal insulin should be the initial choice in most cases **(Grade C; BEL 3)**. The insulin analogs glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because analog insulins are associated with less hypoglycemia (**Grade C; BEL 3**). When control of postprandial hyperglycemia is needed, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or inhaled insulin) over regular human insulin because the former have a more rapid onset and offset of action and are associated with less hypoglycemia (**Grade B; BEL 2**). Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for patients 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 B; BEL 2**). Basal-bolus insulin regimens are flexible and recommended for intensive insulin therapy (**Grade B; BEL 3**).

- **R19**. Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals (e.g., every 3 months) when treatment goals are not achieved or maintained (**Grade C; BEL 3**). The 2015 AACE algorithm outlines treatment choices on the basis of the A1C level (4 [EL 4; NE]).

3.Q5. How Should Glycemia in T1D be Managed?

- **R20.** Insulin must be used to treat T1D (**Grade A; BEL 1**). Physiologic insulin regimens, which provide both basal and prandial insulin, should be used for most patients with T1D (**Grade A; BEL 1**). These regimens involve the use of insulin analogs for most patients with T1D (**Grade A; BEL 1**) and include the following approaches:
    - Multiple daily injections (MDI), which usually involve 1 to 2 subcutaneous injections daily of basal insulin to control glycemia between meals and overnight, and subcutaneous injections of prandial insulin or inhaled insulin before each meal to control meal-related glycemia (**Grade A; BEL 1**)
    - Continuous subcutaneous insulin infusion (CSII) to provide a more physiologic way to deliver insulin, which may improve glucose control while reducing risks of hypoglycemia (**Grade A; BEL 1**)

3.Q6. How is Hypoglycemia Managed?

- **R21.** Oral administration of rapidly absorbed glucose should be used to treat hypoglycemia (generally defined as any blood glucose <70 mg/dL with or without symptoms including anxiety, palpitations, tremor, sweating, hunger, paresthesias, behavioral changes, cognitive dysfunction, seizures, and coma; severe hypoglycemia is defined as any that requires assistance from another person

Table 6
Glucose Testing and Interpretation

Normal	High Risk for Diabetes	Diabetes
FPG <100 mg/dL	IFG FPG ≥100-125 mg/dL	FPG ≥126 mg/dL
2-h PG <140 mg/dL	IGT 2-h PG ≥140-199 mg/dL	2-h PG ≥200 mg/dL Random PG ≥200 mg/dL + symptoms
A1C <5.5%	5.5 to 6.4% For screening of prediabetes[a]	≥6.5% Secondary[b]

Abbreviations: A1C = hemoglobin A1C; FPG = fasting plasma glucose; 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 confirmed with glucose testing.

[b] Glucose criteria are preferred for the diagnosis of DM. In all cases, the diagnosis should be confirmed on a separate day by repeating glucose or A1C testing. When A1C is used for diagnosis, follow-up glucose testing should be done when possible to help manage DM.

Table 7
Comprehensive Diabetes Care Treatment Goals

Parameter	Treatment goal	Reference (evidence level and study design)
Glucose		
A1C, %	Individualize on the basis of age, comorbidities, duration of disease; in general ≤6.5 for most; closer to normal for healthy; less stringent for "less healthy"	(4 [EL 4; NE])
FPG, mg/dL	<110	
2-h PPG, mg/dL	<140	
Inpatient hyperglycemia: glucose, mg/dL	140-180	(5 [EL 4; consensus NE])
Blood pressure	Individualize on the basis of age, comorbidities, and duration of disease, with general target of:	(8 [EL 4; NE])
Systolic, mm Hg	~130	
Diastolic, mm Hg	~80	
Lipids		
LCL-C, mg/dL	<100, moderate risk <70, high risk	(4 [EL 4; NE])
Non-HDL-C, mg/dL	<130, moderate risk <100, high risk	
Triglycerides, mg/dL	<150	
TC/HDL-C ratio	<3.5, moderate risk <3.0, high risk	
ApoB, mg/dL	<90, moderate risk <80, high risk	
LDL particles	<1,200 moderate risk <1,000 high risk	
Weight		
Weight loss	Reduce weight by at least 5 to 10%; avoid weight gain	(4 [EL 4; NE])
Anticoagulant therapy		
Aspirin	For secondary CVD prevention or primary prevention for patients at very high risk[a]	(9 [EL 1; MRCT but small sample sizes and event rates]; 10 [EL 1; MRCT]; 11 [EL 1; MRCT]; 12 [EL 2; PCS])

Abbreviations: ApoB = apolipoprotein B; BEL = best evidence level; CVD = cardiovascular disease; DM = diabetes mellitus; EL = evidence level; FPG = fasting plasma glucose; HDL-C = high-density lipoprotein cholesterol; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; LDL = low-density lipoprotein; MRCT = meta-analysis of randomized controlled trials; NE = no evidence (theory, opinion, consensus, review, or preclinical study); PCS = prospective cohort study; PPG = postprandial glucose; TC = total cholesterol.
[a] High risk, DM without cardiovascular disease; very high risk, DM plus CVD.

to administer carbohydrates or glucagon or take other corrective action). If the patient is unable to swallow or is unresponsive, subcutaneous or intramuscular glucagon or intravenous glucose should be given by a trained family member or medical personnel (**Grade A; BEL 1**). The usual adult dose of subcutaneous glucagon is 1 mg (1 unit). For children weighing less than 44 lbs (20 kg), the dose is half the adult dose (0.5 mg). As soon as the patient is awake and able to swallow, he or she should receive a rapidly absorbed source of carbohydrate (e.g., fruit juice) followed by a snack or meal containing both protein and carbohydrates (e.g., cheese and crackers or a peanut

Table 8
American Association of Clinical Endocrinologists Healthful Eating Recommendations for Patients With Diabetes Mellitus

Topic	Recommendation	Reference (evidence level and study design)
General eating habits	Eat regular meals and snacks; avoid fasting to lose weight Consume plant-based diet (high in fiber, low calories/glycemic index, and high in phytochemicals/antioxidants) Understand Nutrition Facts Label information Incorporate beliefs and culture into discussions Use mild cooking techniques instead of high-heat cooking Keep physician-patient discussions informal	(71 [EL 3; SS]; 72 [EL 4; position NE]; 73 [EL 4; position NE]; 74 [EL 4; review NE]; 75 [EL 3; SS]; 76 [EL 1; RCT]; 86 [EL 3; SS])
Carbohydrate	Explain the 3 types of carbohydrates—sugars, starch, and fiber—and the effects on health for each type Specify healthful carbohydrates (fresh fruits and vegetables, legumes, whole grains); target 7-10 servings per day Lower-glycemic index foods may facilitate glycemic control (glycemic index score <55 out of 100: multigrain bread, pumpernickel bread, whole oats, legumes, apple, lentils, chickpeas, mango, yams, brown rice), but there is insufficient evidence to support a formal recommendation to educate patients that sugars have both positive and negative health effects	(73 [EL 4; position NE]; 77 [EL 4; review NE]; 78 [EL 4; review NE]; 79 [EL 4; review NE]; 80 [EL 4; NE review]; 81 [EL 4; review NE]; 89 [EL 4; review NE])
Fat	Specify healthful fats (low mercury/contaminant-containing nuts, avocado, certain plant oils, fish) Limit saturated fats (butter, fatty red meats, tropical plant oils, fast foods) and *trans* fat; choose fat-free or low-fat dairy products	(82 [EL 4; review NE]; 87 [EL 4; review NE]; 88 [EL 4; NE review])
Protein	Consume protein in foods with low saturated fats (fish, egg whites, beans); there is no need to avoid animal protein Avoid or limit processed meats	(73 [EL 4; position NE]; 83 [EL 2; MNRCT]; 85 [EL 2; PCS, data may not be generalizable to patients with diabetes already])
Micronutrients	Routine supplementation is not necessary; a healthful eating meal plan can generally provide sufficient micronutrients Specifically, chromium; vanadium; magnesium; vitamins A, C, and E; and CoQ10 are not recommended for glycemic control Vitamin supplements should be recommended to patients at risk of insufficiency or deficiency	(84 [EL 4; CPG NE])

Abbreviations: BEL = best evidence level; CPG = clinical practice guideline; EL = evidence level; MNRCT = meta-analysis of non-randomized prospective or case-controlled trials; NE = no evidence (theory, opinion, consensus, review, or preclinical study); PCS = prospective cohort study; RCT = randomized controlled trial.

Table 9
Effects of Diabetes Drug Action[a]

	Met	GLP1RA	SGLT2I	DPP4I	TZD	AGI	Coles	BCR-QR	SU/Glinide	Insulin	Pram
FPG lowering	**Moderate**	**Mild to moderate[b]**	**Moderate**	Mild	**Moderate**	Neutral	Mild	Neutral	**SU: moderate** Glinide: mild	**Moderate to marked (basal insulin or premixed)**	Mild
PPG lowering	Mild	**Moderate to marked**	Mild	**Moderate**	Mild	**Moderate**	Mild	Mild	**Moderate**	**Moderate to marked (short/ rapid-acting insulin or premixed)**	**Moderate to marked**
NAFLD benefit	Mild	Mild	Neutral	Neutral	**Moderate**	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
Hypoglycemia	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	*SU: moderate to severe Glinide: mild to moderate*	*Moderate to severe, especially with short/rapid-acting or premixed*	Neutral
Weight	**Slight loss**	**Loss**	**Loss**	Neutral	*Gain*	Neutral	Neutral	Neutral	*Gain*	*Gain*	**Loss**
Renal impairment/ GU	*Contraindicated in stage 3B, 4, 5 CKD*	*Exenatide not indicated in CrCl <30 mL/ min*	*GU infection risk*	Dose adjustment may be necessary (except linagliptin)	*May worsen fluid retention*	Neutral	Neutral	Neutral	*Increased hypoglycemia risk*	*Increased risks of hypoglycemia and fluid retention*	Neutral
GI adverse effects	*Moderate*	*Moderate (caution in PIs about pancreatitis)*	Neutral	Neutral *(caution in PIs about pancreatitis)*	Neutral	*Moderate*	Mild	*Moderate*	Neutral	Neutral	*Moderate*
CHF	Neutral	Neutral	Neutral	Neutral *(caution: possibly increased CHF hospitalization risk in CV safety trial)*	*Moderate*	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Possible benefit	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Safe	?	Neutral	Neutral
Bone	Neutral	Neutral	*Bone loss*	Neutral	*Moderate bone loss*	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Abbreviations: AGI = α-glucosidase inhibitors; BCR-QR = bromocriptine quick release; CHF = congestive heart failure; CKD = chronic kidney disease; Coles = colesevelam; CrCl = creatinine clearance; CV = cardiovascular; DPP4I = dipeptidyl peptidase 4 inhibitors; FPG = fasting plasma glucose; GI = gastrointestinal; GLP1RA = glucagon-like peptide 1 receptor agonists; GU = genitourinary; Met = metformin; NAFLD = nonalcoholic fatty liver disease; PI = prescribing information; PPG = postprandial glucose; SGLT2I = sodium-glucose cotransporter 2 inhibitors; SU = sulfonylureas; TZD = thiazolidinediones.

[a] Boldface type highlights a benefit or potential benefit; italic type highlights adverse effects.

[b] Mild: albiglutide and exenatide; moderate: dulaglutide, exenatide extended release, and liraglutide.

butter sandwich) (**Grade C; BEL 3**). Patients with severe hypoglycemia and altered mental status or with persistent hypoglycemia need to be hospitalized (**Grade A; BEL 1**). If the patient has hypoglycemic unawareness and hypoglycemia-associated autonomic failure, several weeks of hypoglycemia avoidance may reduce the risk or prevent recurrence of severe hypoglycemia. In patients with T2D who become hypoglycemic and have been treated with an α-glucosidase inhibitor in addition to insulin or an insulin secretagogue, oral glucose or lactose-containing foods (dairy products) must be given because α-glucosidase inhibitors inhibit the breakdown and absorption of complex carbohydrates and disaccharides (**Grade C; BEL 3**).

3.Q7. How is Hypertension Managed in Patients with Diabetes?

- **R22.** The blood pressure goal for persons with DM or prediabetes should be individualized and should generally be about 130/80 mm Hg (Table 7) **(Grade B; BEL 2)**. A more intensive goal (e.g., <120/80 mm Hg) should be considered for some patients, provided this target can be reached safely without adverse effects from medication **(Grade C; BEL 3)**. More relaxed goals may be considered for frail patients with complicated comorbidities or those who have adverse medication effects **(Grade D; BEL 4)**.
- **R23.** Therapeutic lifestyle modification for hypertension should include dietary interventions that emphasize reduced salt intake such as DASH (Dietary Approaches to Stop Hypertension), physical activity, and, as needed, consultation with a registered dietitian and/or certified diabetes educator (CDE) (**Grade A; BEL 1**). Pharmacologic therapy should be used to achieve targets unresponsive to therapeutic lifestyle changes alone **(Grade A; BEL 1)**. The clinician should select antihypertensive agents on the basis of their ability to reduce blood pressure and prevent or slow the progression of nephropathy and retinopathy; angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are preferred in patients with DM (**Grade C; BEL 3**). Combination therapy should be used when needed to achieve blood pressure targets, including calcium channel antagonists, diuretics, combined α/β-adrenergic blockers, and newer-generation β-adrenergic blockers in addition to agents that block the renin-angiotensin system (**Grade A; BEL 1**).

3.Q8. How is Dyslipidemia Managed in Patients with Diabetes?

- **R24**. All patients with DM should be screened for dyslipidemia (**Grade B; BEL 2**). Therapeutic recommendations should include lifestyle changes and, as needed, consultation with a registered dietitian and/or CDE (**Grade B; BEL 2**).
- **R25.** Because macrovascular disease may be evident prior to the diagnosis of DM, lipid levels of patients with prediabetes should be managed in the same manner as those of patients with DM (**Grade D; BEL 4**).
- **R26.** In persons with DM or prediabetes and no atherosclerotic CVD (ASCVD) or major cardiovascular risk factors (i.e., moderate CVD risk), treatment efforts should target a low-density lipoprotein cholesterol (LDL-C) goal of <100 mg/dL and a non-HDL-C goal of <130 mg/dL (**Grade B; BEL 2**). In high-risk patients (those with DM and established ASCVD or at least 1 additional major ASCVD risk factor such as hypertension, family history, low HDL-C, or smoking), a statin should be started along with therapeutic lifestyle changes regardless of baseline LDL-C level (**Grade A; BEL 1**). In these patients, an LDL-C level <70 mg/dL and a non-HDL-C treatment goal <100 mg/dL should be targeted (Table 7) (**Grade B; BEL 2**). If the triglyceride concentration is ≥200 mg/dL, non-HDL-C may be used to predict ASCVD risk (**Grade C; BEL 3**). Secondary treatment goals may be considered, including apolipoprotein B (ApoB) <80 mg/dL and low-density lipoprotein particles (LDL-P) <1,000 nmol/L in patients with ASCVD or at least 1 major risk factor, and <90 mg/dL or <1,200 nmol/L in patients without ASCVD and no additional risk factors, respectively (**Grade D; BEL 4**).
- **R27.** Pharmacologic therapy should be used to achieve lipid targets unresponsive to therapeutic lifestyle changes alone (**Grade A; BEL 1**). Statins are the treatment of choice in the absence of contraindications. Statin dosage should always be adjusted to achieve LDL-C and non-HDL-C goals (Table 7) unless limited by adverse effects or intolerance (**Grade A; BEL 1**). Combining the statin with a bile acid sequestrant, niacin, and/or cholesterol absorption inhibitor should be considered when the desired target cannot be achieved with the statin alone; these agents may be used instead of statins in cases of statin-related adverse events or intolerance (**Grade C; BEL 3**). In patients who have LDL-C levels at goal but triglyceride concentrations ≥200 mg/dL and

low HDL-C (<35 mg/dL), treatment protocols including the use of fibrates, niacin, or high-dose omega-3 fatty acids may be used to achieve the non-HDL-C goal (Table 7) (**Grade B; BEL 2**). High-dose omega-3 fatty acids, fibrates, or niacin may also be used to reduce triglyceride levels ≥500 mg/dL (**Grade C; BEL 3**).

3.Q9. How is Nephropathy Managed in Patients with Diabetes?

- **R28.** Beginning 5 years after diagnosis in patients with T1D (if diagnosed before age 30) or at diagnosis in patients with T2D and those with T1D diagnosed after age 30, annual assessment of serum creatinine to determine the estimated glomerular filtration rate (eGFR) and urine albumin excretion rate (AER) should be performed to identify, stage, and monitor progression of diabetic nephropathy (**Grade C; BEL 3**). Patients with nephropathy should be counseled regarding the need for optimal glycemic control, blood pressure control, dyslipidemia control, and smoking cessation (**Grade B; BEL 2**). In addition, they should have routine monitoring of albuminuria, kidney function electrolytes, and lipids (**Grade B; BEL 2**). Associated conditions such as anemia and bone and mineral disorders should be assessed as kidney function declines (**Grade D; BEL 4**). Referral to a nephrologist is recommended well before the need for renal replacement therapy (**Grade D; BEL 4**).
- **R29.** Renin-angiotensin-aldosterone system (RAAS) blockade is recommended for patients with DM who have chronic kidney disease (CKD) categories G2, G3a, G3b, and if slow progression is demonstrated, G4 (see Fig. 2 for category definitions) (**Grade A; BEL 1**). Serum potassium levels should be closely monitored (**Grade A; BEL 1**). RAAS-blocking drugs are not safe for use in pregnant subjects. ACE inhibitors and ARBs should not be used together due to increased risks of adverse effects, particularly hyperkalemia (**Grade B; BEL 2**).
- **R30.** Weight loss with regular exercise is recommended for patients with DM and category G2 to G4 CKD (**Grade D; BEL 4**).

3.Q10. How is Retinopathy Managed in Patients with Diabetes?

- **R31.** At the time of diagnosis, patients with T2D should be referred to an experienced ophthalmologist for a dilated eye examination (**Grade C; BEL 3**). Follow-up with eyecare specialists should typically occur on an annual basis, but patients with T2D who have had a negative ophthalmologic examination may be screened every 2 years (**Grade B; BEL 2**). In patients with T1D, a referral should be made within 5 years of diagnosis (**Grade C; BEL 3**). Females who are pregnant and have DM should be referred for frequent/repeated eye examinations during pregnancy and 1 year postpartum (**Grade B; BEL 2**). Patients with active retinopathy should have examinations more than once a year, as should patients receiving vascular endothelial growth factor therapy (**Grade C; BEL 3**). Optimal glucose, blood pressure, and lipid control should be implemented to slow the progression of retinopathy (**Grade A; BEL 1**).

3.Q11. How is Neuropathy Diagnosed and Managed in Patients with Diabetes?

- **R32.** Diabetic neuropathy may be diagnosed clinically but also must be differentiated from other neurologic conditions. Patients with T1D should have a complete neurologic evaluation 5 years after the diagnosis of DM and subsequent annual evaluations (**Grade B; BEL 2**). Patients with T2D should have their first neurologic examination at the time of diagnosis and yearly thereafter (**Grade B; BEL 2**). This exam should consist of a complete foot inspection including assessment of foot structure and deformity, skin temperature and integrity, the presence of ulcers, vascular status, presence of pedal pulses, and toe and foot amputations (**Grade B; BEL 2**). For a complete discussion of diabetic foot assessment, refer to the American Diabetes Association (ADA) Foot Care Task Force report, which has been endorsed by the AACE (6). Neurologic testing may include assessment of sensation using 1- and 10-g monofilaments; vibration perception using a 128-Hz tuning fork; ankle reflexes; and touch, pinprick, and warm and cold thermal sensations (**Grade B; BEL 2**). Painful neuropathies may have no physical signs, and diagnosis may require skin biopsy or other surrogate measures of small-fiber neuropathy (SFN) (**Grade D; BEL 4**). Screening for cardiovascular autonomic neuropathy should be performed at diagnosis of T2D or 5 years after the diagnosis of T1D and then annually (**Grade D; BEL 4**). Tests should include time and frequency domain measures of heart rate variability with deep inspiration, Valsalva maneuver, and blood pressure change from a lying to standing position (**Grade D; BEL 4**).

Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category				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
GFR categories (ml/min/1.73 m²) Description and range	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+

Fig. 2. GFR and albuminuria grid illustrating the risk of progression 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, and deep red may require close monitoring at a frequency of 4 times or more per year (at least every 1-3 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 patient. *CKD* = chronic kidney disease; *GFR* = glomerular filtration rate. Frequency of recommendations from the KDIGO CKD Workgroup (263 [EL 4; NE]; 266 [EL 4; NE]). Modified and reprinted with permission from Macmillan Publishers Ltd: *Kidney International* 2011;80(1):17-28, copyright 2011.

- **R33.** Controlling glucose to individual target levels is recommended to prevent the onset of neuropathy (**Grade A; BEL 1**). Although nothing has been shown to reverse neuropathy once it is established, there is speculation that interventions that reduce oxidative stress, improve glycemic control, and/or improve dyslipidemia and hypertension might have a beneficial effect on established diabetic neuropathy.
- **R34.** Tricyclic antidepressants, anticonvulsants, and serotonin and norepinephrine reuptake inhibitors should be considered for the treatment of painful neuropathy (**Grade A; BEL 1**).
- **R35.** Large-fiber neuropathies should be managed with strength, gait, and balance training; pain management; orthotics to treat and prevent foot deformities; tendon lengthening for pes equinus from Achilles tendon shortening; and/or surgical reconstruction and full-contact casting for foot ulcers, as needed (**Grade B; BEL 2**).
- **R36.** SFNs should be managed with foot protection (e.g., padded socks), supportive shoes with orthotics if necessary, regular foot and shoe inspection, prevention of heat injury, and use of emollient creams. For pain management, the medications mentioned in R34 should be considered (**Grade B; BEL 2**).

3.Q12. How is CVD Managed in Patients with Diabetes?

- **R37.** Because CVD is the primary cause of death for most persons with DM, a DM comprehensive care plan should include modifications of CVD

risk factors (**Grade B; BEL 2**). The cardiovascular risk reduction targets are summarized in Table 7.

- **R38.** The use of low-dosage aspirin (75 to 162 mg daily) is recommended for secondary prevention of CVD (**Grade A; BEL 1**). Some patients may benefit from higher doses (**Grade B; BEL 2**). For primary prevention of CVD, aspirin use may be considered for those at high cardiovascular risk (10-year risk >10%) (**Grade D; BEL 4**).
- **R39.** Measurement of coronary artery calcification or coronary imaging may help assess whether a patient is a reasonable candidate for intensification of glycemic, lipid, and/or blood pressure control (**Grade B; BEL 2**). Screening for asymptomatic coronary artery disease with various stress tests in patients with T2D has not been clearly demonstrated to improve cardiac outcomes and is therefore not recommended (**Grade A; BEL 1**).

3.Q13. How is Obesity Managed in Patients with Diabetes?

- **R40.** Obesity should be diagnosed according to body mass index (BMI) (**Grade B; BEL 2**). Individuals with a BMI ≥30 kg/m^2 are classified as obese, and those with a BMI of 25 to <30 kg/m^2 are overweight. For Southeast Asians and Asian Indians, lower BMI cutpoints may be appropriate. Measurement of waist circumference may be considered for individuals with a BMI between 25 and 35 kg/m^2 (**Grade D; BEL 4**). Those with waist circumference values >102 cm (40 in) for males and > 88 cm (35 in) for females are at higher risk for metabolic disease. In addition to these anthropometric measures, patients should be evaluated for obesity-related complications, including other components of metabolic syndrome, sleep apnea, and osteoarthritis to determine disease severity and facilitate obesity staging (**Grade D; BEL 4**).
- **R41.** Lifestyle modifications including behavioral changes, reduced calorie diets, and appropriately prescribed physical activity should be implemented as the cornerstone of obesity management (**Grade A; BEL 1**). Pharmacotherapy for weight loss may be considered when lifestyle modification fails to achieve the targeted goal (**Grade A; BEL 1**). Pharmacotherapy may be initiated at the same time as lifestyle modification in patients with BMIs of 27 to 29.9 kg/m^2 and ≥1 obesity-related complication such as T2D (**Grade D; BEL 4**). Pharmacotherapy and lifestyle modification may be initiated together in patients with BMI ≥30 kg/m^2 regardless of the presence of complications (**Grade D; BEL 4**). Bariatric surgery should be considered in patients with severe obesity-related complications including T2D if the BMI is ≥35 kg/m^2 (**Grade B; BEL 2**). Patients with T2D who undergo malabsorptive procedures, such as Roux-en-Y gastric bypass or biliopancreatic diversion with duodenal switch, must have careful postoperative follow-up because of risks of micronutrient deficiencies and hypoglycemia (**Grade D; BEL 4**).

3.Q14. What is the Role of Sleep Medicine in the Care of the Patient with Diabetes?

- **R42.** Adults with T2D, especially obese males older than 50 years, should be screened for obstructive sleep apnea (OSA), which is common in this population (**Grade D; BEL 4**). This condition should be suspected based on a history of daytime drowsiness and heavy snoring, especially if a bed partner witnesses apneas. Increasing evidence supports home apnea testing. Referral to a sleep specialist should be considered in patients suspected of having OSA or restless leg syndrome and when patients are intolerant of continuous positive airway pressure (CPAP) devices (**Grade A; BEL 1**). CPAP and similar oxygen delivery systems should be used to treat OSA (**Grade A; BEL 1**). Weight loss may also significantly improve OSA.

3.Q15. How is Diabetes Managed in the Hospital?

- **R43.** Insulin can rapidly control hyperglycemia and therefore should be used for the majority of hospitalized patients with hyperglycemia (**Grade A; BEL 1**). Intravenous insulin infusion should be used to treat persistent hyperglycemia among critically ill patients in the intensive care unit (ICU) (**Grade A; BEL 1**). Scheduled subcutaneous insulin therapy with basal, nutritional, and correctional components should be used for glycemic management in noncritically ill patients (**Grade A; BEL 1**). Insulin dosing should be synchronized with provision of meals or enteral or parenteral nutrition (**Grade A; BEL 1**). Exclusive use of "sliding scale" insulin should be discouraged (**Grade A; BEL 1**). Preference should be given to regular insulin for intravenous administration and insulin analogs for subcutaneous administration (**Grade D; BEL 4**).
- **R44.** All patients, independent of a prior diagnosis of DM, should have laboratory blood glucose testing upon hospital admission (**Grade C; BEL 3**). Patients with known history of DM should have their A1C measured in the hospital if this

assessment has not been performed in the preceding 3 months (**Grade D; BEL 4**). A1C should also be measured in patients with hyperglycemia in the hospital who do not have a prior diagnosis of DM (**Grade D; BEL 4**). Glucose monitoring with bedside point-of-care (POC) testing should be initiated in all patients with known DM and in nondiabetic patients receiving therapy associated with high risk of hyperglycemia, such as corticosteroids or enteral or parenteral nutrition (**Grade D; BEL 4**). Patients with persistent hyperglycemia require ongoing POC testing with treatment similar to patients with known history of DM.

- **R45.** A plan for preventing and treating hypoglycemia should be established for each patient, and hypoglycemic episodes should be documented in the medical record (**Grade C; BEL 3**).
- **R46.** Appropriate plans for follow-up and care should be documented at hospital discharge for inpatients with a prior history of DM as well as nondiabetic patients with hyperglycemia or increased A1C levels (**Grade D; BEL 4**). DM discharge planning should start soon after hospitalization, and clear DM management instructions should be provided at discharge (**Grade D; BEL 4**).

3.Q16. How is a Comprehensive Diabetes Care Plan Established in Children and Adolescents?

- **R47.** The pharmacologic treatment of any form of DM in children should not, at this stage of our knowledge, differ in substance from treatment for adults (**Grade D; BEL 4**), except in children younger than about 4 years, when bolus premeal insulin may be administered after rather than before a meal due to variable and inconsistent calorie/carbohydrate intake. In children or adolescents with T1D, MDI or CSII insulin regimens are preferred (**Grade C; BEL 3**). Injection frequencies may become problematic in some school settings. Higher insulin-to-carbohydrate ratios and basal insulin dosages may be needed during puberty (**Grade C; BEL 3**). Insulin requirements may be increased 20 to 50% during menstrual periods in pubescent girls (**Grade C; BEL 3**). In children or adolescents with T2D, diet and lifestyle modification should be implemented first (**Grade A; BEL 1**). Addition of metformin and/or insulin should be considered when glycemic targets are not achievable with lifestyle measures (**Grade B; BEL 2**). An extensive review of guidelines for the care of children with DM from the International Society of Pediatric and Adolescent Diabetes was published in 2009 and is available on their website (13).
- **R48.** T1D in adolescents should be managed in close consultation with the patient and their family members. The ADA; Juvenile Diabetes Research Foundation (JDRF); and National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) offer resources to help with transition planning (14-16).

3.Q17. How Should Diabetes in Pregnancy be Managed?

- **R49.** For females 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 (**Grade C; BEL 3**).
- **R50.** All females with pre-existing DM (T1D, T2D, or previous GDM) should have access to preconception care to ensure adequate nutrition and glucose control before conception, during pregnancy, and in the postpartum period (**Grade B; BEL 2**). Preference should be given to rapid-acting insulin analogs to treat postprandial hyperglycemia in pregnant subjects (**Grade D; BEL 4**). Regular insulin is acceptable when analogs are not available. Basal insulin needs should be met using rapid-acting insulin via CSII or by using long-acting insulin (e.g., NPH or detemir, which are U.S. Food and Drug Administration [FDA] pregnancy category B) (**Grade A; BEL 1**). Although insulin is the preferred treatment during pregnancy, metformin and glyburide have been shown to be effective alternatives that do not cause adverse effects in some females (**Grade C; BEL 3**).

3.Q18. When and How Should Glucose Monitoring be Used?

- **R51.** A1C should be measured at least twice yearly in all patients with DM and at least 4 times yearly in patients not at target (**Grade D; BEL 4**).
- **R52.** SMBG should be performed by all patients using insulin (minimum of twice daily and ideally before any insulin injection) (**Grade B; BEL 2**). More frequent SMBG after meals or in the middle of the night may be required for insulin-taking patients with frequent hypoglycemia, patients not at A1C targets, or those with hypoglycemic symptoms (**Grade C; BEL 3**). Patients not requiring insulin therapy may benefit from SMBG, especially to provide feedback about the effects of

their lifestyle and pharmacologic therapy; testing frequency must be personalized.

- **R53.** Continuous glucose monitoring (CGM) should be considered for patients with T1D and T2D on basal-bolus therapy to improve A1C levels and reduce hypoglycemia (**Grade B; BEL 2**). Early reports suggest that even patients not taking insulin may benefit from CGM (**Grade D; BEL 4**).

3.Q19. When and How Should Insulin Pump Therapy be Used?

- **R54.** Candidates for CSII include patients with T1D and patients with T2D who are insulin dependent (**Grade A; BEL 1**). CSII should only be used in patients who are motivated and knowledgeable in DM self-care, including insulin adjustment. To ensure patient safety, prescribing physicians must have expertise in CSII therapy, and CSII users must be thoroughly educated and periodically reevaluated. Sensor-augmented CSII, including those with a threshold-suspend function, should be considered for patients who are at risk of hypoglycemia (**Grade A; BEL 1**).

3.Q20. What is the Imperative for Education and Team Approach in DM Management?

- **R55.** An organized multidisciplinary team may best deliver care for patients with DM (**Grade D; BEL 4**). Members of such a team can include a primary care physician, endocrinologist, physician assistant, nurse practitioner, registered nurse, dietitian, exercise specialist, and mental health professional. The educational, social, and logistical elements of therapy and variations in successful care delivery associated with age and maturation increase the complexity of caring for children with DM.
- **R56.** Persons with DM should receive comprehensive diabetes self-management education (DSME) at the time of DM diagnosis and subsequently as appropriate (**Grade D; BEL 4**). DSME improves clinical outcomes and quality of life in individuals with DM by providing the knowledge and skills necessary for DM self-care. Therapeutic lifestyle management must be discussed with all patients with DM or prediabetes at the time of diagnosis and throughout their lifetime (**Grade D; BEL 4**). 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 DSME programs outline principles of glycemia treatment options; blood glucose monitoring; insulin dosage adjustments; acute complications of DM; and prevention, recognition, and treatment of hypoglycemia.

3.Q21. Which Vaccinations Should be Given to Patients with Diabetes?

- **R57.** AACE supports the recommendations of the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) that all patients with DM be vaccinated for influenza and pneumococcal infection. An annual influenza vaccine should be provided to those with DM who are ≥6 months old (**Grade C; BEL 3**). Furthermore, a pneumococcal polysaccharide vaccine should be administered to patients with DM age ≥2 years (**Grade C; BEL 3**). A single administration of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) should be administered to adults with DM age 19 to 64 years (**Grade C; BEL 3**). The 13-valent pneumococcal conjugate vaccine should be administered in series with the PPSV23 to all adults aged ≥65 years (**Grade C; BEL 3**). Revaccination is also indicated for those with nephrotic syndrome, chronic renal disease, and other immunocompromised states, such as posttransplantation.
- **R58.** Hepatitis B vaccinations should be administered to adults 20 to 59 years of age as soon after DM diagnosis as possible (**Grade C; BEL 3**). Vaccination of adults ≥60 years should be considered based on assessment of risk and likelihood of an adequate immune response (**Grade C; BEL 3**).
- **R59.** All children and adolescents with DM should receive routine childhood vaccinations according to the normal schedule (**Grade C; BEL 3**).
- **R60.** 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 D; BEL 4**).
- **R61.** Patients with DM may need other vaccines to protect themselves against other illnesses. Healthcare professionals may consider vaccines for the following diseases based on individual needs of the patient: measles/mumps/rubella, varicella (chicken pox), and polio. In addition, patients traveling to other countries may require vaccines for endemic diseases (**Grade D; BEL 4**).

3.Q22. How Should Depression be Managed in the Context of Diabetes?

- **R62.** Screening for depression should be performed routinely for adults with DM because untreated depression can have serious clinical implications for patients with DM (**Grade A; BEL 1**).
- **R63.** Patients with depression should be referred to mental health professionals who are members of the DM care team (**Grade D; BEL 4**).

3.Q23. What is the Association Between Diabetes and Cancer?

- **R64.** In light of the increased risk of certain cancers in patients with obesity or T2D, healthcare professionals should educate patients regarding this risk and encourage a more healthy lifestyle (**Grade D; BEL 4**). Weight reduction, regular exercise, and a healthful diet are recommended (**Grade C; BEL 3**). Individuals with obesity and those with T2D should be screened more often and more rigorously for common cancers and those associated with these metabolic disorders (**Grade B; BEL 2**).
- **R65.** To date, no definitive relationship has been established between specific antihyperglycemic agents and an increased risk of cancer or cancer-related mortality. Healthcare professionals should be aware of potential associations but should recommend therapeutic interventions based on the risk profiles of individual patients (**Grade D; BEL 4**).
- **R66.** When a patient with DM has a history of a particular cancer, the physician may consider avoiding a medication that was initially considered disadvantageous to that cancer, even though no proof has been forthcoming (**Grade D; BEL 4**).

3.Q24. Which Occupations Have Specific Diabetes Management Requirements?

- **R67.** Commercial drivers are at high risk for developing T2D. Persons with DM engaged in various occupations including commercial drivers and pilots, anesthesiologists, and commercial or recreational divers have special management requirements. Treatment efforts for such patients should be focused on agents with reduced likelihood of hypoglycemia (**Grade C; BEL 3**).

4. APPENDIX: EVIDENCE BASE

In this update, there are 671 citations of which 226 (34%) are EL 1 (strong), 121 (18%) are EL 2 (intermediate), 117 (17%) are EL 3 (weak), and 205 (31%) are EL 4 (no clinical evidence). The majority of recommendations are EL 1 or 2: 347/671 (52%), which is slightly increased from 180/375 (48%) in the 2011 AACE CPG (1 [EL 4; NE]). The evidence base presented here provides relevant information for the recommendations in the Executive Summary.

4.Q1. How is Diabetes Screened and Diagnosed?

4.Q1.1. 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 concentrations (Table 6) (17 [EL 4; consensus NE]).

An International Expert Committee has recommended that an A1C level ≥6.5% also be used as a criterion for diagnosis of DM (18 [EL 4; consensus NE]). Subsequent analyses of the fidelity of DM diagnosis using A1C versus FPG or 2-hour OGTT (Table 6) have brought this practice into question (19 [EL 3; SS]). Moreover, A1C is known to be affected by nonglycemic factors such as changes in red blood cell maturity and survival and impaired renal function, and it may be unreliable as a measure of glycemic burden in some patients from certain ethnic groups, including those of African American and Latino heritage (20 [EL 3; SS]; 21 [EL 4; review NE]; 22 [EL 3; SS]). On the basis of these limitations, A1C measurement cannot be recommended as a primary method for diagnosing DM. The diagnosis of DM is best confirmed by 1 of the 3 established direct measures of plasma glucose, with A1C as a secondary criterion (Table 6). In the absence of unequivocal hyperglycemia, the same type of test should be repeated on a different day to confirm the diagnosis of DM because of glucose level variability (23 [EL 4; review NE]). In view of physiological changes in pregnancy that could affect glycated hemoglobin levels, A1C should not be used for GDM screening or diagnosis (24 [EL 3; CCS]).

4.Q1.2. Classification of DM

DM is classified into T1D, T2D, GDM, monogenic DM, and other less common conditions such as chronic pancreatitis, pancreatic resection, or rare insulin resistance and mitochondrial syndromes. T1D accounts for <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 β cells. In a minority of patients with T1D, evidence for autoimmunity is lacking, and the etiology of islet destruction is unclear. Severe insulinopenia in T1D predisposes patients to diabetic ketoacidosis (DKA). However, DKA can also occur in patients with T2D (25 [El 4; NE]; 26 [EL 3; SS]).

T2D accounts for >90% of all cases of DM; it remains undiagnosed for years in many affected persons because they are asymptomatic. Consequently, up to 25% of patients with T2D have already developed at least 1 microvascular complication by the time of diagnosis (27 [EL 1; RCT]). Insulin resistance and concurrent relative insulin deficiency and glucagon dysregulation underlie T2D pathophysiology (28 [EL 4; NE]; 29 [EL 2; PCS]). Cross-sectional surveys indicate a higher prevalence of diagnosed DM in African Americans, Hispanic Americans, and other persons of non-European origin compared with European Americans (30 [EL 3; SS]).

4.Q2. How is Prediabetes Managed?

Prediabetes is a condition defined by an increased risk of developing DM and CVD. Prediabetes can be identified by the presence of IGT (OGTT result of 140 to 199 mg/dL 2 hours after ingesting 75 g of glucose), IFG (FPG value of 100 to 125 mg/dL), or A1C value of 5.5 to 6.4% (Table 6). The metabolic syndrome, based on National Cholesterol Education Program IV Adult Treatment Panel III (NCEP ATP III) criteria, may be considered a prediabetes equivalent. Polycystic ovary syndrome (PCOS) is also a prediabetes condition (31 [EL 4; consensus NE]). Risk factors suggesting a need for screening are listed in Table 5 (31 [EL 4; consensus NE]).

Prevention of T2D depends upon systematic lifestyle modifications including caloric intake reduction (e.g., 500 kcal deficit per day) and regular exercise (30 minutes aerobic work at least 5 days per week) to lose >7% body weight (4 [EL 4; NE]). Lifestyle management alone may be adequate for low-risk states and can reduce DM incidence by as much as 58% (4 [EL 4; NE]). The weight-loss agents orlistat (120 mg 3 times daily) (32 [EL 1; RCT]) and phentermine/topiramate extended release (up to 15/92 mg once daily) (33 [EL 1; RCT]) prevented or delayed new cases of DM in 48 to 79% of patients with prediabetes taking these medications for 2 to 4 years in the respective studies. Weight-loss surgery may normalize glycemia in patients with prediabetes, prevent the appearance of overt T2D, and reduce its progression. In the Swedish Obese Subjects Study, bariatric surgery reduced the incidence of DM by 75% over 10 years (P<.001) (34 [EL 2; PCS]).

For patients in whom lifestyle modification after 3 to 6 months has failed to produce necessary improvement, pharmacologic intervention may be appropriate. In fact many, if not the majority, of patients will benefit from starting medications concomitantly with lifestyle intervention, just as in other metabolic diseases. No antihyperglycemic medications are approved by the FDA solely for the management of prediabetes and/or the prevention of T2D. Metformin (35 [EL 1; RCT]) and acarbose (36 [EL 1; RCT]; 37 [EL 1; RCT]; 38 [EL 4; opinion NE]) might be appropriate for certain patients. TZDs reduced the risk of DM progression by 60 to 72% (39 [EL 1; RCT]; 40 [EL 1; RCT]); however, because of their potential for long-term adverse effects, their usage in this population is controversial. More extensive discussion can be found in the American College of Endocrinology consensus on the management of prediabetes (31 [EL 4; consensus NE]). Metformin is an antihyperglycemic drug that is not approved for obesity; however, the Diabetes Prevention Program (DPP) demonstrated that it reduces the risk of developing DM in persons with IGT (35 [EL 1; RCT]; 41 [EL 1; RCT, follow-up study]). In 3 studies, orlistat reduced conversion to DM (32 [EL 1; RCT]; 42 [EL 1; RCT]; 43 [EL 1; MRCT]). One of these studies reported a reduction from 10.9 to 5.2% (P = .041) in the conversion rate to DM (42 [EL 1; RCT]). Orlistat therapy is also associated with decreases in A1C; in 1 study, A1C decreased by 1.1% and 0.2% in the orlistat and control groups, respectively. Orlistat therapy also resulted in a mean weight loss of 5% (44 [EL 2; MNRCT]).

Phentermine/topiramate extended release reduced the annualized incidence rates of T2D by 70.5 and 78.7% among patients receiving the 7.5/46 mg and 15/92 mg doses, respectively, over 2 years (P<.05 versus placebo). These reductions were related to the degree of weight loss (10.9% and 12.1% in the low- and high-dose groups, respectively, versus 2.5% in the placebo group; P<.0001) and were accompanied by significant improvements in cardiometabolic parameters (33 [EL 1; RCT]).

High-dose liraglutide (3 mg) reduced weight by a mean of 9 kg, and 84% of patients with prediabetes at baseline had normal glucose values after 1 year; after 2 years, up to 62% of patients taking liraglutide 2.4 or 3 mg (pooled analysis) maintained normal glucose levels (45 [EL 1; RCT]; 46 [EL 1; RCT]). This is likely the result of both the substantial weight loss and the incretin effect of this agent on blood glucose control (45 [EL 1; RCT]; 46 [EL 1; RCT]). A large-scale study specifically examining the effect of liraglutide on the incidence of T2D is underway.

4.Q3. What are the Glycemic Treatment Goals of DM?

4.Q.3.1. 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 (47 [EL 1; RCT]; 48 [EL 3; SS]; 49 [EL 1; RCT,

posttrial monitoring]; 50 [EL 3; SS]; 51 [EL 1; RCT]; 52 [EL 1; RCT, posthoc analysis]). What have remained under debate are the specific targets for glucose control in patients with DM.

Healthy persons do not exhibit preprandial plasma glucose concentrations >99 mg/dL or >120 mg/dL 2 hours after meals. Indeed, there was a progressively increased risk of T2D in males with FPG levels >87 mg/dL in 1 study (53 [EL 3; SS]) and >94 mg/dL in another study based on long-term follow-up (54 [EL 3; SS]). Similarly, standardized DCCT (Diabetes Control and Complications Trial)-aligned A1C levels remained <6.0% in healthy individuals. Epidemiologic evidence shows a continuous relationship between A1C and CVD and all-cause mortality, with the lowest rates at A1C levels <5% (55 [EL 2; PCS]).

Logically, one should aim for "normal" A1C levels when treating patients with DM. However, it is unknown whether treating patients with DM—some with pre-existing diabetic complications—using complicated regimens to force glucose concentrations into the normal range actually prevents or delays those complications. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, intensive therapy targeting an A1C <6% significantly reduced the risks and progressions of retinopathy, nephropathy, and neuropathy compared with a standard approach targeting an A1C of 7 to 8% (52 [EL 1; RCT, posthoc analysis]; 56 [EL 1; RCT]). Significant reductions in the risk or progression of nephropathy were seen in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) study, which targeted an A1C <6.5% in the intensive therapy group versus standard approaches (57 [EL 1; RCT]). In ACCORD, mortality increased with increasing A1C among intensively treated patients, with the excess mortality only affecting patients whose A1C remained >7% (58 [EL 1; RCT]). Meanwhile, a U-shaped mortality curve was observed in the standard therapy group, with increasing death rates at both low (<7%) and high (>8%) A1C levels (58 [EL 1; RCT]). Similar U-shaped curves were found in a 7-year observational study of patients with T1D (59 [EL 2; PCS]) and a 22-year observational study of >20,000 patients with T2D (60 [EL 2; RCCS]). 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 (57 [EL 1; RCT]; 61 [EL 1; RCT]; 62 [EL 1; RCT]; 63 [EL 1; RCT]). As discussed in "Q6. How is hypoglycemia managed?," much of the mortality in ACCORD 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 (64 [EL 3; SS]).

No RCTs have yet established optimal glycemic targets. 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 (4 [EL 4; NE]) have recommended a general target A1C level ≤6.5%, while others have recommended a general target of <7% (65 [EL 4; NE]; 66 [EL 4; CPG NE]). In all cases, the potential risks of intensive glycemic control may outweigh its benefits, especially in patients with frequent severe hypoglycemia, hypoglycemia unawareness, or a very long duration of DM, particularly in the presence of established and advanced atherosclerosis, advanced age, and terminal illness.

In patients with DM, an A1C level >7% is associated with increased risk of micro- and macrovascular complications (50 [EL 3; SS]; 51 [EL 1; RCT]; 67 [EL 1; RCT]; 68 [EL 1; RCT]). Strategies aimed at lowering glycemic levels (as evidenced by A1C lowering) have decreased microvascular complications and, in some cases, macrovascular complications (48 [EL 3; SS]; 49 [EL 1; RCT, posttrial monitoring]; 50 [EL 3; SS]; 51 [EL 1; RCT]; 52 [EL 1; RCT, posthoc analysis]; 69 [EL 1; RCT]). As discussed in "Q4. How are glycemic targets achieved?" as well as in the 2015 AACE Algorithm for Diabetes Management (4 [EL 4; NE]), some newer therapies carry a lower risk of hypoglycemia, which may enable more patients to safely achieve individualized target A1C levels. To achieve the target A1C levels, fasting and preprandial glucose levels should be <110 mg/dL. The evidence in support of a PPG target is predominantly based on cross-sectional and prospective epidemiologic studies with few RCTs (4 [EL 4; NE]; 70 [EL 2; PCS]).

4.Q4. How are Glycemic Targets Achieved for T2D?

4.Q4.1. Therapeutic Lifestyle Changes

The components of therapeutic lifestyle changes include healthful eating, regular physical activity, sufficient sleep, avoidance of tobacco products, limited alcohol consumption, and stress reduction.

Nutritional medicine in DM comprehensive care consists of 3 components: counseling about general healthful eating, MNT, and specialized nutrition support. The last category applies to those patients receiving enteral or parenteral nutrition in which medications provided for glycemic control must be synchronized with carbohydrate delivery; however, this topic is beyond the scope of this CPG. The components of healthful eating for patients with DM are described in Table 8 (4 [EL 4; NE]; 71 [EL 3; SS]; 72 [EL 4; position NE]; 73 [EL 4; position NE]; 74 [EL 4; review NE]; 75 [EL 3; SS]; 76 [EL 1; RCT]; 77 [EL 4; review NE]; 78 [EL 4; review NE]; 79 [EL 4; review NE]; 80 [EL 4; NE review]; 81 [EL 4; review NE]; 82 [EL 4; review NE]; 83 [EL 2; MNRCT]; 84 [EL 4; CPG NE]; 85 [EL 2; PCS, data may not be generalizable to patients with diabetes already]; 86 [EL 3; SS]; 87 [EL 4; review NE]; 88 [EL 4; NE review]; 89 [EL 4; review NE]). The physician

or a registered dietitian should discuss these recommendations in plain language with patients at the initial visit after DM diagnosis and then periodically during follow-up office visits (4 [EL 4; NE]). Comments should be broad and nontechnical, about foods suitable for the general population (including those without DM) that promote health versus foods that may promote disease or disease complications. Discussions between patients and healthcare professionals should include information on specific foods and meal planning, grocery shopping, and dining-out strategies.

MNT addresses the metabolic needs of patients with DM and involves a more detailed discussion, usually in terms of calories, grams, and other metrics. The goal is to intensify efforts of healthy eating behaviors aimed at optimizing glycemic control and reducing the risks of DM complications. These recommendations should also be discussed and implemented by the physician or a registered dietitian for all patients with DM.

All patients should be advised how to achieve and maintain a healthful weight. For overweight individuals with a BMI of 25 to 29.9 kg/m^2, this corresponds to achieving a normal range BMI of 18.5 to 24.9 kg/m^2. For obese individuals with a BMI >30 kg/m^2, the initial recommended target is a weight loss of at least 5 to 10% of body weight. Several randomized clinical trials lasting 1 year (90 [EL 1; RCT, single blinded]; 91 [EL 1; RCT, not blinded, adherence not controlled for]) or 2 years (92 [EL 1; RCT, not blinded]; 93 [EL 1; RCT]) have compared diets and report successful weight loss regardless of macronutrient content (e.g., low fat, low carbohydrate, etc.). In a randomized comparison of the Atkins, Ornish, Weight Watchers, and Zone diets, weight change did not differ between diets (about 5 kg), and adherence to the diet was the single most important criterion of successful weight loss (90 [EL 1; RCT, single blinded]). The key to adopting the principles given in Tables 7 and 8 is to personalize the recommendations on the basis of a patient's specific medical conditions, lifestyle, and behaviors. Patients unable to accomplish this should be referred to a registered dietitian or weight-loss program with a proven success rate. In areas underserved by registered dietitians, physicians should take on more responsibility during patient encounters for nutritional counseling and reinforcing healthful eating patterns.

A review and position paper on MNT for both T1D and T2D was recently published (94 [EL 4; NE]). Key recommendations address the need for consistency in day-to-day carbohydrate intake, adjusting insulin doses to match carbohydrate intake (e.g., use of carbohydrate counting), limitation of sucrose-containing or high-glycemic index foods, adequate protein intake, "heart-healthy" diets, weight management, regular physical activity, and increased glucose monitoring. Data from the Look AHEAD (Action for Health in Diabetes) and DPP studies provide additional evidence that lowering caloric intake is the main driver for weight loss. The Look AHEAD trial is the longest RCT to evaluate intensive lifestyle change on weight loss in patients with T2D (95 [EL 1; RCT, not blinded]). The maximal weight loss in patients with T2D in Look AHEAD was greater than among patients with prediabetes in the DPP. 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 sessions (96 [EL 1; RCT]). For a discussion of the Look AHEAD results, see section 4.Q13.4.

There is good evidence that regular physical activity improves glucose control in persons with T2D (97 [EL 1; RCT, small sample size]; 98 [EL 2; NRCT]; 99 [EL 2; NRCT]; 100 [EL 2; NRCT]). Because physical activity is usually combined with caloric restriction and weight loss, as in combined lifestyle intervention programs, distinguishing the effects of increased physical activity alone from those of calorie restriction and weight loss is often difficult. However, studies on exercise alone show improved glucose control (101 [EL 1; RCT]; 102 [EL 4; commentary NE]; 103 [EL 1; RCT]). Regular physical exercise—both aerobic exercise and strength training—is important to improve a variety of CVD risk factors, decrease the risk of falls and fractures, and improve functional capacity and sense of well-being (102 [EL 4; commentary NE]). Physical activity is also a main component in weight loss and maintenance programs. Activity of at least 150 minutes per week of moderate-intensity exercise such as brisk walking (e.g., a 15- to 20-minute mile) or its equivalent (e.g., yoga, walking during golf, water aerobics, physical play with children, etc.), is now well accepted and part of the nationally recommended guideline for physical activity. For persons with T2D, recommendations include flexibility and strength training exercises in addition to aerobic exercise (101 [EL 1; RCT]). The Look AHEAD study had a goal of ≥175 minute/week of moderately intense activity in addition to a focus on increased lifestyle daily activity. The 1-year results revealed a significant association between minutes of physical activity and weight loss, indicating that those who were more active lost more weight (96 [EL 1; RCT]). The benefits and risks of increasing physical activity and the practical aspects of implementing a physical training program in people with T2D are discussed in detail in a position paper (104 [EL 4; consensus NE]). The key points are that patients must be evaluated initially for contraindications and/or limitations to increased physical activity; an exercise prescription should be developed for each patient according to both goals and limitations; and additional physical activity should be started slowly and built up gradually.

People with T1D generally experience the same benefits of regular physical exercise as T2D patients. However, patients requiring insulin therapy must also learn about the acute and chronic effects of exercise on glucose regulation and how to adjust insulin dosages and food intake to

maintain glucose control before, during, and after exercise to avoid significant hypoglycemia or hyperglycemia (105 [EL 4; NE]).

The final component of therapeutic lifestyle change is the use of behavior modification strategies in support of healthy eating and regular activity. However, several studies have shown that attempts to include lifestyle change counseling as part of routine primary care fail to help patients achieve or sustain weight loss. In addition, the initial success of a structured lifestyle program may fade without continued support (106 [EL 1; RCT, not blinded]), suggesting that ongoing behavioral strategies in addition to education on healthy eating and physical activity should be included in lifestyle intervention programs. Look AHEAD's long-term behavior modification program included regular individual and periodic group contact modeled on the DPP. The results demonstrated that extended behavioral support within an intensive lifestyle intervention program helps facilitate meaningful weight loss for up to 8 years (95 [EL 1; RCT, not blinded]). The behavioral strategy "toolbox" in both the DPP and Look AHEAD studies suggested an array of options including motivational interviewing, goal setting to improve adherence, refresher courses, campaigns, and incentives such as prizes.

4.Q4.2. Antihyperglycemic Pharmacotherapy

The goal of glycemic treatment in subjects with T2D is to achieve clinical and biochemical targets with as few adverse consequences as possible. This straightforward statement has important implications for the choice of specific antihyperglycemic agents in T2D, which should be guided by the patient's medical needs and treatment goals, as well as the agent's glucose-reducing potency, tolerability and side-effect profile, ease of administration and convenience, cost effectiveness, and extraglycemic effects. All currently available oral glucose-lowering agents are more or less similar in their glucose-lowering potency (107 [EL 1; MRCT]; 108 [EL 3; CSS]). As monotherapy, most oral antihyperglycemic agents reduce A1C by 0.5 to 2.0%. Larger decrements are seen in patients with more marked A1C elevations, likely explaining the apparent greater efficacy of older agents versus newer ones (4 [EL 4; NE]). However, the various classes of glucose-lowering agents differ widely in other respects (Table 9).

Complete descriptions of available antihyperglycemic agents, their mechanisms of action, and rationale for use in different clinical situations can be found in the 2015 AACE Comprehensive Diabetes Management Algorithm Consensus Statement (4 [EL 4; NE]) as well the 2012 Joint ADA/European Association for the Study of Diabetes (EASD) Algorithm Consensus Statement (109 [EL 4; NE]). In addition to lowering glucose, the priority in DM management is to minimize the risks of hypoglycemia and weight gain. The AACE preferentially recommends agents that do not increase these risks (Table 10).

Metformin carries a low risk of hypoglycemia, is weight neutral, produces durable antihyperglycemic effects, and has robust cardiovascular safety; however, it should not be used in patients with advanced renal impairment (69 [EL 1; RCT]; 110 [EL 1; RCT]; 111 [EL 4; NE]; 112 [EL 2; RCCS]). It is equally efficacious across all weight categories (normal, overweight, and obese) in T2D (113 [EL 1; MRCT]). Metformin may have anorectic effects, is sometimes associated with weight loss, may cause gastrointestinal (GI) adverse effects (e.g., dyspepsia, loose stools, or diarrhea), and may be associated with the development of vitamin B_{12} deficiency over time (114 [EL 1; RCT]). Metformin should be continued as background therapy and used in combination with other agents, including insulin, in patients who do not reach their glycemic target on monotherapy. When metformin is contraindicated or not tolerated, acceptable alternatives include GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, and α-glucosidase inhibitors. TZDs, sulfonylureas, and glinides may also be used, although caution should be exercised owing to the potential for weight gain, hypoglycemia, or other risks.

Sulfonylureas and glinides increase insulin secretion in a glucose level-independent fashion. Ideal candidates for treatment with sulfonylureas are patients with T2D whose duration of DM is <5 years and who do not have end-organ complications (e.g., CKD), and are willing to follow a healthy diet and exercise plan and perform SMBG to reduce the likelihood of hypoglycemia. For unknown reasons, not all patients with T2D respond to sulfonylureas (primary failure), and antihyperglycemic effectiveness declines after several years of treatment in many patients (secondary failure) (115 [EL 1; RCT]). The main side effect of the sulfonylureas is hypoglycemia, which can be more prolonged than that produced by insulin, particularly when longer-acting formulations are used in the elderly (116 [EL 4; NE]). Renal insufficiency also increases the risk of sulfonylurea-associated hypoglycemia.

TZDs have been shown to improve insulin sensitivity and to preserve or improve β-cell secretory function in patients with T2D. In addition to their glycemic effects, these agents also improve a wide range of cardiovascular risk markers (117 [EL 1; RCT]; 118 [EL 1; MRCT]) and may help prevent central nervous system insulin resistance-related cognitive dysfunction (119 [EL 2; PCS]). 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 myocardial infarction, stroke, and all-cause mortality (120 [EL 1; MRCT]). TZDs are also useful in patients with nonalcoholic steatohepatitis (121 [EL 4; review NE]); however, they lead to weight gain comparable to that with sulfonylurea and insulin therapy (122 [EL 2; MNRCT]). TZDs may also cause fluid retention (particularly in patients with cardiac or renal disease), which may contribute

to TZD-associated weight gain and peripheral edema. Because of this, TZDs are contraindicated in patients with New York Heart Association class 3 and 4 congestive heart failure. TZDs can also reduce bone mineralization and are associated with nonosteoporotic bone fractures (123 [EL 1; RCT, posthoc analysis]; 124 [EL 2; PCS]). 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 (125 [EL 4; review NE]). The FDA recently lifted this restriction (126 [EL 4; NE]). 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 (127 [EL 4; NE]). A recent 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 cancer (128 [EL 3; SS]).

The GLP-1 receptor agonists and DPP-4 inhibitors increase insulin secretion in a glycemic level-dependent manner. In addition to glucose lowering, the GLP-1 receptor agonists may slow gastric emptying, promote early satiety, and reduce food intake, which may result in weight loss. Currently approved GLP-1 receptor agonists include albiglutide, dulaglutide, exenatide, and liraglutide, which are administered by injection on a twice daily, daily, or weekly basis. These agents are most useful as add-on therapies for patients with inadequately controlled DM during oral monotherapy (129 [EL 1; RCT]; 130 [EL 1; RCT follow-up study]; 131 [EL 1; RCT]; 132 [EL 1; RCT]; 133 [EL 1; RCT]; 134 [EL 4; animal study NE]; 135 [EL 1; RCT]; 136 [EL 1; RCT]; 137 [EL 1; RCT]). Several clinical trials have compared the effects of adding a GLP-1 receptor agonist (exenatide twice daily or liraglutide) to insulin (glargine insulin or mixed insulin) in patients with inadequately controlled T2D on oral agents (138 [EL 1; RCT]; 139 [EL 1; RCT]; 140 [EL 1; MRCT]). All of the studies show equivalent or slightly better A1C lowering by GLP-1 receptor agonists with the advantages of a 2- to 3-kg weight loss and little or no additional hypoglycemia.

The main adverse effects with GLP-1 receptor agonists are nausea, vomiting, and diarrhea (141 [EL 1; MNCT]), which usually diminish over time. Approximately 5 to 10% of patients cannot tolerate these drugs due to GI effects. In rodents, GLP-1 receptor agonists may increase the frequency of benign and malignant C-cell neoplasms; however, in humans, neither acute pancreatitis nor medullary thyroid carcinoma has been convincingly shown to be caused by incretin-based therapies (142 [EL 4; NE]). Nevertheless, GLP-1 receptor agonists should be used cautiously in patients with a history of pancreatitis and discontinued if acute pancreatitis develops during use. All GLP-1 receptor agonists except twice-daily exenatide are contraindicated in patients with a personal or family history of

Table 10
Pharmacologic Agents for T2D Treatment[a]

Monotherapy	Dual therapy	Triple therapy
	Metformin (or other first-line agent) plus	First- and second-line agent plus
Metformin	**GLP1RA**	**GLP1RA**
GLP1RA	**SGLT2I**	**SGLT2I**
SGLT2I	**DPP4I**	TZD[b]
DPP4I	TZD[b]	Basal insulin[b]
AGI	Basal insulin[b]	**DPP4I**
TZD[b]	**Colesevelam**	**Colesevelam**
SU/glinide[b]	**BCR-QR**	**BCR-QR**
	AGI	**AGI**
	SU/glinide[b]	SU/glinide[b]

Abbreviations: A1C = hemoglobin A1C; AGI = α-glucosidase inhibitors; BCR-QR = bromocriptine quick release; DPP4I = dipeptidyl peptidase 4 inhibitors; GLP1RA = glucagon-like peptide 1 receptor agonists; SGLT2I = sodium-glucose cotransporter 2 inhibitors; SU = sulfonylureas; TZD = thiazolidinediones.

[a] Intensify therapy whenever A1C exceeds individualized target. Boldface denotes little or no risk of hypoglycemia or weight gain, few adverse events, and/or the possibility of benefits beyond glucose lowering.

[b] Use with caution.

medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2. The FDA has stated that patients taking a GLP-1 receptor agonist do not need to be monitored for medullary thyroid carcinoma (e.g., with calcitonin levels).

DPP-4 inhibitors do not cause weight gain; they can be administered in patients with CKD at full dosage when not cleared by the kidneys (linagliptin) or with appropriate dose adjustment for agents that are renally cleared (sitagliptin, saxagliptin, alogliptin); they lack significant GI adverse effects (143 [EL 4; opinion NE]); and they have been associated with reduction in cardiovascular events in analyses of registration trials (144 [EL 1; MRCT]), although neither benefit nor harm was seen in cardiovascular outcome studies conducted in subjects with advanced CVD in placebo-controlled, randomized studies with alogliptin or saxagliptin (145 [EL 1; RCT]; 146 [EL 1; RCT]). The trial comparing saxagliptin with placebo showed an increased likelihood of hospitalization for congestive heart failure and an increase in hypoglycemia (146 [EL 1; RCT]); this should lead to caution in the use of this agent in persons with a history of heart failure who also have existing CVD. With regard to hypoglycemia, it should be noted that approximately 40% of the patients receiving saxagliptin in the trial also received a sulfonylurea, a combination that increases the likelihood of hypoglycemia. 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 versus 6.1% with comparators; risk ratio, 1.2; 95% confidence interval [CI] 1.0 to 1.4) and a rare hypersensitivity reaction (141 [EL 1; MNCT]).

The SGLT2 inhibitors are the newest oral agents approved for the treatment of T2D. The glucosuric effect of these agents leads to weight loss in most patients. Most patients also experience decreases in systolic blood pressure. Elderly patients on loop diuretics need to be monitored for postural hypotension. Because they exert their glycemic effects in the kidney, these agents have limited efficacy in patients with CKD. Also, by increasing glycosuria, SGLT2 inhibitors may increase the risk of urinary infection and fungal genital tract infection. Small increases in LDL-C levels (4 to 8 mg/dL) occurred with canagliflozin, dapagliflozin, and empagliflozin in pivotal trials. Dehydration due to increased diuresis could lead to hypotension and adverse cardiovascular effects, although no cardiac safety signals have been reported (147 [EL 4; NE]). Bone fracture has been described in postmarketing safety reporting. As with all new agents, aggressive postmarketing surveillance for SGLT2 inhibitor adverse effects is ongoing.

Colesevelam, α-glucosidase inhibitors, and bromocriptine primarily affect PPG levels and are worth consideration in selected patients. Colesevelam carries a low risk of hypoglycemia and also reduces LDL-C, for which it was originally developed. Its main adverse effect is constipation, but it is not systemically absorbed and therefore is not likely to have systemic adverse effects (148 [EL 4; NE]).

α-Glucosidase inhibitors also have a low risk for hypoglycemia, although patients may not tolerate the GI side effects (e.g., bloating, flatulence, diarrhea). Clinical trials have shown some cardiovascular benefit in patients with IGT or DM (36 [EL 1; RCT]; 37 [EL 1; RCT]).

The dopamine receptor agonist bromocriptine does not cause hypoglycemia. It can cause nausea and orthostasis and should not be used in patients taking antipsychotic drugs. Bromocriptine may be associated with reduced cardiovascular event rates (149 [EL 1; RCT]).

Because many patients do not achieve adequate glycemic control with monotherapy, combining antihyperglycemic agents is often appropriate (4 [EL 4; NE]). Metformin is quite effective when administered in combination with the other agents, as long as one avoids its use in patients with CKD (creatinine ≥1.4 mg/dL in females or ≥1.5 mg/dL in males) (4 [EL 4; NE]) or GI intolerance. Sulfonylureas, in contrast, are 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 receptor agonists, and SGLT2 inhibitors (122 [EL 2; MNRCT]).

4.Q4.2.1. Insulin Use in T2D

Insulin is usually initiated in T2D when combination therapy with other agents fails to maintain the glycemic goal, or when a patient, whether drug naïve or on a treatment regimen, presents with an A1C level >9.0% and symptomatic hyperglycemia (4 [EL 4; NE]). The traditional postponement of insulin therapy after prolonged failure of lifestyle and oral agents to achieve glycemic control has been revised in the last decade to incorporate primarily basal insulin therapy much sooner, often in combination with oral agents or GLP-1 receptor agonists (4 [EL 4; NE]; 109 [EL 4; NE]).

Insulin therapy may be initiated as a basal, basal-bolus, prandial, or premixed regimen, although for most patients, starting with a basal insulin analog added to the existing antihyperglycemic regimen is preferred (Table 11) (4 [EL 4; NE]). The combination of insulin with any antihyperglycemic agent raises the potential for hypoglycemia. Patients should be closely monitored, and those on sulfonylureas or glinides may require dosage reductions or discontinuation of the oral agent. TZDs can be associated with weight gain, edema, and increased risk of congestive heart failure in combination with insulin. Basal insulin analogs are preferred over NPH insulin because of a reduced risk of hypoglycemia (150 [EL 1; RCT]; 151 [EL 1; MRCT]; 152

Table 11
Recommended Steps for the Addition of Insulin to Antihyperglycemic Therapy (4 [EL 4; NE])

Glucose Value	Total Daily Dose	Notes/Caveats
Step 1. Start basal (long-acting insulin)		Consider discontinuing SU therapy Basal analogs preferred over NPH
A1C <8%	0.1-0.2 units/kg	
A1C >8%	0.2-0.3 units/kg	
Step 2. Titrate insulin every 2-3 days to reach glycemic goals[a]		
Fixed regimen	Increase by 2 units/day	
Adjustable regimen		
FBG >180 mg/dL	Add 4 units	
FBG 140-180 mg/dL	Add 2 units	
FBG 110-139 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; FBG = fasting blood glucose; NPH = neutral protamine Hagedorn; SU = sulfonylureas.
[a] For most patients 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 patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk.

[EL 1; MRCT]; 153 [EL 1; RCT]). The insulin regimen to be prescribed and the exact treatment goals should be discussed with the patient.

Insulin-treated patients should be instructed in SMBG. Most insulin-treated patients with T2D should conduct SMBG ≥2 times daily, but the frequency and timing should be dictated by the particular needs and goals of the patient, as well as hypoglycemia risk (see Q18. When and how should glucose monitoring be used?).

Premixed insulins are popular with patients, but they provide less dosing flexibility and have been associated with a higher frequency of hypoglycemia compared to basal and basal-bolus regimens (154 [EL 1; RCT]; 155 [EL 3; SS]; 156 [EL 1; RCT]). Nevertheless, there are some patients for whom a simpler regimen is a reasonable compromise.

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 receptor agonist, insulin therapy intensification to a basal-bolus regimen (using a rapid-acting insulin analog or inhaled insulin) should be considered (Table 12).

Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with T2D (157 [EL 1; RCT, small sample size]; 158 [EL 1; RCT, not blinded]). The incretins (GLP-1 receptor agonists and DDP-4 inhibitors) have properties similar to those of pramlintide and also increase endogenous insulin 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 receptor agonists and basal insulin analogs have shown an additive effect on blood glucose decreases (138 [EL 1; RCT]; 159 [EL 1; RCT]; 160 [EL 4; NE]; 161 [EL 1; RCT]; 162 [EL 1; RCT, not blinded, not placebo controlled]). The combined use of DPP-4 inhibitors or SGLT2 inhibitors with insulin is also effective in improving glycemic control with a relatively low risk of hypoglycemia (163 [EL 1; RCT]; 164 [EL 1; RCT]).

Hypoglycemia and weight gain are the most common adverse effects of insulin therapy (4 [EL 4; NE]; 165 [EL 4; NE]). Rates and the clinical impact of hypoglycemia are frequently underestimated (166 [EL 4; NE]), but about 7 to 15% of insulin-treated patients with T2D experience at least 1 episode of hypoglycemia per year (167 [EL 1; RCT, not blinded]), and 1 to 2% have severe hypoglycemia (165 [EL 4; NE]; 166 [EL 4; NE]). The frequency of hypoglycemia increases with intensive insulin targets, use of sulfonylureas, decreased caloric intake, delayed meals, exercise, alcohol consumption, CKD, T2D duration, and cognitive impairment (166 [EL 4; NE]). Large randomized trials conducted in subjects with established T2D have revealed that subjects with a history of 1 or more severe hypoglycemic events had an approximately two- to fourfold higher rate of

mortality for reasons that remain unknown (64 [EL 3; SS]; 168 [EL 1; RCT]). It has been proposed that hypoglycemia may be a marker for persons at higher risk of death rather than being its proximate cause (166 [EL 4; NE]); nevertheless, avoidance of hypoglycemia by appropriately reducing insulin dosages seems prudent.

Patients receiving insulin gain about 1 to 3 kg more weight than they do with other treatment agents. Patients with proliferative retinopathy and an A1C >10% are at highest risk of worsening retinopathy (169 [EL 4; NE]).

More detail on insulin therapy initiation, titration, and intensification for T2D can be found in the 2015 AACE Comprehensive Diabetes Management Algorithm (4 [EL 4; NE]).

4.Q5. How Should Glycemia in T1D be Managed?

Insulin therapy is necessary for life in all patients with T1D (EL 1; "all-or-nothing"). Physiologic insulin regimens, using 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 1 component of a comprehensive treatment strategy for patients with T1D.

Numerous RCTs have compared basal insulin analogs with NPH insulin in addition to rapid-acting analogs with regular human insulin. With insulin analogs, no additional improvements in A1C have been shown, but there is a

Table 12
Recommended Steps for the Intensification of Insulin Therapy When Prandial Control is Needed (4 [EL 4; NE])

Therapeutic option	Insulin dose	Notes/caveats
Step 1. Add prandial therapy		
GLP-1 receptor agonist, SGLT2 inhibitor, or DPP-4 inhibitor	—	If glucose goals remain unmet, add prandial insulin
Prandial insulin	TDD 0.3-0.5 units/kg (50% basal; 50% prandial)	Basal + prandial insulin analogs preferred over NPH + regular insulin or premixed insulin
Step 2. Titrate insulin every 2-3 days to reach glycemic goals[a]		
Fixed regimen	Increase TDD by 2 units/day	
Adjustable regimen		
FBG >180 mg/dL	Increase TDD by 4 units	
FBG 140-180 mg/dL	Increase TDD by 2 units	
FBG 110-139 mg/dL	Increase TDD by 1 unit	
2-h PPG or next premeal glucose >180 mg/dL	Increase prandial dose for the next meal by 10%	
Premixed insulin		
FBG/premeal BG >180 mg/dL	Increase TDD by 10%	
Step 3. Monitor for hypoglycemia		
Fasting hypoglycemia	Reduce basal insulin dose	
Nighttime hypoglycemia	Reduce basal insulin or reduce short/rapid-acting insulin taken before supper or evening snack	
Between meal hypoglycemia	Reduce previous premeal short/rapid-acting insulin	

Abbreviations: BG = blood glucose; DPP-4 = dipeptidyl peptidase 4 inhibitors; FBG = fasting blood glucose; GLP-1 = glucagon-like peptide 1 receptor agonists; NPH = neutral protamine Hagedorn; PPG = postprandial glucose; SGLT2 = sodium glucose cotransporter 2; TDD = total daily dose.

[a] For most patients 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 patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk.

consistent reduction of moderate and severe hypoglycemia (170 [EL 4; review NE]). In comparisons of MDI and CSII for T1D, there have been small but consistent improvements in A1C, as well as substantial reductions in severe hypoglycemia (171 [EL 1; MRCT]; 172 [EL 1; MRCT]).

4.Q5.1. Basic Principles of Insulin Therapy in T1D

The starting dose of insulin is usually based on weight, with doses ranging from 0.4 to 0.5 units/kg/day of total insulin with higher amounts required for patients who are obese (increasingly common in T1D) or have a sedentary lifestyle, as well as during puberty.

In general, basal insulin requirements are usually 40 to 50% of the total daily insulin doses. No data support the superiority of 2 injections of a basal insulin analog over 1 injection of basal insulin analog in patients with T1D.

The dose of prandial insulin is usually determined by estimating the carbohydrate content of the meal. Insulin-to-carbohydrate (I:C) ratios usually range from 1:20 for the very insulin sensitive to 1:5 for the insulin-resistant patient. Similarly, correction dose insulin for premeal or between-meal hyperglycemia is based on the insulin sensitivity factor (ISF), which is based on the overall insulin sensitivity of the patient, loosely estimated by the individual's total daily insulin dose. 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 blood glucose. The most commonly used formula is:

1,800/total daily dose of insulin = Number of mg/dL of glucose that will be reduced by 1 unit of insulin

The other key factor that needs to be appreciated is insulin action time. For most subcutaneous injections, this ranges from 4 to 6 hours. There are no data to quantify an individual patient's insulin action time and in fact it can change from day to day.

With the knowledge of the I:C ratio, ISF, and insulin action time, patients on MDI or CSII can calculate the appropriate correction dose insulin. This is significantly simpler with CSII, as most pumps include bolus calculators to perform the calculations by pressing a few buttons. For those using MDI, there are a variety of smart phone apps available, in addition to several blood glucose meters that can assist patients with these calculations. Most patients using MDI, however, will need to estimate the "insulin on board" from the last injection of prandial insulin based on standard curves that can be provided to them (170 [EL 4; review NE]).

4.Q5.2. Adjunctive Medications for T1D

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 patients do not appropriately reduce the prandial insulin dosage (173 [EL 1; RCT]; 174 [EL 1; RCT]; 175 [EL 1; RCT]; 176 [EL 1; MRCT]). Tachyphylaxis is often seen after several years of therapy.

While there is growing interest and anecdotal reports of successful use of both GLP-1 receptor agonists and SGLT2 inhibitors in T1D, to date appropriate trials have not been published, and formal recommendations cannot be provided. In addition, recommendations for the use of metformin in T1D cannot be made due to lack of indication and concerns of lactic acidosis in a population predisposed to ketoacidosis. Nevertheless, the use of metformin in T1D has been of great interest, and new data should be available in the future (177 [EL 1; MRCT]).

4.Q6. How is Hypoglycemia Managed?

4.Q6.1. Definition

The classical definition of hypoglycemia in patients with DM is a low blood glucose level accompanied by symptoms of hypoglycemia (e.g., palpitations, hunger; see section 4.Q6.2) that are relieved by the ingestion of glucose (i.e., the Whipple triad) (178 [EL 4; review NE]). However, hypoglycemia may be asymptomatic, and any blood glucose <70 mg/dL is generally considered hypoglycemia (179 [EL 4; NE]). In addition, hypoglycemia symptoms can occur in the normal glucose range in a patient with very high glucose levels that drop quickly. SMBG can be helpful but is not necessarily diagnostic because of glucose meter inaccuracy.

Severe hypoglycemia is defined as any low blood glucose event that requires assistance from another person to administer carbohydrates or glucagon or take other corrective action (179 [EL 4; NE]).

4.Q6.2. Symptoms

Hypoglycemia manifests as neurogenic and/or neuroglycopenic symptoms that range in severity from mild to life threatening and include anxiety, palpitations, tremor, sweating, hunger, paresthesias, behavioral changes, cognitive dysfunction, seizures, and coma. Certain hypoglycemia-related responses (psychomotor function) are altered in the elderly compared with younger patients. Although severe hypoglycemia generally results in recognizable symptoms, mild-to-moderate hypoglycemia may remain asymptomatic and unreported in patients with T2D or with hypoglycemia unawareness (179 [EL 4; NE]).

4.Q6.3. Etiology

In patients with DM, iatrogenic hypoglycemia stems from an imbalance among insulinogenic therapy, food intake, physical activity, organ function (gluconeogenesis), and counterregulation with glucagon and/or

epinephrine (hypoglycemia-associated autonomic failure). Hyperinsulinemia, increased alcohol intake, starvation, and organ failure may be aggravating factors (166 [EL 4; NE]; 180 [EL 4; NE]). Noniatrogenic hypoglycemia (i.e., insulinoma) is beyond the scope of these guidelines.

4.Q6.4. Risks

The primary cause of hypoglycemia is intensification of therapy to achieve a lower A1C target, as demonstrated by intensive therapy trials. Over 3.5 years in the ACCORD study, severe hypoglycemia occurred at an annualized rate of 3.1% of patients in the intensive therapy group (mean endpoint A1C 6.4%; target <6.0%) versus 1.0% per year in the standard therapy group (mean endpoint A1C 7.5%) (62 [EL 1; RCT]). During the ADVANCE study, in which the goal A1C of 6.5% was met in the intensive group, 0.7% of intensively treated patients experienced severe hypoglycemia on an annual basis compared with 0.4% of patients per year in the standard care group (57 [EL 1; RCT]). Finally, in the UKPDS (United Kingdom Prospective Diabetes Study), wherein intensive treatment led to a mean endpoint A1C of 7.0%, hypoglycemia occurred in 1.8% of insulin-treated patients per year in the intensive group versus 0.7% of conventionally treated patients per year (69 [EL 1; RCT]). The risk of hypoglycemia is greater in older patients 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 (181 [EL 3; SS]; 182 [EL 2; RCCS]; 183 [EL 2; PCS]). 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 (180 [EL 4; NE]).

4.Q6.5. Sequelae

Recent studies have suggested an association of hypoglycemia with adverse cardiovascular events. In ADVANCE, severe hypoglycemia was associated with significant risk increases for cardiovascular events including death (168 [EL 1; RCT]). 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 (58 [EL 1; RCT]; 64 [EL 3; SS]). Moreover, the HR for hypoglycemia-related mortality was even higher in the standard therapy arm of that study (adjusted HR in intensive treatment arm: 1.41, 95% CI, 1.03 to 1.93; in standard therapy arm: 2.30, 95% CI, 1.46 to 3.65) (64 [EL 3; SS]). A recent meta-analysis of prospective and retrospective clinical trials demonstrated that severe hypoglycemia doubled the risk of cardiovascular events (184 [EL 2; MNRCT]), while an observational trial showed that, over a period of 5 years, mortality was 3.4 times higher among patients who reported severe hypoglycemia at baseline (185 [EL 2; PCS]). 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 (186 [EL 4; NE]).

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, myocardial infarction, acute cardiac failure, ventricular arrhythmias, and sudden death (166 [EL 4; NE]; 180 [EL 4; NE]; 187 [EL 4; NE]). The complications of hypoglycemia are also associated with short-term disability and higher healthcare costs (188 [EL 4; NE]).

4.Q6.6. Management

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 (166 [EL 4; NE]).

Long-term management of hypoglycemia depends on appropriate adjustment of therapy to prevent hypoglycemia or reduce its frequency and severity in patients prone to hypoglycemia (e.g., the elderly and patients with T1D). In T2D, hypoglycemia typically occurs in association with use of exogenous insulin, sulfonylureas (especially glyburide) (189 [EL 1; MRCT]), 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 sulfonylureas or insulin. Therefore, in adults with T2D, treatment strategies should emphasize classes of pharmaceutical agents that are not associated with severe hypoglycemia, many of which are available (Table 9). Also, the role of hypoglycemia must be considered in determining ideal A1C goals for each patient. These issues are reviewed in the AACE algorithm for T2D (4 [EL 4; NE]).

SMBG is an important tactic to help patients document hypoglycemia, although it is essential that the glucose meter meet accuracy standards. CGM may be useful in patients with recurrent asymptomatic hypoglycemia (hypoglycemia unawareness) (179 [EL 4; NE]).

Patients who have marked swings in glucose levels are particularly susceptible to hypoglycemia unawareness. This condition can be reversed by a period of therapy that dampens glycemic excursions and hypoglycemia avoidance (190 [EL 2; NRCT]; 191 [EL 3; SCR]).

4.Q7. How is Hypertension Managed in Patients with Diabetes?

The majority of persons with T2D either have uncontrolled hypertension or are on treatment for elevated blood pressure (192 [EL 3; SS]). Hypertension is not only more

prevalent in persons with T2D than in the general population, it also predicts progression to DM. Once diagnosed with hypertension, an individual is 2.5 times more likely to be diagnosed with DM within the next 5 years (193 [EL 2; PCS]; 194 [EL 4; review NE]). The combination of hypertension and DM magnifies the risk of DM-related complications. The UKPDS demonstrated that hypertension treatment decreased both micro- and macrovascular complications of DM (195 [EL 1; RCT]). This study showed that each 10 mm Hg decrease in systolic blood pressure (achieved with either an ACE inhibitor [captopril] or an β-adrenergic blocker [atenolol]) was associated with a 15% reduction in rates of DM-related mortality, an 11% reduction in myocardial infarction, and a 13% reduction in the microvascular complications of retinopathy or nephropathy (196 [EL 2; PCS]).

Subsequent trials that have included large numbers of persons with DM, including the HOT (Hypertension Optimal Treatment) trial (197 [EL 1; RCT]), the HOPE (Heart Outcomes Prevention Evaluation) study (198 [EL 1; RCT]), the LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) study (199 [EL 1; RCT]), and ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (200 [EL 1; RCT]), have demonstrated that blood pressure control improves cardiovascular outcomes when aggressive blood pressure targets are achieved. Numerous other studies have also demonstrated decreased nephropathy and retinopathy progression. Based on these data, the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), AACE, and ADA previously recommended that blood pressure in DM be controlled to <130/80 mm Hg (201 [EL 4; NE]; 202 [EL 4; CPG NE]; 203 [EL 4; NE]; 204 [EL 4; NE]).

However, the target for blood pressure lowering remains somewhat controversial as clinical trial data to support the level of 130/80 mm Hg are sparse. Epidemiologic data suggest no evidence of a threshold for adverse outcomes, with a normal blood pressure level <115/75 mm Hg (205 [EL 4; review NE]). Clinical trial data show that intensifying therapy with blood pressure-lowering medications slows the progression of nephropathy and retinopathy (195 [EL 1; RCT]; 196 [EL 2; PCS]; 206 [EL 1; RCT, questionnaires and other variables may have confounded]). Neither the ACCORD blood pressure trial nor subanalyses of other large blood pressure trials have shown that targeting a systolic blood pressure <120 mm Hg (compared with <140 mm Hg) has any impact on the standard composite outcome of fatal and nonfatal major cardiovascular events in persons with DM, although stroke was significantly reduced (HR 0.59; 95% CI, 0.39 to 0.89; $P = .01$) (207 [EL 1; RCT]). Thus, data from prospective RCTs do not support a positive effect of blood pressure targets below 130/80 mm Hg on cardiovascular outcomes. Consequently, various recently published guidelines from different societies have generally recommended a blood pressure target for persons with DM of <140/80 to 90 mm Hg, with an option to individualize to the lower target of <130/80 mm Hg (8 [EL 4; NE]; 208 [EL 4; NE]; 209 [EL 4; NE]; 210 [EL 4; NE]; 211 [EL 4; NE]; 212 [EL 4; NE]).

Once the diagnosis of hypertension is established, the data are clear that blood pressure lowering prevents both micro- and macrovascular complications associated with DM. Analysis of the UKPDS data suggests that blood pressure lowering should be the first priority in managing a patient presenting with newly diagnosed hypertension and DM. While glucose and lipid management remain important, blood pressure lowering will have the greatest and most immediate impact on morbidity and mortality (195 [EL 1; RCT]; 206 [EL 1; RCT, questionnaires and other variables may have confounded]).

Accurate measurement of blood pressure remains fundamental to the diagnosis and effective management of hypertension (8 [EL 4; NE]). 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 provides consistency in measurements. The patient must be properly prepared and positioned; blood pressure should 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 blood pressure in the standing position is indicated periodically, especially in those at risk for postural hypotension. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. At least 2, and preferably 3, measurements should be made and the average recorded.

While 24-hour ambulatory blood pressure monitoring (ABPM) is not included as part of the diagnostic criteria for hypertension, it has become an important tool for guiding patient management. Patients whose 24-hour ABPM mean blood pressure exceeds 135/85 mm Hg are nearly twice as likely to have a cardiovascular event as those with values that remain <135/85 mm Hg, irrespective of the level of the office blood pressure (213 [EL 4; review NE]). Routine use of ABPM, at least annually, should 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.

Blood pressure targets are based upon the combination of data from clinical trials and epidemiology studies and should be individualized for patients with consideration of their anticipated lifespan and risk factors for heart disease and stroke (e.g., presence of metabolic syndrome, smoking, and evidence of end organ damage). In the presence of multiple risk factors, consideration can be given to

an intensive goal of <120/80 mm Hg, provided it can be attained safely, with a less intense goal of <130/80 mm Hg in patients with complicated comorbidities and/or medication side effects. Frequent reassessment is needed to ensure that the blood pressure goal is maintained without unacceptable adverse effects. If side effects develop, consideration should be given to reducing dosage and/or changing the class of medication. If such changes do not alleviate symptoms, consideration should be given to relaxing the target to the higher level of <140/80 to 90 mm Hg, which will still provide cardiovascular protection.

The selection of medications can be guided by disease- and ethnic-specific considerations. Clinical trials with diuretics, ACE inhibitors, ARBs, β-adrenergic blockers, and calcium antagonists have a demonstrated benefit in the treatment of hypertension in both T1D and T2D (Table 13) (8 [EL 4; NE]; 197 [EL 1; RCT]; 198 [EL 1; RCT]; 199 [EL 1; RCT]; 214 [EL 1; RCT, posthoc analysis]). Whether any class is superior to another is no longer considered when choosing therapy because most patients with DM will need at least 2 to 4 drugs to achieve target blood pressure. The choice of pharmacologic agents is guided by additional considerations such as the presence of albuminuria, CVD, heart failure, or postmyocardial infarction status; possible metabolic side effects; number of pills per day; and cost. Early in the disease process, the primary concerns will be slowing of nephropathy and retinopathy while minimizing impact on triglycerides (Table 13). As heart disease develops, consideration of cardiovascular benefits factor into the choice of agents for blood pressure lowering; given that diastolic heart disease develops early in T2D, the use of ARBs could be considered earlier, before the diagnosis of systolic heart failure. However, the combination of multiple RAAS blockers (i.e., ACE inhibitor, ARB, and/or renin inhibitor) should generally be avoided (215 [EL 1; RCT]; 216 [EL 4; NE]).

The UKPDS study group performed a 10-year posttrial monitoring observational study that demonstrated a loss of benefit within 2 years if tight blood pressure control was not maintained (206 [EL 1; RCT, questionnaires and other variables may have confounded]). These data reinforce the imperative to initiate blood pressure-lowering therapy with continued reinforcement to maintain compliance with therapy. The introduction of fixed-dose combination tablets combining 2 or 3 agents in 1 pill has facilitated patient compliance and adherence with multidrug regimens and should be encouraged as part of initial therapy. The use of multiple fixed-dose combination tablets can provide a 4-drug regimen with just 2 tablets, thus allowing a patient to reach their blood pressure goal while optimizing compliance with therapy. ABPM should be utilized to guide blood pressure management because it allows assessment of the patient's blood pressure variability, thus facilitating medication adjustments to develop an appropriate individualized treatment regimen and avoid overtreatment.

4.Q8. How is Dyslipidemia Managed in Patients with Diabetes?

4.Q8.1. Lipid Targets

Treatment targets for dyslipidemia in DM are based on the presence of ASCVD risk factors including hypertension, a family history of ASCVD, low HDL-C, and smoking, as well as serum levels of LDL-C, other lipids, lipoproteins, or lipoprotein components (Table 7). T2D carries a high lifetime risk for developing ASCVD, so risk should be stratified as *moderate* (patients <40 years of age, no major risk factors) or *high* (≥1 major risk factors). A potential third category of *very high* risk (patients with T2D and established ASCVD) could also be considered. Risk stratification in this manner can guide management strategies. In patients at high or very high risk for ASCVD, the goals for LDL-C, non-HDL-C, and ApoB should be <70 mg/dL, <100 mg/dL, and <80 mg/dL, respectively. In patients at moderate risk, the respective goals should be <100 mg/dL, <130 mg/dL, and <90 mg/dL (4 [EL 4; NE]; 7 [EL 4; CPG NE]; 217 [EL 3; SS]). Other targets include a triglyceride concentration <150 mg/dL in all patients, and LDL-P <1,200 nmol/L in patients at moderate risk and <1,000 nmol/L in those at high risk (4 [EL 4; NE]; 7 [EL 4; CPG NE]).

4.Q8.2. Managing Dyslipidemia

A thorough review of the management of dyslipidemia can be found in the 2012 AACE Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis (218 [EL 4; NE]), and updated targets are discussed in the 2015 AACE Comprehensive Diabetes Management Consensus Statement (4 [EL 4; NE]). In prediabetes and DM, multiple disturbances in lipoprotein metabolism result from the combined effects of insulin deficiency, insulin resistance, and hyperglycemia. T2D dyslipidemia is characterized by increased levels of triglyceride-rich lipoproteins (very low-density lipoprotein, intermediate-density lipoprotein, and remnant particles), low levels of HDL-C, and increased levels of small, dense LDL-P (219 [EL 4; review NE]). Hypertriglyceridemia is thus indirectly linked with changes in HDL-C and LDL-C composition that are conducive to accelerated atherogenesis (220 [EL 4; review NE]). Patients who have T1D with persistent proteinuria are at particularly increased risk of premature atherosclerosis (221 [EL 4; NE]). However, the rising prevalence of overweight and obesity may contribute to increased rates of the lipid and lipoprotein pattern related to insulin resistance among prediabetic individuals and those with T2D (222 [EL 1; RCT]).

4.Q8.3. Dyslipidemia Screening and Follow-Up (7 [EL 4; CPG NE])

- Screen all adult patients with yearly fasting lipid profile: total cholesterol, triglycerides, HDL-C, and LDL-C.

- If not at goal, lipid profiling should be repeated more frequently after initiation of treatment. ApoB determination may also be useful to confirm goal attainment but is not recommended for routine screening (4 [EL 4; NE]; 218 [EL 4; NE]).
- LDL-C and calculated non-HDL-C (total cholesterol – HDL-C) are the primary targets of therapy, with respective goals set according to risk levels (Table 7). If LDL-C is at goal but non-HDL-C is above goal, consider additional LDL-C or triglyceride-lowering therapies (preferably first with maximally tolerated statin therapy). Once both LDL-C and non-HDL-C targets have been achieved, consider evaluation of secondary targets, either ApoB or LDL-P, and treat accordingly (218 [EL 4; NE]) (4 [EL 4; NE]).
- Additional biomarkers, including high sensitivity C-reactive protein (hs-CRP), lipoprotein(a), and lipoprotein-associated phospholipase A2 (LpPLA2), are independent risk factors shown to increase ASCVD risk. Measuring these biomarkers may enhance understanding of an individual patient's risk for consideration of more aggressive therapy (218 [EL 4; NE]).

4.Q8.4. Dyslipidemia Therapeutic Recommendations

All patients should receive information about physical activity recommendations, a meal plan designed to improve glucose and lipids, and cardiovascular risk reduction strategies. Consultation with a CDE is desirable (7 [EL 4; CPG NE]; 223 [EL 1; RCT]).

CARDS (Collaborative Atorvastatin Diabetes Study), an RCT involving patients with T2D plus hypertension, smoking, retinopathy, and/or microalbuminuria, demonstrated the benefits of statin therapy for primary prevention of CVD in patients with DM (224 [EL 1; RCT]). To date, no RCT dedicated solely to patients with DM has examined CVD secondary prevention. However, several trials with large DM subpopulations, including the GREACE (Greek Atorvastatin and Coronary-Heart-Disease Evaluation), TNT (Treating to New Targets), and PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trials, have shown significant reductions in mortality and CVD events (225 [EL 1; RCT]; 226 [EL 1; RCT]; 227 [EL 1; RCT, retrospective study]). Therefore, in high-risk patients with DM who have had a prior ASCVD event or those who have DM plus at least 1 additional major ASCVD risk factor (hypertension, family history of ASCVD, low HDL-C, or smoking), a statin should be started along with therapeutic lifestyle changes regardless of baseline LDL-C level (7 [EL 4; CPG NE]; 228 [EL 1; MRCT]; 229 [EL 1; MRCT]). Lipids should be rechecked within 12 weeks. If the LDL-C or non-HDL-C concentration remains >70 mg/dL or >100 mg/dL, respectively, the statin dosage should be titrated with the goal of lowering LDL-C to <70 mg/dL and non-HDL-C to <100 mg/dL (Table 7). If these targets cannot be achieved with maximally tolerated statin therapy, the goal should be to reduce LDL-C by >50%; more potent statins can reduce LDL-C up to 60% (7 [EL 4; CPG NE]; 218 [EL 4; NE]).

Table 13
Suggested Priority of Initiating Blood Pressure-Lowering Agents

Therapy	Reference (evidence level and study design)
Evidence based	
RAAS blockers (ACE inhibitor or ARB)	(198 [EL 1; RCT]; 199 [EL 1; RCT])
Thiazide diuretic	(194 [EL 4; review NE])
β-Adrenergic blocker	(199 [EL 1; RCT])
Individualized therapy	
Calcium channel blockers	(214 [EL 1; RCT, posthoc analysis])
Aldosterone receptor blockers	(202 [EL 4; CPG NE])
Direct renin inhibitor	
Selective α_1-adrenergic blockers	
Central α_2 agonists	
Direct vasodilators	

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; RAAS = renin-angiotensin-aldosterone system.

Measurement of ApoB may be useful in some cases to confirm an ApoB goal of <80 mg/dL (or LDL-P <1,000 nmol/L), even if LDL-C is ≤70 mg/dL (218 [EL 4; NE]). The combination of a statin with another lipid-lowering agent may be required to achieve these targets.

The *moderate risk* category describes persons with DM without known ASCVD or any of the other major cardiovascular risk factors (hypertension, family history, low HDL-C, smoking). In such patients, treatment should begin with therapeutic lifestyle changes for an initial 6- to 8-week trial. Goals for the primary targets—LDL-C and non-HDL-C—are <100 mg/dL and <130 mg/dL, respectively (212 [EL 4; NE]; 223 [EL 1; RCT]; 224 [EL 1; RCT]; 230 [EL 1; RCT]). The secondary targets ApoB (<90 mg/dL) or LDL-P (<1,200 nmol/L) may also be considered. When goals of therapy are not achievable, for whatever reason, a 30 to 50% reduction in LDL-C is desirable. For patients older than 40 years without diagnosed ASCVD but who have ≥1 additional major ASCVD risk factor, statin therapy may be considered even if the LDL-C concentration is <100 mg/dL (212 [EL 4; NE]; 223 [EL 1; RCT]; 224 [EL 1; RCT]; 230 [EL 1; RCT]). In patients younger than 40 years, initiation of statin therapy for primary prevention of CVD in both males and females needs to be individualized, based on other risk factors and comorbidities. The use of various 10-year or life-time risk calculators is an option to decide the intensity of treatment, but currently available risk calculators lack sufficient accuracy and are limited by discrepancies between predicted and observed event rates (231 [EL 4; NE]; 232 [EL 4; NE]). In patients with statin intolerance or unacceptable adverse events, a bile acid sequestrant (233 [EL 1; RCT]), niacin (234 [EL 1; RCT]; 235 [EL 4; review NE]; 236 [EL 1; RCT]), or cholesterol absorption inhibitor (237 [EL 1; RCT]; 238 [EL 1; RCT]) should be considered alone or in combination. No study has yet been designed to investigate the cardiovascular outcomes benefit of adding bile acid sequestrants, niacin, or cholesterol absorption inhibitors to statins in patients whose atherogenic markers (LDL-C, non-HDL-C, ApoB, and LDL-P) are not already at target levels.

In patients with end-stage renal disease (ESRD) or advanced heart failure, or in those on hemodialysis, no clear evidence supports an ASCVD benefit from LDL-C-lowering therapy (239 [EL 4; NE]; 240 [EL 4; NE]). Patients with eGFR <60 mL/min/1.73 m^2 who are not dialysis-dependent are at high risk for ASCVD events and should be managed using the LDL-C, non-HDL-C, and ApoB goals defined here. Such patients should be monitored closely to determine whether statin dose adjustment is necessary depending on comorbidities, drug interactions, and renal status (239 [EL 4; NE]; 240 [EL 4; NE]).

In patients with LDL-C at goal but a fasting triglyceride concentration ≥150 mg/dL or low HDL-C (≤35 mg/dL), the following actions should be implemented:

- Optimize glycemic control and emphasize weight loss (if indicated) (7 [EL 4; CPG NE]; 223 [EL 1; RCT])
- Modify, if possible, any medications that may contribute to hypertriglyceridemia
- In patients with fasting triglyceride concentrations of 200 to 499 mg/dL, titrate statin therapy to maximum tolerated dose to achieve goals for LDL-C and non-HDL-C as well as the secondary target (ApoB or LDL-P) (7 [EL 4; CPG NE]; 217 [EL 3; SS]; 241 [EL 2; PCS]); nonstatin therapies in combination with statins are often required in these settings
- In the setting of persistently elevated fasting triglycerides (>200 mg/dL) against the background of maximally tolerated LDL-C-lowering therapies, triglyceride-reducing therapies such as a fibrate, high-dose omega-3 fatty acid, or niacin may be utilized to further reduce non-HDL-C (218 [EL 4; NE]; 242 [EL 4; consensus]; 243 [EL 4; review NE]; 244 [EL 3; SS]; 245 [EL 1; RCT]; 246 [EL 3; SS])
- If the fasting triglyceride concentration is ≥500 mg/dL (i.e., severe hypertriglyceridemia), begin treatment with a very low-fat diet and reduced intake of simple carbohydrates and initiate a fibrate, high-dose omega-3-fatty acid, and/or niacin. All 3 of these triglyceride-lowering therapies may be required in combination in patients with severe hypertriglyceridemia (247 [EL 4; review NE]). No RCT has yet been designed to investigate the additive benefit of reducing severe hypertriglyceridemia to prevent pancreatitis. Observational data and retrospective analyses, however, do support triglyceride-lowering therapy for prophylaxis against or treatment of acute pancreatitis (248 [EL 4; NE]; 249 [EL 3; SS]). Rule out other secondary causes and reassess lipid status when the triglyceride concentration is <500 mg/dL (235 [EL 4; review NE]; 250 [EL 4; NE]). Additional statin therapy and possibly other agents are usually required to achieve the primary LDL-C and non-HDL-C goals (235 [EL 4; review NE]), as well as secondary goals for ApoB or LDL-P, for the purpose of cardiovascular event prevention (248 [EL 4; NE]; 249 [EL 3; SS]). No RCT has yet been designed to investigate the benefit of reducing severe (triglycerides >500 mg/dL) or moderate (>200 mg/dL) hypertriglyceridemia to prevent CVD.

Modification of triglycerides with the proliferator-activated receptor-α agonist fenofibrate failed to reduce ASCVD events in 2 separate trials in patients with T2D:

FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) (251 [EL 1; RCT]) and ACCORD-Lipid (245 [EL 1; RCT]). The mean baseline triglyceride levels were 153 mg/dL in FIELD (251 [EL 1; RCT]) and 162 mg/dL in ACCORD-Lipid (245 [EL 1; RCT]). Posthoc and prespecified subgroup analyses and meta-analyses of 5 major fibrate trials—HHS (Helsinki Heart Study), VA-HIT (Veterans Affairs HDL Intervention trial), BIP (Bezafibrate Infarction Project), FIELD, and ACCORD-Lipid—have shown a cardiovascular benefit in patients with moderate dyslipidemia (triglycerides >200 mg/dL and HDL-C <40 mg/dL, either isolated or together) but not in patients without dyslipidemia (218 [EL 4; NE]; 252 [EL 4; NE]; 253 [EL 1; MRCT]; 254 [EL 1; MRCT]; 255 [EL 4; NE]).

Two separate RCTs tested the HDL-C-raising hypothesis in patients with coronary artery disease optimally treated with statins with or without ezetimibe. In AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes), the atherogenic markers LDL-C, non-HDL-C, and ApoB were 74, 108, and 81 mg/dL, respectively, prior to randomization (256 [EL 1; RCT]). Before randomization in HPS2-THRIVE (Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events), LDL-C, non-HDL-C, and ApoB were 63, 84, and 68 mg/dL, respectively, and triglyceride and HDL-C levels were 120 mg/dL and 44 mg/dL, respectively (257 [EL 1; RCT]). 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 (256 [EL 1; RCT]; 257 [EL 1; RCT]). Thus niacin cannot be recommended as adjunctive therapy if LDL-C, non-HDL-C, and ApoB goals are already met. However, in other settings, where the goals of these atherogenic markers have not been met, niacin remains a viable treatment option.

4.Q8.5. Lipid Management in Prediabetes

The principles and goals of lipid management in prediabetes are the same as those for DM described previously (Table 7). No randomized intervention trials dedicated to patients with prediabetes use ASCVD events as outcome measures. Diet, exercise, and weight loss or maintenance should be emphasized for all prediabetes patients.

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 ApoB or LDL-P goals in prediabetes (7 [EL 4; CPG NE]). Low HDL-C is also common in prediabetes. Low HDL-C and high triglycerides are both associated with increased levels of LDL-P. 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 patients with prediabetes: a 9% increase with moderate statin dosing and 12% increase with intensive statin dosing (258 [EL 1; MRCT]; 259 [EL 1; MRCT]). Patients with prediabetes should be warned of the potential added risk of conversion to DM with statin use. The net comparison of benefit versus risk is >4 ASCVD events prevented for 1 conversion from prediabetes to DM (260 [EL 4; NE]). A thorough risk-benefit analysis, taking into account the patient's individual risk of converting to DM versus prevention of ASCVD, should be discussed with the patient.

4.Q9. How is Nephropathy Managed in Patients with Diabetes?

Diabetic nephropathy accounts for 40 to 50% of all cases of ESRD in the U.S. and occurs in about 40% of patients with DM, increasing with age (261 [EL 3; SS]). Diabetic nephropathy is represented histologically by the presence of basement membrane thickening, mesangial expansion, podocyte loss, and nodular or diffuse glomerulosclerosis (262 [EL 4; NE]). The pathologic changes, which modestly correlate with the degree of kidney injury as measured by blood and urine tests, are typically present before functional tests are positive (262 [EL 4; NE]). Consequently, prevention of microvascular complications such as nephropathy should be started upon diagnosis of DM and be intensified in those with evidence of kidney damage. Guidelines for the diagnosis and management of CKD in patients with DM have recently been updated by the Kidney Disease: Improving Global Outcomes (KDIGO) working group (263 [EL 4; NE]) and the Kidney Disease Outcomes Quality Initiative (KDOQI) Committee (264 [EL 4; NE]). The AACE concurs with both guidelines in general.

The KDIGO guidelines recommend phasing out the term *microalbuminuria* 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. AER levels >30 mg/g creatinine or 30 mg/day indicate kidney damage and are also a marker of cardiovascular risk (263 [EL 4; NE]; 264 [EL 4; NE]). 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 diabetic nephropathy. An AER of >300 mg/g creatinine or >300 mg/day indicates greater damage and greater risk for progression of renal insufficiency, anemia, CVD, and infections. Sudden onset or rapidly increasing AER should prompt additional

tests to rule out other kidney diseases. Table 14 lists correlations between AER, urine dipstick, and tests of total protein excretion.

GFR should be estimated from a creatinine-based calculation such as the Modification in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology (CKD-EPI) equations. The CKD-EPI equation is more accurate for calculation of eGFR above 60 mL/min/1.73 m^2, and this equation is currently preferred (263 [EL 4; NE]). However, most laboratories report a calculated eGFR using the MDRD when eGFR is <60 mL/min/1.73 m^2. Figure 2 depicts the new classification system for CKD in patients with DM that incorporates both eGFR and albuminuria in the risk assessment. Note that in Figure 2, 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 AER. For example, a patient with DM, an eGFR of 40 mL/min/1.73 m^2, and an AER of 250 mg/g creatinine would be categorized as "diabetes/G3b/A2." The "heat grid" shown in Figure 2 indicates the new terminology, the level of risk for cardiovascular events and progression of kidney disease by color intensity, and the recommended frequency for monitoring renal parameters (263 [EL 4; NE]; 265 [EL 2; MNRST]; 266 [EL 4; NE]). Progression of CKD is classified as rapid if the decline in eGFR is ≥5 mL/min per 1.73 m^2 per year or if the patient has a dramatic increase in AER.

Prevention of the development of diabetic nephropathy includes optimal control of plasma glucose (A1C goal <6.5% unless limited by hypoglycemia), blood pressure control with RAAS inhibition as first-line therapy, treatment of hyperlipidemia, and smoking cessation (264 [EL 4; NE]). Intensive glucose control (A1C levels <7% in T2D and <7.5% in T1D) in several early intervention studies reduced the risk of incident albuminuria (A2) and progression of AER to proteinuria (47 [EL 1; RCT]; 51 [EL 1; RCT]; 57 [EL 1; RCT]; 68 [EL 1; RCT]; 69 [EL 1; RCT]). Intensive glucose control has not been shown to diminish the progression of diabetic nephropathy or cardiovascular mortality in patients with advanced CKD, but

Table 14
Relationship Among Categories For Albuminuria and Proteinuria (263 [EL 4; NE])[a,b]

	Categories		
Measure	**Normal to mildly increased (A1)**	**Moderately increased (A2)**	**Severely increased (A3)**
AER (mg/24 hours)	<30	30-300	>300
PER (mg/24 hours)	<150	150-500	>500
ACR (mg/mmol)	<3	3-30	>30
(mg/g)	<30	30-300	>300
PCR (mg/mmol)	<15	15-50	>50
(mg/g)	<150	150-500	>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 International Supplement*. 2013;3(1):1-150, copyright 2013.

[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/day. 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 10-30 mg/g (1-3 mg/mmol) is considered "high normal." ACR >2,200 mg/g (>220 mg/mmol) is considered "nephrotic range." The relationship between urine reagent strip results and other measures depends on urine concentration.

these patients have an increased risk of hypoglycemia, so glycemic targets and therapies may need to be modified as diabetic nephropathy progresses.

The KDIGO guidelines recommend that patients without albuminuria be treated to a blood pressure <140/90 mm Hg, but <130/80 mm Hg in the presence of albuminuria (267 [EL 4; NE]). Although care must be taken to avoid orthostasis and drug side effects, AACE recommends individualized blood pressure targets, with a goal of about 130/80 mm Hg for most patients (see Q7. How is hypertension managed in patients with diabetes?).

Smoking cessation and lipid lowering are also important interventions for prevention of cardiorenal complications of DM, which are increased at every level of CKD (265 [EL 2; MNRST]). Therapy with statins reduces the relative risk of major vascular events in patients with DM by 17% for every 39 mg/dL decrease in LDL-C (228 [EL 1; MRCT]). Patients with DM and CKD up to stage 4, including posttransplant patients, benefit from lipid lowering with statins. However, the beneficial effect of statins is lost in patients who require dialysis (228 [EL 1; MRCT]; 268 [EL 1; RCT]; 269 [EL 1; MRCT]; 270 [EL 1; RCT]; 271 [EL 1; MRCT]).

Slowing the progression of kidney dysfunction is critical for patient survival and quality of life. Therapies shown to positively affect AER and declining eGFR include ACE inhibitors and ARBs. Consequently, T1D and T2D patients with albuminuria should be treated with an ACE inhibitor or ARB at the highest tolerated dose (198 [EL 1; RCT]; 272 [EL 1; RCT]). Data are lacking on the effectiveness of ACE inhibitor and ARBs in patients with DM and reduced eGFR who do not have albuminuria. However, AACE recommends RAAS blockade in all patients with DM who have CKD categories G2, G3a, G3b, and if slow progression is demonstrated, category G4. The RAAS-blocking drugs may potentiate hyperkalemia and may cause harm when used with nonsteroidal anti-inflammatory drugs (NSAIDs) or in patients with renovascular hypertension or dehydration. They are not safe for use in pregnancy. Combination therapy with an ACE inhibitor and ARB or with a renin inhibitor added to 1 of the other RAAS-blockading agents does not prolong survival or prevent progression of CKD (216 [EL 4; NE]; 273 [EL 1; RCT]; 274 [EL 1; RCT]). In patients with advanced CKD (G3b and higher), combination therapy increases the risk of hyperkalemia and acute kidney injury and is therefore not recommended (216 [EL 4; NE]; 274 [EL 1; RCT]; 275 [EL 4; review NE]). Data on the use of aldosterone antagonists with ACE inhibitors or ARB classes is limited, but the same cautions apply.

If the GFR continues to decline despite excellent glycemic and blood pressure control, protein restriction may be of some benefit. KDIGO recommends limiting protein intake to 0.8 g/kg per day (approximately 10% of daily calories) in patients with progressive diabetic nephropathy or eGFR <30 mL/min/1.73 m^2. Additional dietary restrictions may be required to control potassium and phosphorus levels. Salt intake should be limited to 2 g per day in all patients with DM who require antihypertensive medications. Obesity is a risk factor for hypertension and incident CKD, so weight loss along with exercise is recommended for patients with DM without evidence of kidney disease as well as patients with category G2 to G4 CKD. Unintended weight loss is associated with poorer outcomes in dialysis patients.

Patients with CKD are at risk for drug toxicity and acute kidney injury. Antihyperglycemic therapies should be modified to reduce excessive drug exposure and hypoglycemia (276 [EL 3; CSS]). Many other drugs should be avoided or used with caution in patients with CKD. Patients 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 dyes.

Patients with diabetic nephropathy 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, vitamin D, and parathyroid hormone (PTH) measurements to assess mineral metabolism (263 [EL 4; NE]). Hyperkalemia is managed by dietary restriction and adjustment of antihypertensive medications. For those with a bicarbonate level <22 mEq/L, the addition of oral sodium bicarbonate is recommended to correct the acidosis. Anemia, defined as hemoglobin (Hb) <13 g/dL in males and <12 g/dL in females, should be further investigated with iron, transferring saturation (TSAT), ferritin, vitamin B_{12}, and folate levels (277 [EL 4; NE]). Deficiencies should be replaced, and a TSAT target of ≥30% achieved, regardless of ferritin level (277 [EL 4; NE]). Iron given intravenously may produce better results than oral replacement. AACE recommends adequate calcium intake and achievement of 25(OH)D_3 levels of >30 ng/dL in all patients. Supplementing vitamin D_2 or D_3 may reduce PTH without causing harm (277 [EL 4; NE]; 278 [EL 3; SS]). Active vitamin D preparations may be necessary to keep the PTH level from increasing as kidney function declines. Hyperphosphatemia should be corrected into the normal range with dietary modification and judicious 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 patients with stage 4 CKD to a nephrologist allows time for sufficient planning to accommodate individual patient needs (279 [EL 4; opinion NE]). Renal transplantation is the preferred replacement therapy for patients with DM and ESRD because long-term outcomes are superior to those achieved with dialysis. For patients with T1D, the possibility of combined kidney-pancreas transplantation allows for considerably better outcomes (280 [EL 2; PCS]).

4.Q10. How is Retinopathy Managed in Patients with Diabetes?

Diabetic retinopathy is the leading cause of blindness in adults. The lesions of diabetic retinopathy include background or nonproliferative retinopathy, macular edema, preproliferative retinopathy, and proliferative retinopathy. Approximately 50% of patients with T1D develop background retinopathy after 7 years, and most have some form of retinopathy after 20 years (281 [EL 4; review NE]). Diabetic retinopathy is present in 25 to 45% of patients with T2D, and between 2 and 8% of patients with T2D have proliferative retinopathy and/or macular edema (282 [EL 3; SS]). Diabetic retinopathy is present in approximately 20, 40, and 70% of patients 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 (283 [EL 2; MNRCT]). Higher levels of glucose and blood pressure, as well as the presence of nerve and renal diabetic complications, are associated with greater likelihood of developing retinopathy (284 [EL 3; SS]).

The goal is to detect clinically significant retinopathy before vision is threatened. Funduscopy performed by internists or endocrinologists is often suboptimal; therefore, referral to an experienced ophthalmologist for an annual dilated eye examination is recommended (285 [EL 2; MNRCT]). The complete 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, POC screening for retinopathy (286 [EL 3; SS]). Patients with abnormal retinal photographs are then triaged to full examination by an ophthalmologist. This 2-step approach can be an efficient strategy for retinopathy screening at the population level, particularly in remote areas (287 [EL 3; SS]). However, the system is still under development and does not replace the current recommendation for an annual dilated eye examination by an ophthalmologist from the time of diagnosis because of the lag between onset and diagnosis of T2D (288 [EL 3; CSS]). Given the relatively low prevalence of proliferative retinopathy and/or macular edema in T2D during the first decade after diagnosis, however, the suggestion is now being made that T2D patients who have had a negative ophthalmologic examination may safely have the screening interval increased to 2 years (289 [EL 4; NE]; 290 [EL 2; RCCS]). As retinopathy develops over a period of 5 or more years from initial hyperglycemia, screening should be initiated within 5 years of diagnosis in patients with T1D (291 [EL 3; SS]). Pregnancy is a risk factor for progression of retinopathy, and ophthalmologic examinations should be performed repeatedly during pregnancy and for 1 year postpartum (292 [EL 2; PCS, longitudinal follow-up study]). Patients with active lesions may be followed up more frequently, while those who have had repeatedly normal eye findings can be seen less frequently.

Optimization of glucose and blood pressure are proven strategies for primary prevention of diabetic retinopathy (68 [EL 1; RCT]; 195 [EL 1; RCT]; 196 [EL 2; PCS]; 293 [EL 2; PCS]). Good control of glycemia and blood pressure are also effective in slowing the progression of pre-existing background retinopathy.

There is, in addition, evidence that certain pharmacologic treatment approaches may have specific benefit in diabetic retinopathy, including ACE inhibitors, ARBs (294 [EL 1; RCT]; 295 [EL 1; RCT]), and fibrate lipid-lowering agents (56 [EL 1; RCT]; 296 [EL 1; RCT, substudy]; 297 [EL 2; RCCS]). Research into other novel pharmacologic agents with potential benefits may lead to additional medical treatments (298 [EL 1; RCT, small sample size]).

Panretinal scatter laser photocoagulation is the treatment of choice for high-risk proliferative retinopathy (299 [EL 4; review NE]). For macular edema, the combination of focal laser photocoagulation with intravitreal antivascular endothelial growth factor modalities appears to offer optimal benefit (300 [EL 1; MRCT]). Vitrectomy is reserved for patients with persistent vitreous hemorrhage or significant vitreous scarring and debris (299 [EL 4; review NE]).

4.Q11. How is Neuropathy Diagnosed and Managed in Patients with Diabetes?

Diabetic neuropathy affects about half of all patients with DM, contributing to substantial morbidity and mortality and resulting in a huge economic burden for DM care (301 [EL 4; NE]; 302 [EL 3; SS]). It is the most common form of neuropathy in developed countries and is responsible for 50 to 75% of nontraumatic amputations (302 [EL 3; SS]; 303 [EL 4; NE]). It is a major cause of falls in older patients that lead to lacerations, fractures, and traumatic brain injuries (304 [EL 4; NE]). Diabetic neuropathy is a set of clinical syndromes that affect distinct regions of the nervous system, singly or in combination. It may be silent and go undetected while exercising its ravages, or it may present with clinical symptoms and signs that, although nonspecific and insidious with slow progression, also mimic those seen in many other diseases. Diabetic neuropathy is, therefore, diagnosed by exclusion. Unfortunately neither endocrinologists nor nonendocrinologists have been trained to recognize the condition, and even when diabetic neuropathy is symptomatic, less than one-third of physicians recognize the cause or discuss this with their patients (305 [EL 1; RCT]).

Diabetic neuropathy encompasses multiple different disorders involving proximal, distal, somatic, and autonomic nerves. It may be acute and self-limiting or a chronic, indolent condition. It may be focal such as a mononeuritis involving single nerves or entrapment neuropathies (e.g., carpal tunnel syndrome, ulnar entrapment,

and peroneal entrapment, among others). Proximal lumbosacral, thoracic, and cervical radiculoplexus neuropathies involving the proximal limb girdle are, for the most part, inflammatory demyelinating conditions requiring immunotherapy and, if caught early, are reversible (306 [EL 4; NE]; 307 [EL 4; review NE]; 308 [EL 4; position NE]; 309 [EL 4; NE]). The distal neuropathies are characteristically symmetric, glove and stocking distribution, length-dependent sensorimotor polyneuropathies that develop on a background of long-standing chronic hyperglycemia superimposed upon CVD risk factors (310 [EL 3; CSS]; 311 [EL 2; PCS]; 312 [EL 2; PCS]). They may be acute or chronic. The acute variety usually occurs within 8 weeks of initiating intensification of glycemic control with insulin or oral agents that results in a too-rapid lowering of blood glucose by >30% or A1C by >2% (313 [EL 2; PCS]; 314 [EL 4; review NE]). There may also be atypical variants of diabetic neuropathy such as SFNs, which present predominantly with pain and autonomic features (306 [EL 4; NE]; 315 [EL 2; CSS]). Risk factors include metabolic syndrome (316 [EL 3; CSS]), IFG, and IGT (317 [EL 2; PCS]; 318 [EL 3; retrospective chart review SS]). The scope of diabetic neuropathy is reviewed elsewhere (304 [EL 4; NE]; 319 [EL 4; review NE]; 320 [EL 4; NE]; 321 [EL 4; NE]; 322 [EL 4; NE]; 323 [EL 4; NE]; 324 [EL 4; NE]; 325 [EL 1; MRCT]; 326 [EL 4; NE]).

Prevalence rates of neuropathy in DM are between 5 and 100%, depending on diagnostic criteria used (327 [EL 3; CSS]; 328 [EL 3; CSS]). Because of the lack of agreement on the definition and diagnostic assessment of neuropathy, several consensus conferences were convened to overcome the current problems. The most recent of these has redefined the minimal criteria for the diagnosis of typical distal symmetric polyneuropathy (DSPN) (305 [EL 1; RCT]):

1. Possible DSPN. The presence of symptoms or signs of DSPN, which may include the following:
    - Symptoms: decreased sensation, positive neuropathic sensory symptoms (e.g., "asleep numbness," prickling or stabbing, burning, or aching pain) predominantly in the toes, feet, or legs
    - Signs: symmetric decrease of distal sensation or unequivocally decreased or absent ankle reflexes
2. Probable DSPN. The presence of a combination of symptoms and signs of neuropathy including any 2 or more of the following: neuropathic symptoms, decreased distal sensation, or unequivocally decreased or absent ankle reflexes
3. Confirmed DSPN. The presence of an abnormality of nerve conduction plus a symptom or symptoms, or a sign or signs, of neuropathy. If nerve conduction is normal, a validated measure of SFN (with class 1 evidence) may be used. To assess for the severity of DSPN, several approaches have been recommended (329 [EL 4; NE]).
4. Subclinical DSPN. Abnormal nerve conduction or a validated measure of SFN (with class 1 evidence) without signs or symptoms of neuropathy. Definitions 1, 2, or 3 can be used for clinical practice, and definitions 3 or 4 can be used for research studies.
5. SFN should be graded as follows (330 [EL 4; NE]):
    a. Possible: the presence of length-dependent symptoms and/or clinical signs of small-fiber damage
    b. Probable: the presence of length-dependent symptoms, clinical signs of small-fiber damage, and normal sural nerve conduction
    c. Definite: the presence of length-dependent symptoms, clinical signs of small-fiber damage, normal sural nerve conduction, and altered intraepidermal nerve-fiber density at the ankle and/or abnormal thermal thresholds at the foot

Several reviews discuss useful approaches to the treatment of the common forms of diabetic neuropathy, as well as algorithms for pain management, diagnosis, and treatment of the manifestations of autonomic neuropathy (331 [EL 4; review NE]; 332 [EL 4; review NE]). Treatment guidelines published by the American Academy of Neurology, Toronto Expert Panel, and European Federation of Neurological Societies suggest that pregabalin, gabapentin, venlafaxine, duloxetine, tricyclic antidepressants, and opioids are the drugs with the best evidence to support their use for painful neuropathy (329 [EL 4; NE]; 333 [EL 4; NE CPG]; 334 [EL 1; NE CPG]). However, no treatments have been approved for the prevention or reversal of diabetic neuropathy. Even tight glycemic control at best limits the progression of neuropathy in patients with T1D, as shown in the DCCT and EDIC (Epidemiology of Diabetes Interventions and Complications) studies, and does not affect neuropathy in patients with T2D, as seen in the ACCORD, UKPDS, and ADVANCE studies (335 [EL 4; NE]).

Large-fiber neuropathies may involve sensory and/or motor nerves, and most affected patients present with a glove and stocking distribution of sensory loss (336 [EL 4; review NE]). Once large-fiber diabetic neuropathy has been diagnosed, therapy should be initiated to reduce symptoms and prevent further progression. It is vitally important to institute measures to prevent foot ulcers that lead to amputations. In general these are daily inspection, protective socks, appropriate footwear, and avoidance of injury. Cardinal interventions to prevent falls and fractures are to improve strength and balance in patients with large-fiber

neuropathy (337 [EL 2; PCS]; 338 [EL 1; RCT]; 339 [EL 1; RCT]). Patients with DM who have large-fiber neuropathies are uncoordinated and ataxic and are 17 times more likely to fall than their counterparts without neuropathy (340 [EL 2; RCCS]). Low-impact activities that emphasize muscular strength and coordination and challenge the vestibular system such as a Bosu ball; use of rubber bands to strengthen lower limb muscles; and Pilates, yoga, and Tai Chi to strengthen the body core, may also be particularly helpful (341 [EL 2; PCS, small sample size]; 342 [EL 2; PCS, small sample size]).

Small-nerve fiber dysfunction usually occurs early and is often present without objective signs or electrophysiologic evidence of nerve damage (343 [EL 3; SS]).

Skin punch biopsy, a minimally invasive procedure, allows morphometric quantification of intraepidermal nerve fibers. The European Federation of the Neurological Societies and the Peripheral Nerve Society endorse intraepidermal nerve fiber quantification to confirm the clinical diagnosis of SFN with a strong (Level A) recommendation (344 [EL 4; consensus NE]). Intraepidermal nerve fiber density inversely correlates with both cold and heat detection thresholds (345 [EL 3; CSS]). Intraepidermal nerve fiber density is significantly reduced in symptomatic patients with normal findings from nerve conduction studies and those with metabolic syndrome, IGT, and IFG, suggesting early damage to small nerve fibers (346 [EL 3; CSS]; 347 [EL 3; CSS]). Intraepidermal nerve fiber density is also reduced in painful neuropathy compared with that observed in painless neuropathy (348 [EL 3; SS]). Diet and exercise intervention in IGT leads to increased intraepidermal nerve fiber density (349 [EL 2; PCS]). These data suggest that intraepidermal nerve fiber loss is an early feature of the metabolic syndrome, prediabetes, and established DM, and the loss progresses with increasing neuropathic severity. There may be nerve regeneration with treatment.

Noninvasive tests of small nerve fiber function have recently been recognized. Corneal confocal microscopy may be used to detect small nerve fiber loss in the cornea. This technique correlates with neuropathy severity and can be used to monitor responses to transplantation and other procedures (347 [EL 3; CSS]). Contact heat-evoked potentials use nociceptive heat as a stimulus, and the response is recorded through electroencephalographic readings. This technique can be used to detect SFN in the absence of other indices (350 [EL 2; NRCT]). Sudomotor function assesses the sweat response by analyzing sweat production or sweat chloride concentrations and detects early neurophysiologic abnormalities in peripheral autonomic function (351 [EL 2; PCS]).

Strategies for management of SFN include simple measures that can protect the foot deficient in functional C fibers from developing ulceration, and therefore, from gangrene and amputation. Wearing padded socks can promote ulcer healing and/or reduce the likelihood of ulcer development (352 [EL 2; PCS]). Patients should inspect the plantar surface of their feet with a mirror on a daily basis and test bathwater with a part of the body that is not insensate before submerging a numb foot. Patients should also be cautioned against falling asleep in front of the fireplace with their insensate feet close to the fire. Emollient creams can moisturize dry skin and prevent cracking and infection.

A definition of peripheral neuropathic pain in DM, adapted from one recently proposed by the International Association for the Study of Pain (308 [EL 4; position NE]), is "pain arising as a direct consequence of abnormalities in the peripheral somatosensory system in people with diabetes." It has been estimated that between 3 and 25% of persons with DM might experience neuropathic pain (353 [EL 4; review NE]). In practice, the diagnosis of neuropathic pain in DM is a clinical one, relying on the patients' description of pain: the symptoms are distal, symmetric, and associated with nocturnal exacerbations, and they are commonly described as prickling, deep aching, sharp, electric-shock like, and burning with hyperalgesia (354 [EL 4; review]). There is frequently allodynia on examination (353 [EL 4; review NE]; 354 [EL 4; review]). Symptoms are usually associated with clinical signs of peripheral neuropathy, although occasionally in acute neuropathic pain, symptoms may occur in the absence of signs. A number of simple numeric rating scales can be used to assess the frequency and severity of painful symptoms (353 [EL 4; review NE]), and other causes of neuropathic pain must be excluded. Outcome measures to assess response to therapy should include patient-reported improvements in the measures and numeric rating scales (355 [EL 4; review NE]), including the Neuropathic Pain Symptoms Inventory, the Brief Pain Inventory, and the Neuropathic Pain Questionnaire. Quality of life improvement should also be assessed, preferably using a validated neuropathy-specific scale such as NeuroQol or the Norfolk Quality of Life Scale (356 [EL 3; SS]).

Physicians must be able to differentiate painful diabetic neuropathy from other unrelated or coexisting conditions. The most common of these are claudication, Morton's neuroma, Charcot neuroarthropathy, fasciitis, osteoarthritis, and radiculopathy. The algorithm provided (Fig. 3) distinguishes between the different conditions that can produce pain and provides recommendations for their management (314 [EL 4; review NE]; 357 [EL 4; NE]). The FDA has approved only the serotonin and norepinephrine reuptake inhibitor duloxetine, the anticonvulsant pregabalin, and the opioid tapentadol for neuropathic pain, but level 1 evidence also exists to support the use of tricyclic antidepressants (e.g., amitriptyline) and the anticonvulsant gabapentin (358 [EL 1; MRCT]; 359 [EL 1; MRCT]). Recent studies have shown improvement of pain with an $\alpha 2\delta 1$ calcium antagonist (360 [EL 1; RCT, posthoc analysis]) and tapentadol, a weak opioid agonist with norepinephrine

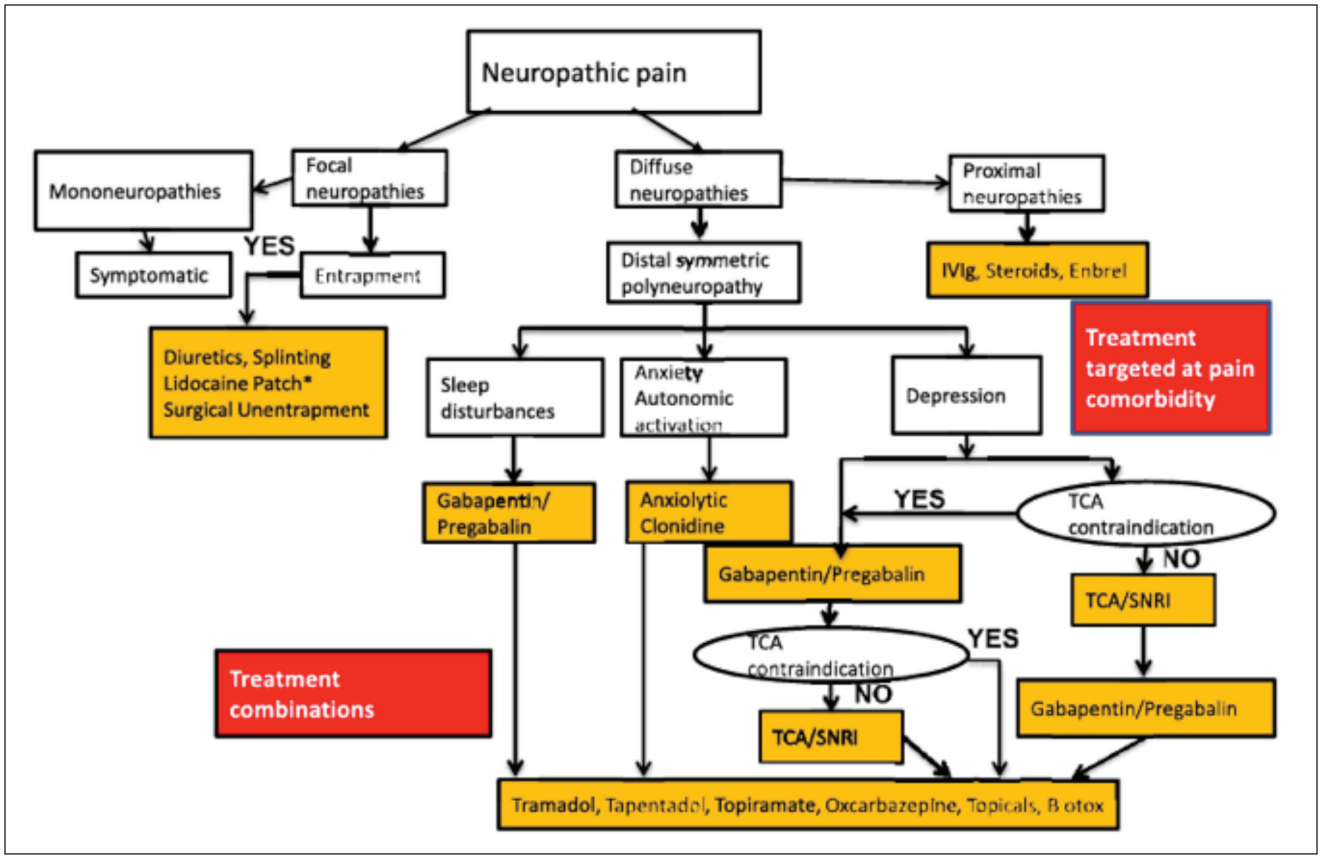

Fig. 3. Treatment algorithm for neuropathic pain after exclusion of nondiabetic etiology and stabilization of glycemic control (314 [EL 4; review NE]; 357 [EL 4; NE]). Reprinted from the *Journal of Clinical Endocrinology and Metabolism*, Vol. 95, A. Vinik, "The approach to the management of the patient with neuropathic pain," pp. 4802-4816. Copyright 2010, with permission from Elsevier.

reuptake inhibition, which thereby combines 2 pain relief mechanisms (361 [EL 1; RCT]). Topical treatment using a 5% lidocaine plaster applied to the most painful area (362 [EL 1; RCT]) is effective in some studies.

Recent studies have highlighted metformin-associated B_{12} deficiency, which can lead to neuropathy-like symptoms. These symptoms can be reversed by supplementation with methylcobalamin, the biologically active form of vitamin B_{12} (363 [EL 1; RCT]; 364 [EL 4; NE]; 365 [EL 3; CSS]; 366 [EL 4; NE]). New thresholds for B_{12} levels have now been established (364 [EL 4; NE]; 365 [EL 3; CSS]).

Cardiovascular autonomic neuropathy is significantly associated with overall mortality (367 [EL 4; review NE]; 368 [EL 2; MNRCT]) and in some studies, but not all, with morbidity including silent myocardial ischemia, coronary artery disease, stroke, diabetic neuropathy progression, and perioperative morbidity. Some pathogenetic mechanisms may link cardiovascular autonomic neuropathy to cardiovascular dysfunction and diabetic complications (367 [EL 4; review NE]). Cardiovascular autonomic neuropathy assessment may be used for cardiovascular risk stratification in patients with and without established CVD, as a marker for patients requiring more intensive monitoring during the perioperative period and other physiological stresses, and as an indicator for more or less intensive pharmacotherapeutic and lifestyle management of comorbid conditions. Cardiovascular autonomic neuropathy may be useful for prediction of cardiovascular risk, and a combination of cardiovascular autonomic neuropathy (369 [EL 3; SS]) and symptoms of peripheral neuropathy increase the odds ratio to 4.55 for CVD and mortality (314 [EL 4; review NE]). Indeed, this is the strongest predictor of CVD risk, far greater than blood pressure, lipoprotein profile, and even adenosine scans (370 [EL 4; NE]). The reported prevalence of diabetic autonomic neuropathy varies widely (7.7 to 90%) depending on the cohort studied and the methods used for diagnosis (371 [EL 4; review NE]; 372 [EL 4; review NE]). All the manifestations of autonomic nerve dysfunction, along with suggested testing, the symptom complex, and possible therapies, are listed in Table 15 (310 [EL 3; CSS]). A more complete discussion can be found in recent reviews (369 [EL 3; SS]; 373 [EL 4; NE]).

Cardiovascular reflex tests are the criterion standard in clinical autonomic testing (374 [EL 4; position NE]). The most widely used tests assessing cardiac parasympathetic function are based on the time-domain heart rate response to deep breathing, a Valsalva maneuver, and postural change. Valsalva maneuvers must not be performed

Table 15
Clinical Features, Diagnosis, and Treatment of Diabetic Autonomic Neuropathy (310 [EL 3; CSS])

Symptoms	Tests	Treatments
Cardiac		
Resting tachycardia, exercise intolerance	HRV, MUGA thallium scan, MIBG scan	Graded supervised exercise, ACE inhibitors, β-adrenergic blockers
Exercise bradycardia Exercise intolerance	HRV, MUGA thallium scan, MIBG scan, dopamine levels and scans	Graded supervised exercise, dopaminergic agonists
Postural hypotension, dizziness, weakness, fatigue, syncope	HRV, supine and standing blood pressure, catecholamines	Mechanical measures, clonidine, midodrine, octreotide, erythropoietin
Gastrointestinal		
Gastroparesis, erratic glucose control	Gastric emptying study, barium study	Frequent small meals and prokinetic agents (metoclopramide, domperidone; erythromycin; lubiprostone; linaclotide; oral gastric analgesics; the combination of atropine, hyoscyamine, phenobarbital, and scopolamine; Maalox; and viscous xylocaine)
Abdominal pain, early satiety, nausea, vomiting, bloating, belching	Endoscopy, manometry, electrogastrogram	Antibiotics, antiemetics, bulking agents, tricyclic antidepressants, pyloric botulinum toxin, gastric pacing
Constipation	Endoscopy	High-fiber diet, bulking agents, osmotic laxatives, lubricating agents
Diarrhea (often nocturnal alternating with constipation)	None	Soluble dietary fiber, gluten and lactose restriction, anticholinergic agents, cholestyramine, antibiotics, somatostatin, pancreatic enzyme supplements
Sexual dysfunction		
Erectile dysfunction	H&P, HRV, penile-brachial pressure index, nocturnal penile tumes	Sex therapy, psychological counseling, 5′-phosphodiesterase inhibitors, prostaglandin E1 injections, devices, or prostheses
Vaginal dryness	None	Vaginal lubricants
Bladder dysfunction		
Frequency, urgency, nocturia, urinary retention, incontinence	Cystometrogram, postvoiding sonography	Bethanechol, intermittent catheterization
Sudomotor dysfunction		
Anhidrosis, heat intolerance, dry skin, hyperhidrosis	Quantitative sudomotor axon reflex, sweat test, sudorimetry, skin blood flow	Emollients and skin lubricants, scopolamine, glycopyrrolate, botulinum toxin, vasodilators, arginine supplementation
Pupillomotor and visceral dysfunction		
Vision blurring, impaired light adaptation to ambient light, Argyll-Robertson pupil	Pupillometry, HRV	Care with driving at night
Impaired visceral sensation: silent myocardial infarction, hypoglycemia unawareness	Physical assessment, medical history	Recognition of unusual presentation of myocardial infarction, control of risk factors, control of plasma glucose levels

Abbreviations: ACE = angiotensin-converting enzyme; H&P = history and physical; HRV = heart rate variability; MIBG = metaiodobenzylguanidine; MUGA = multiunit gated blood pool.

in patients with proliferative retinopathy. Cardiovascular sympathetic function is assessed by measuring the blood pressure response to orthostatic change and a Valsalva maneuver. The combination of cardiovascular autonomic tests with sudomotor function tests may allow a more accurate diagnosis of diabetic autonomic neuropathy (375 [EL 4; NE]). Frequency domain measurements of the total spectral power, the standard deviation of normal R-R intervals, and the root means squared of the standard deviation of R-R intervals have recently been shown to be the most sensitive indicator of autonomic imbalance. These changes also precede the rise in circulating levels of inflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α), as well as a fall in the high molecular weight adiponectin/leptin ratios in newly diagnosed DM (376 [EL 2; PCS]; 377 [EL 4; NE]).

Patients with DM and features of cardiac autonomic dysfunction such as unexplained tachycardia, bradycardia, orthostatic hypotension, and poor exercise tolerance or those with other symptoms of autonomic dysfunction should be evaluated for the presence of cardiovascular autonomic neuropathy. Screening for cardiovascular autonomic neuropathy should be performed at diagnosis of T2D and 5 years after the diagnosis of T1D.

Retrospective and prospective studies have suggested a relationship between hyperglycemia and the development and severity of diabetic neuropathy, as well as significant effects of intensive insulin treatment on prevention of neuropathy (378 [EL 4; review NE]). Treating oxidative stress may improve peripheral and autonomic neuropathy in adults with T2D (379 [EL 1; RCT]; 380 [EL 1; RCT]; 381 [EL 1; RCT]; 382 [EL 1; RCT]). A systematic review of α-lipoic acid in the treatment of diabetic neuropathic pain found that this drug may help relieve pain and improve neuropathy, possibly through its potent antioxidant properties to reduce glutathione concentrations (383 [EL 4; NE]). The SYDNEY (Symptomatic Diabetic Neuropathy), ALADIN (Alpha-Lipoic Acid in Diabetic Neuropathy), and SYDNEY 2 trials showed benefit in painful neuropathy, and the NATHAN (Neurological Assessment of Thioctic Acid in Diabetic Neuropathy) 1 trial showed improvement in neuropathy scores and delayed progression (384 [EL 1; RCT]; 385 [EL 1; RCT]).

TZDs, which reduce hyperglycemia through reductions in insulin resistance, may also reduce chronic inflammation and potentially affect pathways leading to peripheral neuropathy (386 [EL 4; review NE]; 387 [EL 1; RCT]; 388 [EL 3; SS]). Fibrates and statins may protect against peripheral nerve function decline in adults with T2D (389 [EL 2; PCS]; 390 [EL 2; PCS]). Older adults taking statins show a greater benefit than younger adults because of their higher attributable risk of CVD (391 [EL 4; review NE]). A modest association between statin use and peripheral neuropathy was found in a review of the 1999-2004 National Health and Nutrition Examination Survey (NHANES) data, but the authors cautioned not to overinterpret the findings, which may be explained by many uncontrolled, confounding factors, so no causal inference can be made (392 [EL 3; SS]).

Small studies in patients with DM have shown that aerobic exercise improved quantitative test results for peripheral nerve function and cardiac autonomic neuropathy (393 [EL 2; PCS]). Among participants and/or those with peripheral neuropathy and DM, balance training is effective in improving balance outcomes and probably reduces risk of falls (394 [EL 3; SS]; 395 [EL 2; NRCT single-blinded]).

4.Q12. How is CVD Managed in Patients with Diabetes?

CVD is increased two- to threefold in patients with DM. The best data have come from studies that ascertained cardiovascular mortality as a function of FPG, 2-hour PPG, or A1C in nondiabetic and diabetic populations (55 [EL 2; PCS]; 396 [EL 2; RCCS]; 397 [EL 3; SS]; 398 [EL 2; PCS]). In a meta-analysis involving 447,064 patients, the rate of fatal coronary heart disease in patients with DM was reported to be 5.4% versus 1.6% in nondiabetic subjects. Diabetic females had a significantly higher relative fatal cardiovascular risk than males (3.50 versus 2.06) (399 [EL 2; MNRCT]). The original 7-year East-West Study in a Finnish population showed that the incidence of myocardial infarction in patients with DM and no preceding myocardial infarction at baseline was equivalent to that of persons without DM who had had a previous myocardial infarction at baseline. The incidence of myocardial infarction in the diabetic population was almost sixfold greater than the incidence in nondiabetic persons with no previous myocardial infarction at baseline (400 [EL 3; SS]). A subsequent 18-year follow-up of the same cohort confirmed that the patients with DM without evidence of any ischemic heart disease at baseline had as great or a greater risk for CVD-related death and total CVD as persons without DM who had had previous ischemic heart disease at baseline (401 [EL 3; SS]). A nationwide study of 3.3 million residents in Denmark with a 5-year follow-up showed similar results (402 [EL 3; SS]).

It is difficult to quantitatively define the factors responsible for DM being a CVD risk factor because insulin resistance, hypertension, lipid abnormalities, endothelial dysfunction, inflammation, and procoagulant factors are all present in patients with T1D and T2D, as well as in those with less severe forms of hyperglycemia. Early epidemiologic studies indicated that the age-adjusted cardiovascular event rate for patients with DM was twofold greater than that of the nondiabetic individual at each identical level of systolic blood pressure from 105 to 195 mm Hg (403 [EL 4; review NE]). The 12-year follow-up of MRFIT (Multiple Risk Factor Intervention Trial) showed

that at every level of total cholesterol, the rate of CVD-related death was threefold higher for patients with DM versus the rate in patients without DM (404 [EL 2; PCS]). Patients with DM not only have an increase in risk factors for CVD, but the risk factors cause more disease in a hyperglycemic environment. Autonomic neuropathy is a risk factor for CVD and a strong predictor for CVD events (369 [EL 3; SS]; 405 [EL 1; RCT]).

Comprehensive risk reduction programs have decreased the incidence of acute myocardial infarction in patients with DM by 67.8% from 1990 to 2010 (406 [EL 3; SS]). The recent American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines recommends the use of a newly developed risk prediction algorithm based on atherosclerotic events to determine the 10-year risk of patients developing a cardiovascular event (407 [EL 4; NE]). However, Ridker and Cook presented analyses from several large studies suggesting that the new risk prediction algorithm significantly overpredicts event rates (232 [EL 4; NE]). The AACE recommends starting a statin in patients with DM and at least 1 major additional ASCVD risk factor regardless of LDL-C level if they are >40 years of age; primary prevention strategies for younger patients should be individualized (see Q8. How is dyslipidemia managed in patients with diabetes?).

4.Q12.1. Glycemic Control

Hyperglycemia increases CVD both by its direct effects and indirectly via effects on other cardiovascular risk factors. Abnormal glucose regulation is common in patients referred to a cardiologist for coronary artery disease and is associated with poor outcomes (408 [EL 3; SS]; 409 [EL 2; PCS]; 410 [EL 3; SS]). Intensive glycemic control reduces micro- and macrovascular complications in patients with DM. The 2 large clinical trials of glycemic control in patients with DM of only a few years' duration (DCCT and UKPDS) both showed marked decreases in microvascular complications with intensive glycemic control versus standard glucose control: DCCT, 60 to 70% (68 [EL 1; RCT]); UKPDS, 25% reduction (50 [EL 3; SS]). While neither showed a decrease in myocardial infarction during the trial, both showed reductions in macrovascular events in the intensively treated cohort in long-term extension studies (49 [EL 1; RCT, posttrial monitoring]; 411 [EL 1; RCT]).

The beneficial effects of intensive glycemic control in reducing vascular complications appear to be inversely related to the extent of vascular disease at the time it is initiated. The ACCORD (62 [EL 1; RCT]), ADVANCE (57 [EL 1; RCT]), and VADT (Veterans Affairs Diabetes Trial) (61 [EL 1; RCT]) trials investigated the effect of intensive glycemic control versus standard glycemic control on the development of new cardiovascular events in patients with mean durations of diagnosed T2D of 8.5 to 11 years either with baseline previous cardiovascular events (35 to 45% of patients) or high cardiovascular risk. The duration of the trials was 3.5 to 7.0 years. All 3 trials failed to show a significant benefit of intensive glycemic control in reducing new cardiovascular events.

Subanalyses of the ACCORD study indicated that patients without a previous cardiovascular event or those who entered the study with an A1C level ≤8% had a significant benefit from intensive glycemic control (62 [EL 1; RCT]). A subanalysis from the VADT trial indicated that patients who entered the trial with a duration of DM <15 years had a decrease in cardiovascular events with intensive glycemic control (412 [EL 2; PCS]).

A randomized controlled substudy in the VADT trial investigated the utility of measuring coronary artery calcification in predicting subsequent clinical cardiovascular events (413 [EL 1; RCT, posthoc analysis with other methodological limitations]). At the end of the 6-year study, the extent of baseline coronary artery calcification was found to correlate very well with the development of clinical cardiovascular events. Patients who entered the study with high coronary artery calcification scores (>100) had no reduction in clinical cardiovascular events with intensive glycemic control, while those who entered with low scores (<100) had a 90% reduction in clinical events with the intensive glycemic control regimen.

Glycemic control can have a long-term effect on the rate and severity of future vascular complications (49 [EL 1; RCT, posttrial monitoring]; 411 [EL 1; RCT]). In contrast, there is no such legacy effect of blood pressure control on cardiovascular risk (206 [EL 1; RCT, questionnaires and other variables may have confounded]).

4.Q12.2. Antiplatelet Therapy

The use of aspirin for primary prevention has become controversial owing to recent data showing little to no benefit in certain patient populations (9 [EL 1; MRCT but small sample sizes and event rates]). In patients with proven CVD, aspirin (75 to 162 mg daily) is generally indicated (9 [EL 1; MRCT but small sample sizes and event rates]). Adjuvant therapies such as adenosine diphosphate receptor antagonists may also be helpful, especially if peripheral vascular disease is present.

Data from the many clinical trials and observational studies on the use of low-dosage aspirin in the primary prevention of CVD in patients with DM continue to be controversial (405 [EL 1; RCT]). Several recent meta-analyses show no statistically significant benefit on either total cardiovascular outcomes or individual events such as death, myocardial infarction, or stroke (10 [EL 1; MRCT]). An observational study in patients with T2D reported that low-dosage aspirin was associated with a paradoxical increase in CVD risk in primary prevention, and the risk of GI bleeding was rather high (414 [EL 1; RCT]). Observational studies such as The Fremantle Diabetes Study reported

beneficial reductions in all-cause and CVD-related mortality with regular low-dosage aspirin use, particularly in males older than 65 years (12 [EL 2; PCS]). These conflicting findings may reflect the results of studies showing that patients with DM have an increased resistance to the effects of aspirin (415 [EL 1; MRCT]). This aspirin resistance has been linked in part to an effect of hyperglycemia (416 [EL 2; PCS]). Most studies (11 [EL 1; MRCT]; 12 [EL 2; PCS]; 415 [EL 1; MRCT]), but not all (416 [EL 2; PCS]), support the use of low-dosage aspirin in the secondary prevention of CVD in patients with DM. Once-daily low-dose aspirin may be associated with incomplete inhibition of cyclooxygenase 1 (COX-1) activity and thromboxane A2 (TXA2)-dependent platelet function in patients with DM (417 [EL 2; PCS]). Some data support the use of twice-daily low-dose aspirin in patients with DM and CVD (418 [EL 1; RCT]).

4.Q12.3. Asymptomatic Coronary Artery Disease

Although screening for asymptomatic coronary artery disease in patients with T2D does not improve cardiac outcomes, the measurement of coronary artery calcification may be useful in assessing whether some patients with long-standing DM are reasonable candidates for intensification of glycemic control and or lipid lowering. The impression in the past was that diagnosing asymptomatic CVD in patients with DM would result in improved care and better long-term clinical outcomes; however, findings from well-conducted clinical trials have not supported this idea (405 [EL 1; RCT]).

The use of coronary calcification scores might help to identify those patients who will receive the most benefit from intensive glycemic control (413 [EL 1; RCT, posthoc analysis with other methodological limitations]). A large prospective study is necessary to validate such an approach. Meanwhile, in those patients with long-standing DM, coronary artery calcification scores could separate those who already have extensive disease from those with significantly less severe disease.

4.Q13. How is Obesity Managed in Patients with Diabetes?

The natural history of obesity reflects a small positive energy balance over a prolonged period of time, which produces excess fat storage and adipose tissue mass. BMI (weight in kilograms divided by height in meters squared) is used to differentiate normal weight (18.5 to 24.9 kg/m^2); overweight (25 to 29.9 kg/m^2); and obesity classes I (30 to 34.9 kg/m^2), II (35 to 39.9 kg/m^2), and III (≥40 kg/m^2) (419 [EL 4; NE]). Clinical correlation is required since BMI may not reflect adipose tissue mass in muscular athletes, sarcopenic obesity, paraplegia, frailty, and other conditions. Also, lower BMI criteria for obesity have been recommended for some ethnicities (e.g., ≥23 kg/m^2 is considered overweight in southeast Asians) (420 [EL 4; NE]).

While insulin resistance can exist independent of obesity, excess weight gain, particularly with accumulation of fat in ectopic compartments such as visceral adipose tissue, can exacerbate insulin resistance and increase risk for the development of metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), hypertension, prediabetes, and T2D. Whether individuals are insulin sensitive or resistant, increased adiposity can also lead to biomechanical complications of obesity including osteoarthritis, OSA, gastroesophageal reflux disease (GERD), urinary stress incontinence, and disability. Thus, primary prevention is needed to prevent obesity, and secondary treatment and prevention is required to stabilize or decrease body weight and prevent the emergence of complications in patients who are overweight or obese without complications. When excess adiposity adversely impacts health by causing obesity-related complications, more aggressive interventions are needed to induce and sustain weight loss and treat the complications (421 [EL 4; NE]).

4.Q13.1. Lifestyle Modification for Weight Loss

Lifestyle change is a cornerstone for weight management in the patient with or without DM, and includes 3 components: caloric restriction, increased energy expenditure through increased physical activity, and behavior changes related to lifestyle. All diets are superior to no diet, and differences between individual diets with different macronutrient composition are minimal (93 [EL 1; RCT]; 422 [EL 1; MRCT]). Therefore, healthy meal plans such as the Mediterranean, low carbohydrate, low fat (with an emphasis on high-water content, low-energy-dense foods), low glycemic index, DASH Diet (which emphasizes fruits, vegetables, and low-fat dairy products), and vegetarian diets have been advocated to take into account personal and cultural preferences that accommodate nutrition guidelines (423 [EL 4; NE]). Caloric reduction is critical for weight loss regardless of the meal plan. For longer-term compliance, a moderate calorie deficit of ~500 kcal below energy expenditure is commonly advocated, although many patients are successfully initiated on very low calorie diets (~800 kcal/day) including the use of meal replacements (bars and shakes) that add structure to the diet (96 [EL 1; RCT]).

Increased physical activity is important for maintaining weight loss. For cardiometabolic conditioning, a recommendation consistent with guidelines proposed by the ADA, AHA, and American College of Sports Medicine (ACSM) would 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 (104 [EL 4; consensus NE]; 424 [EL 4; NE]).

However, it is important to individualize the prescription for physical activity. Reduction in sedentary behavior can be helpful.

The third component of lifestyle focuses on behavior modification (423 [EL 4; NE]). The components of a lifestyle program include education and behavior modification including self-monitoring of food intake and physical activity, learning to cope with negative thoughts by means other than eating, portion control, and consuming meals at regular times and in places where one can focus on the act of eating. A mental health professional is commonly needed to address issues such as disordered eating and depression, which, if not treated proactively, can jeopardize the effectiveness of lifestyle therapy.

4.Q13.2. Obesity Pharmacotherapy

The first step in evaluating medications for the overweight patient is to determine whether the patient is taking drugs that produce weight gain, including some antihyperglycemic agents (Table 9), antidepressants, and antiseizure medications (425 [EL 4; NE]; 426 [EL 4; NE]; 427 [EL 1; RCT]). If such agents are identified and there are acceptable weight-neutral or weight loss-inducing alternatives, the healthcare professional should consider changing the medication (425 [EL 4; NE]).

Several drugs are approved by the FDA for weight reduction in patients with and without DM (426 [EL 4; NE]; 428 [EL 4; NE]). These include several sympathomimetic amines (phentermine, benzphetamine, and phendimetrazine), which are approved for short-term use (≤12 weeks). Five medicines are approved for long-term use and, therefore, are more useful in the treatment of obesity as a chronic if not lifelong disease. These include orlistat (32 [EL 1; RCT]; 429 [EL 1; MRCT]), lorcaserin (430 [EL 1; RCT]; 431 [EL 1; RCT]; 432 [EL 1; RCT]), phentermine/topiramate extended release (33 [EL 1; RCT]; 433 [EL 1; RCT]; 434 [EL 1; RCT]; 435 [EL 1; RCT]; 436 [EL 1; RCT]), naltrexone/bupropion extended release (437 [EL 1; RCT]; 438 [EL 1; RCT]; 439 [EL 1; RCT]; 440 [EL 1; RCT]), and a high-dose formulation of liraglutide (45 [EL 1; RCT]; 46 [EL 1; RCT]; 441 [EL 1; RCT]).

All weight-loss medications are approved for patients with BMI 27 to 29.9 kg/m^2 with at least 1 obesity-related complication and BMI ≥30 kg/m^2 regardless of complications. These drugs vary with respect to efficacy as defined by weight loss in RCTs and differ regarding adverse effect profile, cautions, and warnings. In addition, lorcaserin and phentermine/topiramate extended release are classified by the U.S. Drug Enforcement Administration as having the potential for abuse and are schedule IV controlled substances (442 [EL 4; NE]). However, these differences enable individualized treatment. On any treatment program there are patients who do very well and for whom the medication should be continued; for others, the treatment may be ineffective, and the patient may lose little weight or even gain weight. The FDA has advised drug discontinuation if <5% of body weight is lost after 12 weeks on the maximal dose of the medication. At that point, an alternative weight-loss medication may be prescribed.

All weight-loss medications serve as an adjunct to lifestyle modification therapy. Except for orlistat, these medications act to decrease appetite and enhance compliance with a reduced-calorie meal plan. Therefore, maximal benefit is achieved in conjunction with lifestyle therapy, and all clinical trials demonstrated greater weight loss when the medication was added to lifestyle modification than that achieved with lifestyle modification plus placebo. The patient should be familiarized with the drugs and their potential side effects and should receive effective lifestyle support for weight loss during pharmacologic therapy (443 [EL 1; MRCT]; 444 [EL 1; MRCT]).

4.Q13.3. Bariatric Surgery

Bariatric surgery is an effective approach for attaining significant and durable weight loss in severely obese patients with and without DM. Because metabolic as well as weight-related comorbidities are often improved or resolved through weight loss due in part to neuroendocrine mechanisms, the term metabolic surgery is often used instead of bariatric surgery. In general, metabolic operations alter the GI tract by reducing stomach capacity (gastric restrictive operations); rerouting nutrient flow, leading to some degree of malabsorption (bypass procedures); or combining both concepts. Metabolic procedures have evolved since the jejunoileal bypass was abandoned in the 1970s. Commonly performed procedures along with frequency of use include Roux-en-Y gastric bypass (RYGB, 49%), sleeve gastrectomy (SG, 30%), adjustable gastric banding (AGB, 19%), and biliopancreatic diversion (BPD, 2%). A meta-analysis of 136 mostly short-term studies in more than 22,000 patients showed an overall loss of 61.2% of excess body weight, with effects differing by procedure. In those with gastric banding, the loss of excess body weight was 47.5%. It was 61.6% after gastric bypass and 68.2% with gastroplasty. The highest success rate of 70.1% reduction in excess body weight was seen with BPD (445 [EL 2; MNRCT]). In patients with severe obesity and T2D, bariatric surgery has been shown to provide significantly improved outcomes at 12 months for weight loss, number of DM medications used, and glycemic control (e.g., A1C and fasting glucose levels) compared to patients receiving intensive lifestyle therapy (446 [EL 1; RCT, not blinded]; 447 [EL 1; RCT, not blinded]).

These procedures carry a mortality risk (which is low when performed in centers of excellence), as well as morbidity due to surgical and nutritional complications. The patients require life-long medical follow-up and must adhere to ongoing lifestyle modification for optimal outcomes. However, the development of laparoscopic approaches to all these metabolic operations in the mid

1990s has significantly reduced perioperative morbidity and mortality.

The indications for weight-loss surgery have evolved since the seminal National Institutes of Health (NIH) guidelines from 1991 (448 [EL 4; NE]). In the 2011 guidelines for bariatric surgery specifically in patients with T2D, the International Diabetes Federation (IDF) recommended considering surgery for individuals with T2D who are obese (BMI >30 kg/m^2) and had not achieved the IDF treatment targets with an optimal medical regimen, especially if other cardiovascular risk factors were present (449 [EL 4; NE]). In 2013, joint clinical practice guidelines from the AACE, Obesity Society (TOS), and American Society for Metabolic & Bariatric Surgery (ASMBS) recommended consideration of surgical weight loss for all patients with BMI >40 kg/m^2 (unless surgery would pose significant risk) and for patients with BMI >35 kg/m^2 who have at least 1 major obesity-related comorbidity (450 [EL 4; NE]).

4.Q13.4. Effects of Weight Loss in T2D

Weight loss has long been known to enhance insulin sensitivity and improve glycemia in patients with T2D (451 [EL 4; NE]). It is highly effective whether achieved through lifestyle modification (452 [EL 1; RCT]; 453 [EL 2; PCS]; 454 [EL 1; MRCT]; 455 [EL 1; RCT]), pharmacotherapy (431 [EL 1; RCT]; 436 [EL 1; RCT]; 438 [EL 1; RCT]; 456 [EL 1; RCT]), or bariatric surgery (34 [EL 2; PCS]; 446 [EL 1; RCT, not blinded]; 447 [EL 1; RCT, not blinded]; 457 [EL 2; PCS]). These studies have consistently shown that weight loss lowers A1C while decreasing the need for conventional DM medications and producing significant decreases in blood pressure and improvements in lipids and lipoproteins.

The long-term benefits of weight reduction in T2D were underscored by the Look AHEAD study, which randomized patients with T2D to either intensive lifestyle intervention consisting of a moderate calorie reduction diet, regular exercise, and behavioral interventions or the standard DM support and education program (452 [EL 1; RCT]; 458 [EL 1; RCT]). Mean weight loss from baseline was greater in the intensive subgroup (~9% after 1 year and 4.7% after 4 years) than in the standard subgroup (1.1% weight loss at 4 years) and was associated with more marked reductions in A1C. In fact, progressive declines in FPG, A1C, systolic and diastolic blood pressure, and triglycerides, together with progressive increments in HDL-C, were observed as the amount of weight loss increased from 5 to >15%. The Look AHEAD study was terminated early because the subgroups did not differ in terms of a complex cardiovascular outcome measure (459 [EL 1; RCT]).

Until 2012, the only obesity medication approved for chronic use in the U.S. was orlistat, which has been shown to be effective in T2D (456 [EL 1; RCT]; 460 [EL 1; RCT]; 461 [EL 1; RCT]). The weight loss produced by orlistat led to A1C reductions of 0.75% units after 1 year of therapy (baseline value 8.9%) in patients with T2D who were overweight or obese; sulfonylurea dosages also decreased in 1 study (461 [EL 1; RCT]). The other long-term weight-loss medications approved by the FDA have also been shown to be safe and effective in treating patients with T2D who are overweight or obese. In the 52-week study of lorcaserin 10 mg twice daily plus lifestyle modification in patients with T2D (BLOOM-DM [Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus] trial) A1C decreased by 0.9% (baseline 8.1%, P<.001 versus placebo), together with a 4.5% weight loss and reduced need for antihyperglycemic medications (431 [EL 1; RCT]). Phentermine/topiramate extended release significantly reduced A1C values below that observed in patients randomized to lifestyle plus placebo in a cohort of patients with mild-to-moderate, shorter-duration T2D and also in patients with severe, long-standing T2D on multiple medications (433 [EL 1; RCT]; 435 [EL 1; RCT]; 436 [EL 1; RCT]). In both cohorts, patients randomized to phentermine/topiramate extended release experienced a decreased need for antihyperglycemic medications and improvements in cardiovascular risk factors. Naltrexone/bupropion extended release (COR [Contrave Obesity Research]–Diabetes study) produced greater weight loss (5.0% versus 1.8% from baseline), A1C reduction (0.6% versus 0.1% units), and improvements in triglycerides and HDL-C compared with lifestyle alone (438 [EL 1; RCT]). The high dose (3 mg) formulation of liraglutide significantly reduced weight in persons without diabetes who were obese (45 [EL 1; RCT]; 46 [EL 1; RCT]; 441 [EL 1; RCT]), while lower dosages of this agent have significantly reduced both weight and A1C in glucose-control studies involving patients with T2D (4 [EL 4; NE]).

Bariatric surgery procedures in patients with T2D have produced marked reductions in both A1C and DM medications and can result in DM remission (normal A1C values without antihyperglycemic agents) in some patients. In the Swedish Obese Subjects Study, bariatric surgery produced DM remission rates of 72% and 30% after 2 and 15 years, respectively, and was associated with a reduction in microvascular DM complications (457 [EL 2; PCS]; 462 [EL 2; PCS]). In addition, follow-up over 20 years demonstrated that both cardiovascular disease events and mortality were reduced in patients treated by surgery (457 [EL 2; PCS]). In the STAMPEDE (Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently) trial, glycemic control in subjects with T2D following bariatric surgery was improved compared with that in medically treated patients (447 [EL 1; RCT, not blinded]). These data should be interpreted cautiously because glycemic control in the medically treated patients will vary depending on the intensity of therapy. In addition, there was no weight-loss arm using intensive lifestyle/behavior therapy plus weight-loss

medications. Thus, the data support bariatric surgery as an effective therapeutic approach in T2D patients with BMI ≥35 with uncontrolled DM and obesity refractory to lifestyle and pharmacotherapy.

4.Q14. What is the Role of Sleep Medicine in the Care of the Patient with Diabetes?

Daytime drowsiness is the most obvious symptom of a sleep disorder and has been shown to be associated with an increased risk of accidents, increased errors in judgment, and diminished performance (463 [EL 3; SS]). Sleep deprivation also increases major risk factors for heart disease as it aggravates insulin resistance, hypertension, hyperglycemia, dyslipidemia, and inflammatory cytokines. Restless leg syndrome is increasingly being recognized as a medical cause of sleep disturbance, and medication can be quite successful in relieving it (464 [EL 3; CSS]). When OSA or restless leg syndrome is suspected, the usual course is to refer to a sleep specialist who may choose to do an overnight study in a sleep laboratory, although most sleep disturbances can be diagnosed with overnight oximetry testing at home after a careful history and physical (465 [EL 4; NE]; 466 [EL 1; RCT, not blinded]). OSA is especially common in adults with DM, occurring in approximately 2 of 3 males with DM older than 65 years (467 [EL 4; review NE]).

OSA is the most common type of sleep apnea and is caused by physical obstruction of the airway during sleep. OSA refers to numerous episodes during sleep where the individual stops breathing and is then awakened by the need for oxygen. Usually the individual is unaware of the awakenings, which may happen hundreds of times per night and are accompanied by very loud snoring and grunts and snorts when breathing resumes. OSA is more common in males, the elderly, and individuals with obesity (468 [EL 3; CSS]; 469 [EL 3; CSS]). Treatment of OSA in patients with DM can lower FPG, PPG, and A1C levels as much as or more than oral agents (470 [EL 3; CSS]; 471 [EL 3; SS]). Successful OSA treatment may lead to improvements in cardiovascular outcomes (472 [EL 2; PCS]; 473 [EL 1; RCT, single-blind]; 474 [EL 1; RCT, single-blind]), although data have not shown a consistent benefit in terms of metabolic control (470 [EL 3; CSS]; 471 [EL 3; SS]; 475 [EL 1; RCT, small sample size]; 476 [EL 1; RCT, small sample size]; 477 [EL 2; PCS]). Patients with newly diagnosed OSA should persevere through the initial, often frustrating phase of CPAP when finding the right equipment can be a challenge. When CPAP is successful, it can dramatically improve quality of life (478 [EL 2; CPS]). Because of recent improvements in the technology, this treatment should be re-evaluated for patients in whom CPAP failed in the past. For certain subgroups with OSA, surgery to widen the airway or devices that reposition the jaw may be appropriate.

4.Q15. How is Diabetes Managed in the Hospital?

DM represents the seventh leading cause of death (479 [EL 3; SS]) and is the second-leading comorbid condition among hospital discharges in the United States (480 [EL 3; SS]). The association between inpatient hyperglycemia and increased risk for complications and mortality is well established (481 [EL 3: SS]; 482 [EL 2; PCS]). Hyperglycemia is associated with prolonged hospital stay, increased incidence of infections, greater disability after hospital discharge, and death (483 [EL 2; RCCS]; 484 [EL 2; PCS]).

Substantial evidence indicates that correction of hyperglycemia with insulin administration reduces hospital complications and mortality in the critically ill, as well as in general medicine and surgery patients (485 [EL 1; RCT]; 486 [EL 2; MNRCT]). Several RCTs including the real-world NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) study (487 [EL 1, RCT]; 488 [EL 1; RCT, protocol violations]; 489 [EL 1 RCT, not blinded]) and meta-analyses (486 [EL 2; MNRCT]; 490 [EL 1, MRCT]; 491 [EL 1, MRCT]) have reported higher rates of severe hypoglycemia and increased morbidity and mortality with intensive insulin therapy (glycemic targets of 80 to 110 mg/dL) compared to more relaxed glycemic targets. The AACE/ADA consensus statement on inpatient glycemic control outlines the argument in favor of more relaxed glycemic targets in the ICU, as high as 140 to 180 mg/dL (5 [EL 4; consensus NE]). Although strong evidence is lacking, somewhat lower glucose targets may be appropriate in selected patients, such as surgical populations in units that have shown low rates of hypoglycemia. However, glucose targets <110 mg/dL are not recommended. In addition, minimizing glycemic variability, independent of glucose levels, could result in lower rates of complications and cardiovascular mortality in critically ill patients (492 [EL 2; PCS]; 493 [EL 3: SS]; 494 [EL 2; RCCS]), and in reduced hospital stays and mortality in non-ICU settings (495 [EL 2; RCCS]).

4.Q15.1. Treatment of Hyperglycemia in Hospitalized Patients

Patients with DM have a threefold greater chance of hospitalization compared to those without DM (496 [EL 3; SS]; 497 [EL 3; SS]), and it is estimated that 20% of all adults discharged have DM, with 30% requiring 2 or more hospitalizations in any given year (496 [EL 3; SS]). It is well established that hyperglycemia in patients with or without a prior diagnosis of DM increases both mortality and disease-specific morbidity in hospitalized patients (5 [EL 4; consensus NE]; 481 [EL 3: SS]; 483 [EL 2; RCCS]; 498 [EL 2; PCS]), and that goal-directed insulin therapy can improve outcomes (485 [EL 1; RCT]; 499 [EL 1, RCT]; 500 [EL 2; PCS]). This topic has been extensively

reviewed in the AACE/ADA Consensus Statement on Inpatient Hyperglycemia (5 [EL 4; consensus NE]), 2014 ADA Standards of Medical Care in DM (212 [EL 4; NE]), and 2012 Endocrine Society Clinical Practice Guideline for the Management of Hyperglycemia in Hospitalized Patients in the Noncritical Care Setting (501 [EL 4; NE]).

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 most critically ill patients in the ICU, a glucose concentration range of 140 to 180 mg/dL is recommended, provided these targets can be safely achieved. For patients in non-ICU settings, a premeal glucose target of <140 mg/dL and a random blood glucose of <180 mg/dL is recommended; however, glycemic targets should be modified according to clinical status. For patients who are able to achieve and maintain glycemic control without hypoglycemia, a lower target range may be reasonable. For patients with terminal illness and/or with limited life expectancy or at high risk for hypoglycemia, a higher target range (<180 mg/dL) may be reasonable.

Insulin therapy is the preferred method of glycemic control in most hospitalized patients. In ICUs, intravenous infusion of insulin is the preferred route of administration. In the critical care setting, a variety of continuous insulin infusion protocols have been shown to be effective in achieving glycemic control with a low rate of hypoglycemic events and also to improve hospital outcomes (499 [EL 1, RCT]; 500 [EL 2; PCS]; 502 [EL 3; SS]; 503 [EL 3; SS]). Recently, computer-based algorithms aiming to direct nursing staff adjustment of insulin infusion rate have become commercially available (504 [EL 3; SS]; 505 [EL 3; SS]). No major clinical outcome differences have been reported in the frequency of hypoglycemic events, length of ICU or hospital stay, or mortality among different intravenous insulin algorithms. Thus, most insulin algorithms appear to be appropriate alternatives for managing hyperglycemia in critically ill patients, and the choice depends on physicians' preferences and cost considerations.

Most patients with T2D and all patients with T1D in the ICU receiving intravenous insulin infusion will require transition to a subcutaneous regimen (5 [EL 4; consensus NE]). Patients suitable for this transition ideally have a stable infusion rate and blood glucose levels in the target range. Several studies recommend starting at a daily insulin dose ~80% of the intravenous insulin used in the preceding 12 to 24 hours and splitting it into basal and bolus insulin (5 [EL 4; consensus NE]). Nondiabetic patients with stress or newly diagnosed hyperglycemia who have required an insulin rate ≤1 to 2 units/hour at the time of transition may not require a scheduled subcutaneous insulin regimen (506 [EL 4; NE]). Many of these patients can be treated with correction insulin to determine if they will require scheduled subcutaneous insulin.

Outside of the critical care 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. RCTs have shown that treatment with a basal prandial regimen using insulin analogs is preferred to sliding scale regular insulin alone. This approach results in improved glycemic control and lower rates of hospital complications in general medical and surgical patients with T2D (485 [EL 1; RCT]; 507 [EL 1; RCT]; 508 [EL 1; RCT]). Patients with T1D should be treated with basal-prandial insulin regimens to avoid severe hyperglycemia and DKA. In insulin-naïve patients with T2D, a starting total daily insulin dose between 0.3 and 0.5 units/kg/day has been shown to be effective and safe in general medicine and surgery patients. Patients 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 insulin regimen is important as requirements vary according to clinical stressors and altered caloric intake (5 [EL 4; consensus NE]; 509 [EL 4; NE]). Lower starting total daily insulin doses of 0.20 to 0.25 units/kg are recommended in patients with impaired kidney function (510 [EL 1; RCT, not blinded, small sample size]; 511 [EL 2; RCCS]), in the elderly, and in those with poor caloric intake (511 [EL 2; RCCS]; 512 [EL 3; SS]). In addition, for those receiving insulin prior to admission, reducing the total daily insulin dose by 20 to 25% is recommended to avoid hypoglycemia in hospitalized patients with poor caloric intake (512 [EL 3; SS]).

Each of the major classes of noninsulin antihyperglycemic agents has substantial limitations for inpatient use, so they are generally not recommended (5 [EL 4; consensus NE]; 501 [EL 4; NE]). These agents provide limited flexibility or opportunity for rapid titration in a setting where acute changes in patient status often demand such action. A recent randomized pilot study reported that the use of the DPP-4 inhibitor sitagliptin plus correction doses with rapid-acting insulin resulted in similar daily glucose control compared to patients treated with basal-bolus insulin or basal insulin plus sitagliptin (513 [EL 1; RCT, not blinded]). Patients with an admission glucose >180 mg/dL treated with DPP-4 inhibitors, however, had worse glucose control compared with patients treated with basal-bolus insulin therapy. Despite the shortcomings of oral antihyperglycemic therapy in the hospital setting, transition to oral agents 1 or 2 days before discharge is often necessary for patients whose glycemia was well controlled on oral agents before admission.

4.Q15.2. ***Glucose Monitoring in the Hospital***

Bedside capillary POC testing is the preferred method for guiding ongoing glycemic management of hospitalized patients (5 [EL 4; consensus NE]; 501 [EL 4; NE]). POC testing is usually performed 4 times a day: before meals and at bedtime for patients who are eating. For nil per os patients or those receiving continuous enteral nutrition, POC testing is recommended every 4 to 6 hours. More frequent glucose monitoring is indicated in patients treated with continuous intravenous insulin infusion 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.

4.Q15.3. ***Medical Nutrition Therapy***

MNT is an essential component of inpatient glycemic management in patients with DM and hyperglycemia. The goals of inpatient MNT for patients 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 patients require 25 to 35 calories/kg/day; critically ill patients require between 15 and 25 calories/kg/day (514 [EL 4; NE]; 515 [EL 4; NE]). This translates to a diet containing approximately 1,800 to 2,000 calories/day or ~200 g carbohydrate per day divided between meals. Care must be taken not to overfeed hospitalized patients because this can exacerbate hyperglycemia. No single meal planning system is ideal for hospitalized patients; however, hospitals should provide a consistent carbohydrate DM meal-planning system (514 [EL 4; NE]). 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. Patients requiring clear or full liquid diets should receive ~200 g carbohydrate per day in equally divided amounts at meal and snack times. Patients on liquid diets, in particular during the perioperative period, do not meet these nutritional needs. Increasing evidence indicates that food intake should be initiated as quickly as possible with progression from clear liquids to full liquids to solid foods as rapidly as tolerated in surgical patients (516 [EL 4; NE]). 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 (516 [EL 4; NE]).

4.Q15.4. Hypoglycemia and Hospital Outcomes

Several meta-analyses of RCTs have reported a 6- or 7.7-fold risk ratio for occurrence of hypoglycemia with intensive insulin therapy versus conventional glycemic control in critically ill patients (490 [EL 1, MRCT]; 517 [EL 1; MRCT]), with some studies showing a risk ratio >10 (490 [EL 1, MRCT]). Inpatient hypoglycemia has been associated with higher rates of hospital complications, longer hospital stays, higher healthcare resource utilization, and increased hospital mortality, creating a J-shaped relationship between glucose levels and death rates (518 [EL 3; CSS]; 519 [EL 3; SS]). A glucose <50 mg/dL has been found to be associated with 22.2% mortality compared to 2.3% in patients without hypoglycemia (520 [EL 2; PCS]). Hypoglycemia is associated with adverse cardiovascular outcomes, such as prolonged QT intervals, ischemic electrocardiogram changes, angina, arrhythmias, and death (521 [EL 2; PCS]).

Despite these epidemiologic associations between hypoglycemia and poor clinical outcomes, data demonstrating that insulin-induced hypoglycemia is the direct cause of harm in hospitalized patients are sparse. It is the severity of hypoglycemia, not the insulin therapy, that is associated with an increased risk of mortality in the critically ill (519 [EL 3; SS]). Hypoglycemia resulting from severe systemic illness (spontaneous hypoglycemia), rather than insulin-induced hypoglycemia, is associated with increased risk of inpatient mortality and complications (522 [EL 3; SS]; 523 [EL 2; RCCS]; 524 [EL 2; PCS]).

4.Q15.5. Recommendations After Hospital Discharge

Patients with stress, or hospital-related, hyperglycemia, defined as any blood glucose concentration >140 mg/dL without evidence of previous DM, should undergo hemoglobin A1C testing during the hospital stay (501 [EL 4; NE]). Measurement of A1C provides the opportunity to differentiate patients with stress hyperglycemia from those with DM who were previously undiagnosed, as well as to identify patients with known DM who would benefit from intensification of their glycemic management. In the presence of hyperglycemia, an A1C >6.5% suggests the diagnosis of DM. Because about half of patients admitted with stress-related hyperglycemia have confirmed DM at 1 year (525 [EL 2; PCS]), they should be closely monitored after discharge.

Few studies have focused on the optimal management of hyperglycemia after hospital discharge. Although insulin is used for most patients with DM in the hospital, many patients do not require insulin after discharge. Clinical guidelines (5 [EL 4; consensus NE]; 501 [EL 4; NE]) recommend tailoring the discharge treatment regimen for patients with DM based on the admission A1C value. Patients with acceptable DM control could be discharged on their prehospitalization treatment regimen (oral agents and/or insulin therapy) if there are no contraindications. Patients with preadmission suboptimal control should have intensification of therapy at discharge, either by additional or increased dosage of oral agents, addition of basal insulin, or a more complex insulin regimen as warranted by their admission glucose control (526 [EL 2; PCS]).

4.Q16. How is a Comprehensive Diabetes Care Plan Established in Children and Adolescents?

Advances in molecular and genetic science have uncovered multiple causes of DM in the neonatal period through the first year of life. It is beyond the scope of this paper to elucidate each genetic cause of neonatal DM. Clinically, these vary from permanent neonatal DM to transient forms, which remit only to recur later in childhood (transient neonatal DM). Although all forms of neonatal DM result from compromised insulin secretion, there is variation in presentation ranging from early and acute onset of DKA to mild, asymptomatic hyperglycemia resulting from heterozygous glucokinase mutations. Important advances have been made in understanding the molecular mechanisms of those forms produced by mutations in the *KCNJ1* gene encoding the potassium channel protein Kir6.2 in β cells (527 [EL 3; SS]) and in the *ABCC8* gene encoding the sulfonylurea receptor protein SUR1 (528 [EL 3; SS]). Other causes have also been defined, including mutations in the insulin gene (529 [EL 3; SS]). Recognizing these disorders and distinguishing them from T1D is important. Most cases result from new mutations, but they are heritable, and several forms respond to sulfonylureas, negating the need for insulin therapy and improving glycemic control (530 [EL 2; PCS]). Excellent reviews on this topic are available (531 [EL 4; review NE]; 532 [EL 4; guidelines NE]).

Monogenic DM, initially called MODY (533 [EL 4; review NE]) because of its description as "maturity-onset diabetes" occurring in young adults, is currently being described with greater frequency in children and adolescents, as well as in adults. These genetic forms of DM result from compromised insulin secretion, in 1 case by mutations in the gene encoding the enzyme glucokinase (*GK*), and in the other cases by mutations in genes encoding transcription factors important for pancreas formation and later for insulin secretion (534 [EL 3; SS]). They are uncommon, and most cases in surveyed populations are the result of mutations in *GK* or in the gene encoding hepatic nuclear factor 1a (*HNF1A*) (535 [EL 3; SS]). Diagnosing these cases is important for many reasons. Although new mutations do occur, these conditions are usually inherited as autosomal dominant traits. Diagnosis in 1 family member frequently leads to discovery of pedigrees in which many family members are being inappropriately treated as having T1D or T2D (536 [EL 4; review NE]), or GDM (537 [EL 3; SS]). Making the correct diagnosis is important for genetic counseling and instituting proper therapy. Many affected patients respond to insulin secretagogues, do not require insulin or insulin sensitizers, or require no therapy (in the case of glucokinase deficiency).

Cystic fibrosis-related diabetes (CFRD) is a combination of insulin resistance plus insulin deficiency disorder. Oral agents such as TZDs or DPP-4 inhibitors can usually control glucose levels in these patients for several years, but the insulin deficiency will eventually require insulin therapy, which may involve intensive regimens such as basal-bolus insulin or even insulin pumps. The main goal is prevention of glucosuria, weight loss, and asthenia rather than tight glucose control. Steroid use in patients with CFRD may radically affect glucose levels. The patient, family, and endocrinologist should remain in close communication so insulin dosages can be adjusted as needed.

T1D is the most common form of DM occurring in children and adolescents, and its incidence is increasing in most populations throughout the world. The same types of insulin and administration regimens used in older patients are also used in children. Most physicians treating DM in children use MDI regimens, and when appropriate, CSII (538 [EL 3; SS]). Some use morning NPH insulin when it is difficult for the child to receive or administer a midday injection. CSII is also being used more often in infants and toddlers who eat frequently; the use of pumps can help parents improve the care of very young patients (539 [EL 2; PCS]). In adolescents, the main problems with glycemic control often involve social and behavioral complications (540 [EL 3; SS]). The increased insulin resistance associated with puberty, especially when coupled with obesity, sometimes requires large insulin doses and high insulin-to-carbohydrate ratios.

Although T2D has been reported in preschool children, one must be cautious making this diagnosis in preadolescent children, taking care to exclude T1D by assessing immune markers and monogenic DM through a careful family history and genetic testing. Guidelines for differentiating T1D from T2D in children have been published (532 [EL 4; guidelines NE]), but several reports have demonstrated that these are imperfect and that phenotypic overlap between these disorders in children is common. T2D remains a diagnosis of exclusion in adolescents. Lifestyle modification (healthy diet and increased physical activity) is always the first treatment choice, but the effectiveness in children has not been extensively studied. Treatment of T2D in children does not differ appreciably from its treatment in adults. Metformin has been studied (541 [EL 1; RCT]) and remains the only oral medication formally indicated by the FDA for use in children with T2D, although rosiglitazone and glimepiride report pediatric studies in their labels. Insulin is effective and used widely alone or in combination with metformin.

The TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) trial demonstrated that current therapy for children or adolescents with T2D is inadequate; monotherapy with metformin was associated with durable glycemic control in only half of children and adolescents with T2D, and its effectiveness lasted <18 months (542 [EL 1; RCT]). Multiple ongoing trials are examining the use of newer medications in adolescents with T2D, including DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors. These agents may improve glucose levels

without weight gain (or with weight loss) and/or hypoglycemia. However, although these classes are approved for adults, none are currently FDA approved for people younger than 18 years of age. Nevertheless, many pediatric endocrinologists use these agents in combination in younger patients to avoid the use of insulin and TZDs due to risks of weight gain and hypoglycemia.

SMBG frequency in pediatric patients with T1D has been shown to be predictive of A1C levels and complications (543 [EL 3; SS]). However, CGM benefits pediatric patients only when used on a virtually daily basis. When CGM was used ≥6 days per week, decreases in both A1C and the frequency and severity of hypoglycemia have been reported (544 [EL 2; PCS]; 545 [EL 1; MRCT]).

Incorporation of an exercise and nutrition plan are critical for managing either T1D or T2D in children and adolescents. Ideally, a nutritionist should consult with the entire family. The care of children and adolescents with DM involves not only parents and the healthcare team, but also grandparents, older siblings, teachers, coaches, and any other adults in regular contact with the child. It is important for these caregivers to maintain regular contact with each other and the healthcare team. Texting and emailing of glucose values can be helpful.

The management approach to treating the adolescent with T1D is like playing jazz: it requires improvisation and persistence. The healthcare professional should discuss the following with adolescents who have DM: drug and alcohol avoidance and abuse prevention, cigarette smoking prevention and cessation, sexual activity, pregnancy prevention and consequences, and automobile responsibilities and hypoglycemia prevention and management while driving. Transitioning to DM care for adults requires a well thought out plan with patients and their families. The ADA, JDRF, and NIDDK offer resources to help with transition planning (14 [EL 4; NE]; 15 [EL 4; NE]; 16 [EL 4; NE]).

An extensive review of CPGs for the care of DM in children from the International Society of Pediatric and Adolescent Diabetes was published in 2009 and is available on their website (13 [EL 4; CPG NE]).

4.Q17. How should Diabetes in Pregnancy be Managed?

Abnormal glucose tolerance develops at higher rates and at younger ages among offspring of females with DM. Maternal DM is one of the strongest risk factors for the development of T2D among Pima Indian children (546 [EL 2; PCS]; 547 [EL 3; CCS]; 548 [EL 3; SS]). By the time these offspring reach childbearing age, they are very likely to be obese and have DM, thereby perpetuating a vicious cycle (548 [EL 3; SS]). That this is not simply a genetic predisposition is inferred from the finding of lower rates of DM in offspring of females who were born before their mothers developed DM (549 [EL 3; SS]); this is true among sibling pairs whose birth dates straddle the onset of their mother's DM (546 [EL 2; PCS]). Thus, all females with DM in the childbearing years should have preconception care and guidance to target an A1C level of <6.5% (212 [EL 4; NE]; 550 [EL 2; PCS]). Frequent POC A1C monitoring allows the clinician to assess the most recent average glucose by comparing the current A1C POC test with the previous week's POC A1C. The rate of change and direction of the change reflects the trend of recent glucose levels. Although the steady state is not achieved until 6 to 8 weeks later, a rising A1C reflects recent hyperglycemia and allows the clinician an opportunity to discuss the observation and work with the patient for solutions.

The HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) study confirmed findings in the Pima Indians (546 [EL 2; PCS]) that, even among offspring of females without GDM as it is currently defined (551 [EL 2; PCS]; 552 [EL 4; consensus NE]; 553 [EL 4; review NE]; 554 [EL 3; PCS]; 555 [EL 3; SS]), there is a linear association between maternal glucose concentration during pregnancy and newborn weight, rates of large-for-gestational-age, and cesarean delivery. DM during pregnancy and even maternal obesity itself (552 [EL 4; consensus NE]) 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 (554 [EL 3; PCS]). 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 (555 [EL 3; SS]). 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 females with DM or at risk for GDM, and meticulous control of glucose abnormalities throughout pregnancy are currently our best hope to break this cycle (556 [EL 4; review NE]). Thus, subjects with DM risk factors (Table 5) should be screened at the first prenatal visit for undiagnosed T2D using standard criteria (Table 6), and all pregnant subjects without a prior diagnosis of DM should be screened for GDM with a 2-hour OGTT using a 75-g glucose load at 24 to 28 weeks' gestation. Glucose criteria diagnostic for GDM are an FPG >92 mg/dL, 1-hour post-glucose challenge value ≥180 mg/dL, or 2-hour value ≥153 mg/dL (557 [EL 4; CPG]).

In T1D, optimal care may necessitate CGM and CSII. The rapid-acting insulin analogs for pump therapy that have been studied in pregnancy include lispro and aspart (558 [EL 2; NRCT]; 559 [EL 3; retrospective study SS]; 560 [EL 3; retrospective study SS]; 561 [EL 1; RCT]). The data that detemir is safe in pregnancy are convincing, and this agent is now considered pregnancy category B (562

[EL 3; SCR]; 563 [EL 3; retrospective study SS]; 564 [EL 1; RCT, not blinded]; 565 [EL 1; RCT, not blinded]). Glargine is widely used; however, there are still no conclusive reports on its safety, and it remains pregnancy category C. Although insulin is the preferred treatment approach, metformin and glyburide have been shown to be effective alternatives without adverse effects in some females. Metformin crosses the placenta and is classified as category B for pregnancy; sulfonylureas do not cross the placenta. Regardless, the optimal therapy for subjects with GDM or T2D who are not able to maintain normoglycemia with a proper meal plan is insulin (212 [EL 4; NE]).

4.Q18. When and How Should Glucose Monitoring be Used?

Current glucose monitoring strategies can be classified into 2 categories: patient self-monitoring, which would allow patients to change behavior (diet and/or exercise) or medication dose (most often insulin), and long-term assessment, which allows both the patient and the clinician to evaluate overall glucose control and risk for complications over weeks or months. Although some form of glucose self-monitoring has long been available, current forms of self-monitoring include SMBG and CGM, while long-term assessment is most often by A1C.

A1C is defined as the stable adduct of glucose at the N-terminal amino group of the β chain of hemoglobin. 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 and mean glucose are directly related over the lifespan of the red blood cell (100 to 120 days), but 50% of A1C is determined by glycemia during the 1 month preceding measurement. Currently, 99% of laboratories in the United States use a standardized and certified assay traced to the DCCT. More recently, using CGM, each level of A1C was measured as "estimated average glucose." There are numerous patient populations in which A1C may not reflect average glucose. These reasons can include changes in erythrocyte survival time (e.g., hemolysis, splenomegaly, or use of epoetin alfa), alterations in the hemoglobin molecule (hemoglobinopathies), iron status, or recent blood transfusion (23 [EL 4; review NE]). Renal failure also results in a different A1C level than would be seen in those with normal kidney function (566 [EL 2; PCS]).

Current glucose meters perform rapid tests with small blood volumes and are easily operated by laypersons with DM in the outpatient setting. They are equipped with a variety of features, ranging from storing results of glucose tests performed to simple pattern analysis to Bluetooth connectivity to smartphones. The ISO (Institutional Organization for Standardization) specifies requirements for in vitro glucose monitoring systems that measure capillary blood glucose, for specific design verification procedures, and for the validation of self-measurement performance by laypersons with DM. The 2013 ISO 15197 standard for glucose meter accuracy is stricter than the 2003 version. The new standard requires that 95% of values fall within 15% for glucose levels >100 mg/dL and within ±15% for glucoses <100 mg/dL. The 2003 version allowed ±20% difference for glucose >75 mg/dL. Each of the meter chemistries has its own set of potential interfering substances; however, newer technology is helping to reduce these.

In T1D, SMBG has not been studied on its own, but rather as one component of a comprehensive treatment strategy (68 [EL 1; RCT]). SMBG frequency (in a retrospective analysis) has been shown to be predictive of A1C levels (543 [EL 3; SS]; 567 [EL 3; SS]; 568 [EL 2; RCCS]; 569 [EL 3; CSS]).

Patient adherence to monitoring and treatment is the greatest predictor of glycemic control. When used appropriately, CGM can lead to decreased A1C and reduced hypoglycemic exposure (570 [EL 1; RCT]; 571 [EL 1; RCT]). CGM currently uses interstitial fluid glucose as an alternative to plasma glucose. Both currently approved systems use glucose oxidase embedded on the sensor. With current technology, there is usually a lag time of up to 7 minutes between the plasma and interstitial glucose and the receiver display. Despite improvements, accuracy of the current generation of CGM devices is not yet deemed sufficient by the FDA to approve them to replace standard glucose meters for insulin-dosing decisions. Additional research is needed before recommendations can be made regarding CGM use in patients with T2D.

4.Q19. When and How Should Insulin Pump Therapy be Used?

Insulin pumps have been used for more than 30 years (572 [EL 4; review NE]). By definition, they provide constant, continuous infusion of short-acting insulin driven by mechanical force and delivered via a soft cannula under the skin. In the United States, it is estimated that 20 to 30% of patients with T1D and <1% of insulin-treated patients with T2D use CSII (573 [EL 3; SS]). The FDA estimates that the number of U.S. patients with T1D using CSII was ~375,000 in 2007, up from approximately 130,000 in 2002 (574 [EL 4; review NE]).

Recent advances in insulin pumps include dose calculators ("wizards"), which are standard on all current models; the ability to program different basal insulin rates to match activities; color touch screens; universal serial bus (USB)-rechargeable batteries; prefilled insulin cartridges; and disposability. In addition, pumps now offer multiple infusion set types, various catheter tubing lengths, and tubeless pumps with an integrated infusion set and reservoir. Clinical trials are underway to validate methods that

accelerate insulin action, including the addition of hyaluronidase to the tubing, heating of the injection site, intradermal insulin injection, and new formulations of rapid-acting insulin (575 [EL 4; NE]; 576 [EL 4; NE]; 577 [EL 4; NE]; 578 [EL 2; PCS]). CGM sensor-augmented pumps with a "threshold suspend" function represent the first step toward an automatic or semiautomatic closed-loop insulin delivery device. Such pumps suspend insulin delivery for 2 hours (or until the suspension is manually overridden) when the CGM sensor glucose level declines below a specified threshold (579 [EL 3; CCS]; 580 [EL 1; RCT, not blinded]).

Prompted by these advances in pump technology, the AACE recently updated its Consensus Statement on CSII (581 [EL 4; NE]), which includes a thorough review of the state of the art. Numerous other position statements and guidelines are available from the ADA (582 [EL 4; review NE]); the American Association of Diabetes Educators (583 [EL 4; CPG NE]); the American Academy of Pediatrics (584 [EL 4; position NE]); and the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, which published a joint consensus statement regarding the use of insulin pumps in children (585 [EL 4; consensus NE]).

Table 16 presents a summary of important clinical research findings on CSII efficacy and safety in patients with T1D, including the results of key meta-analyses covering clinical research on insulin pump therapy published after 2003 (172 [EL 1; MRCT]; 586 [EL 1; MRCT]; 587 [EL 1; MRCT]; 588 [EL 1; MRCT]; 589 [EL 1; MRCT]). Table 17 summarizes evidence from RCTs of CSII in T2D (590 [EL 1; RCT, not blinded]; 591 [EL 1; RCT, not blinded, small sample size]; 592 [EL 1; RCT, not blinded]; 593 [EL 1; RCT, small sample size, not blinded]; 594 [EL 3; CCS]; 595 [EL 3; CCS]; 596 [EL 1; RCT, not blinded]; 597 [EL 1; RCT, small sample size, not blinded]).

Based on this evidence and other currently available data, CSII appears to be justified for basal-bolus insulin therapy in appropriately selected patients with T1D who have inadequate control with MDI. The ideal CSII candidate is a patient with T1D or absolutely insulin-deficient T2D (as confirmed with C-peptide measurement) who currently takes insulin multiple times per day, assesses blood glucose levels multiple times daily, is motivated to achieve tighter glycemic control, and is willing and intellectually and physically able to undergo the rigors of insulin pump therapy initiation and maintenance. Eligible patients should be capable of frequent SMBG (at least initially) and/or CGM device use. Furthermore, candidates must be able to master carbohydrate counting, insulin correction, and adjustment formulas and be prepared to troubleshoot problems related to pump operation and plasma glucose levels. Lastly, patients should be emotionally mature, with a stable life situation, and be willing to maintain frequent contact with members of their healthcare team, in particular their pump-supervising physician and CDE.

Concerns have been raised about the costs incurred by CSII. However, recent evidence indicates that CSII is a cost-effective treatment option, both in general and compared with MDI for children and adults with T1D. Table 18 summarizes the key assumptions and findings of recent representative cost-effectiveness analyses comparing CSII with MDI in specific patient populations (598 [EL 3; SS]; 599 [EL 3; SS]; 600 [EL 3; SS]; 601 [EL 3; retrospective review SS]; 602 [EL 3; SS]; 603 [EL 1; RCT, posthoc analysis]; 604 [EL 3; SS]).

4.Q20. What is the Imperative for Education and Team Approach in DM Management?

A team must be involved in DM care. Working with different healthcare professionals allows the patient to learn in-depth information about a variety of topics related to their stated, and usually unstated, health concerns. It also ensures that the patient's needs are cared for and addressed. Use of other healthcare professionals' skills and specialties ensures the patient has the best care and understanding of their condition. Often, problems may be apparent to one healthcare professional but go unnoticed by another. For example, recognizing a patient's illiteracy or vision problems in a group class may be difficult, but these problems may be obvious during a one-on-one encounter.

Diabetes Healthsense from the National Diabetes Education Program, a joint venture of the NIH and CDC, is an important resource for all diabetes care teams (605 [EL 4; NE]). This website offers over 150 resources developed by behavior change experts to help patients better adhere to clinician recommendations about diabetes management.

4.Q20.1. Certified Diabetes Educators

A CDE is generally a nurse or registered dietitian but could be another healthcare professional. CDEs teach in a variety of inpatient and outpatient settings. They cover all topics related to DM management from insulin administration to foot care. They often have more time than physicians to devote to each patient, which allows them to focus on specific needs. Often patients report they receive more practical knowledge from their CDE than they do from their physician. Having a CDE credential indicates the passing of the certification examination and special ability in this area.

4.Q20.2. Registered Dietitians

A healthful diet is necessary for everyone to maintain good health. However, persons with DM especially need to follow their prescribed meal plan and physical activity program as an integral part of their therapy. Registered

Table 16
Meta-Analyses of Studies of CSII Published Since 2003

Reference (evidence level and study design)	Meta-analysis objectives	Number/types of studies included in meta-analysis	Clinical findings
(586 [EL 1; MRCT])	Investigation of metabolic and psychosocial impact of CSII therapy vs. other treatment modalities (e.g., MDI, conventional therapy) in children, adolescents, and adults (n = 1,547)	2,483 studies identified; 61 met initial criteria; final review consisted of 52 studies (37 paired, 4 randomized crossover, and 11 parallel) published between 1979 and 2001	Compared with MDI, CSII therapy was associated with significant improvements in glycemic control on the basis of decreases in A1C and mean blood glucose levels Analysis of CSII complications before 1993 revealed decreased risk of hypoglycemic events with insulin pump therapy, but a potential increased risk of diabetic ketoacidosis *Notes:* Changes in insulin requirements and body weight not included in analysis because of insufficient data CSII did not appear to be associated with increased risk of poor psychosocial outcomes, although effects on patient perspectives and psychosocial functioning were difficult to assess because of inconsistencies in study design and methodology
(587 [EL 1; MRCT])	Comparison of effects of CSII vs. MDI on glycemic control, hypoglycemic risk, insulin requirements, and adverse events in adults with T1D (n = 908), children with T1D (n = 74), and patients with T2D (n = 234)	673 studies identified; final review consisted of 22 RCTs (17 T1D, 2 T2D, 3 pediatric) published through March 2007	A1C reduction greater and insulin requirements lower with CSII than MDI in adults and adolescents with T1D; risk of hypoglycemia comparable among adult patients (data unavailable for adolescent patients); no conclusive CSII benefits seen for patients with T2D
(588 [EL 1; MRCT])	Comparison of effects of CSII and MDI on glycemic control and hypoglycemia in adults and children with T1D (n = 669) or T2D (n = 239)	107 studies identified; final review consisted of 15 RCTs published between 2002 and March 2008	In patients with T1D, A1C was mildly decreased with CSII vs. MDI; CSII effect on hypoglycemia unclear CSII and MDI outcomes were similar among patients with T2D *Notes:* CSII efficacy in patients with hypoglycemia unawareness or recurrent severe hypoglycemia inconclusive because of lack of data
(589 [EL 1; MRCT])	Examination of CSII and MDI effects on glycemic control and incidence of severe hypoglycemia in patients with T1D (n = 1,414); focused on studies with 36 months of CSII therapy and >10 episodes of severe hypoglycemia per 100 patient-years with MDI therapy	61 studies identified; final review consisted of 22 RCTs and before/after studies published between 1996 and 2006	Risk of severe hypoglycemia was decreased with CSII vs. MDI; greatest reduction observed in patients with DM of longest duration and in those with highest baseline rates of severe hypoglycemia with MDI therapy A1C was lower for CSII than for MDI, with greatest improvement seen in patients with highest initial A1C values on MDI
(172 [EL 1; MRCT])	Comparison of glycemic control and hypoglycemic incidence with short-acting, analog-based CSII (n = 444) vs. MDI (n = 439) therapy of ≥12 weeks' duration in patients with T2D	177 studies identified; final review consisted of 11 RCTs published between 2000 and 2008	A1C was significantly lower with CSII vs. MDI; A1C reduction was only evident for studies with mean patient age >10 years Severe hypoglycemia occurred at a comparable rate with CSII and MDI therapy

Abbreviations: A1C, hemoglobin A1C; CSII, continuous subcutaneous insulin infusion; EL, evidence level; MDI, multiple daily injections; MRCT, meta-analysis of randomized controlled trials; RCT, randomized controlled trial; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus.

Table 17
RCTs Comparing CSII and MDI for Patients With T2D

				A1C (%) (SD)[a]			
Reference	**Number randomized**	**Design**	**Follow-up**	**Baseline**	**CSII**	**MDI**	***P* value**
(595 [EL 3; CCS])	15	Observational	30 weeks	7.9 (1.9)	5.0 (0.9)	NA	<.001
(594 [EL 3; CCS])	10	Observational	3 successive nights	FPG: 209 (52.3) mg/dL	FPG: 99.1 (28.8) mg/dL	NA	<.0001
(593 [EL 1; RCT, small sample size, not blinded])	17	Crossover	2 periods of 12 weeks	9 (1.6)	7.7 (0.8)	8.6 (1.6)	<.03
(592 [EL 1; RCT, not blinded])	107	Parallel	1 year	CSII: 8.4 (1.1) MDI: 8.1 (1.2)	6.6 (0.8)	6.4 (0.8)	.19
(591 [EL 1; RCT, not blinded, small sample size])	40	Crossover	2 periods of 18 weeks	CSII-MDI: 10.1 (1.6) MDI-CSII 10.2 (1.4)	–0.8 (1.5)[b]	+0.4 (1.3)[b]	.007
(590 [EL 1; RCT, not blinded])	132	Parallel	24 weeks	CSII: 8.2 (1.4) MDI: 8.0 (1.1)	7.6 (1.2)	7.5 (1.2)	NS
(597 [EL 1; RCT, small sample size, not blinded])	20	RCT	4 months	CSII: 13.2[c] MDI: 12.8	9.2 (HbA_1)	10.6 (HbA_1)	<.05
(596 [EL 1; RCT, not blinded])	331	RCT	6 months	9	1.1 (1.2)	0.4 (1.1)	<.0001

Abbreviations: A1C = hemoglobin A1C; CSII = continuous subcutaneous insulin infusion; FPG = fasting plasma glucose; MDI = multiple daily injections; NS = not significant; RCT = randomized controlled trial; T2D = type 2 diabetes mellitus.

[a] Change in glycemic control reported as A1C unless otherwise noted.

[b] A1C values for CSII and MDI are presented by Wainstein et al as a direct treatment effect in the completers' cohort.

[c] Reported in study as median mmol hydroxymethylfurfural (HMF) per mol hemoglobin (Hb) and converted to median percentage HbA_1 based on the following formula, which was determined via comparison with a column chromatography method over the range of 4 to 13%: HbA_1 (%) = 0.21 (A1C in mmol HMF/mol Hb) - 0.35 (597 [EL 1; RCT, small sample size, not blinded]).

Table 18
Summary Data from Cost-effectiveness Analyses Comparing Continuous Subcutaneous Insulin Infusion with Multiple Daily Injections in Adults and Children with T1D

Reference	Study objective, perspective, data source	QALYs gained	Cost per QALY (ICER)	Additional key findings
(599 [EL 3; SS])	To estimate long-term (60-year) cost-effectiveness of CSII compared with MDI in adults and children with T1D U.S. third-party payer perspective Computer simulation model (CORE Diabetes Model)	QALY gains for CSII vs. MDI were 0.262	CSII: $16,992 MDI: $27,195	Improved glycemic control from CSII led to reduced incidence of DM complications including PDR, ESRD, PVD The NNT for PDR was 9 (i.e., only 9 patients need to be treated with CSII to avoid 1 case of PDR)
(598 [EL 3; SS])	To evaluate the long-term (60-year) cost-effectiveness of CSII compared with MDI in adult patients with T1D Canadian payer perspective Computer simulation model (CORE Diabetes Model)	QALY gains for CSII vs. MDI were 0.655	CSII: Can$27,265 MDI: Can$23,797	
(600 [EL 3; SS])	Assessment report to examine the clinical and cost-effectiveness of using CSII to treat DM (T1D and during pregnancy) NICE, United Kingdom Systematic review and economic evaluation (74 studies included)	NA	NA	CSII is cost-effective for T1D in both children and adults No evidence that CSII is better than MDI in pregnancy
(602 [EL 3; SS])	To project the long-term (60-year) costs and outcomes of CSII compared with MDI in patients with T1D United Kingdom; third party NHS perspective Computer simulation model (CORE Diabetes Model)	QALY gains for CSII vs. MDI were 0.76	CSII: £80,511 MDI: £61,104 (variance = £25,648/QALY gained with CSII)	Improvements in glycemic control with CSII vs. MDI led to a reduced incidence of DM-related complications For patients with T1D, CSII represents good value on the basis on current UK standards
(603 [EL 1; RCT, posthoc analysis])	To estimate the long-term cost-effectiveness of SAPT compared to MDI in T1D	QALY gains for SAPT vs. MDI were 0.376	Lifetime cost: SAPT: $253,493 MDI: $167,170 ICER = $(c_1\text{-}c_2)/q_1 - q_2$ = $229,582	Despite superior clinical benefits of SAPT compared to MDI, SAPT did not appear to be economically attractive in the U.S. for adults with T1D in its current state of development Further clinical development to reduce disposable costs of the system could improve this
(604 [EL 3; SS])	To project the long-term clinical and economic outcomes of CSII treatment compared to MDI in T1D in Denmark Meta-analysis of CSII treatment from over 50 studies	CSII was associated with improved quality-adjusted life expectancy compared to MDI (QALY not calculated)	Lifetime costs were higher for CSII than for MDI with ICERs in terms of cost per QALY within the range considered good value for money	CSII led to improved long-term clinical outcomes due to improved glycemic control vs. MDI Economic impact of CSII vs. MDI would likely represent good value for cost

Abbreviations: CORE = Center for Outcomes Research; CSII = continuous subcutaneous insulin infusion; EL = evidence level; ESRD = end-stage renal disease; ICER = incremental cost-effectiveness; MDI = multiple daily injections; NA = not applicable; NHS = National Health Services (United Kingdom); NICE = National Institute for Health and Clinical Excellence; NNT = number needed to treat; PDR = proliferative diabetic retinopathy; PVD = peripheral vascular disease; QALY = quality-adjusted life year; SAPT = sensor-augmented pump therapy; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus.

dietitians can develop a healthful eating plan and can also provide related DM education. They can document problems such as disordered meal patterns, timing of meals, eating disorders, lack of money for food, or other physiologic and psychosocial problems. These issues may not be identified during physician office visits.

4.Q20.3. Nurses and Medical Assistants

Registered nurses, as well as licensed practical nurses (LPNs) and medical assistants (MAs), can provide an assessment before the physician sees the patient, which allows for a better focus on any identified problems. Teaching medication administration is another important area that can be delegated to a nurse or MA. Physician time can be saved when the nurse fields phone calls related to medication administration, assessment of medication tolerability, and other DM-related management issues.

4.Q20.4. Nurse Practitioners and Physician Assistants

A patient may see these nonphysician clinicians in conjunction with the physician. These healthcare professionals can set up treatment plans and set goals that other team members will implement in the patient's care, allowing the physician to focus on specific treatment issues. These clinicians may also be able to assume some treatment decisions, thus freeing the physician to concentrate on other healthcare issues.

4.Q20.5. Primary Care Physicians

Each patient should have a primary care physician who addresses other aspects of care beyond DM alone. Typically, specialists have longer wait times for appointments, so that patients might not be seen on a timely basis for medical issues that need more immediate evaluation. Other specialists such as a cardiologist, nephrologist, ophthalmologist, psychologist, and podiatrist might be warranted as part of the DM healthcare team. It is important for patients to see the appropriate specialist as part of their care.

4.Q21. Which Vaccinations Should be Given to Patients with Diabetes?

Bacterial and viral infections cause significant morbidity and mortality in patients with DM (606 [EL 4; NE]). A recent Canadian cohort study of adults with DM <65 years of age showed that DM increased the risk of influenza-associated hospitalizations by 6% (risk ratio 1.06, 95% CI 1.02 to 1.10; absolute risk difference 6 per 1,000 adults per year) even though the rates of influenza and pneumonia were similar between diabetic and nondiabetic populations ($P = .11$) (607 [EL 3; SS]). Both community-acquired and nosocomial infections with pneumococcal bacteria may also be higher among patients with DM, who may also be at greater risk of death from these diseases (608 [EL 3; CSS]; 609 [EL 2; PCS]; 610 [EL 2; PCS]). However, vaccines can safely and effectively reduce serious complications from influenza. A case-control study demonstrated that vaccines reduced DM-related hospital admissions by as much as 79% during flu epidemics (611 [EL 2; RCCS]). In addition, no evidence suggests that people with DM have inadequate serologic or clinical responses to these vaccinations. The 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 patients with DM has not been established. Inactivated influenza vaccine may be considered for patients with DM (612 [EL 4; NE]). The CDC ACIP also recommends single administration of the 23-valent pneumococcal vaccine (PPSV23) for adults with diabetes aged 19 to 64 years (613 [EL 4; NE]). Furthermore, the 13-valent pneumococcal conjugate vaccine (PCV13) should be administered in series with the PPSV23 to all adults ≥65 years (614 [EL 4; NE]).

4.Q21.1. Hepatitis B Vaccine

Over the past 2 decades, the CDC has received 29 case reports of hepatitis B virus (HBV) infection in hospitals and long-term care facilities; of these, 25 were in patients with DM who were receiving blood glucose monitoring from healthcare personnel who were providing care for more than 1 patient. HBV remains stable and highly transmissible for long periods of time on surfaces such as lancing devices, blood glucose meters, and insulin pens. The reservoirs of these devices can retain sufficient blood to transmit the virus and thus should never be shared between patients (615 [EL 4; NE]).

Other CDC analyses suggest that acute HBV infections occur in approximately twice as many adults with DM as those without when persons with HBV-related risk behaviors are excluded. Acute infections are also more likely to progress to chronic hepatitis B. Seroprevalence of antibody to the HBV core antigen, which suggests past or current infection, is 60% higher among adults with DM than those without. DM may also increase HBV-associated mortality (615 [EL 4; NE]).

As a result of these findings, the CDC ACIP now recommends that all adults with DM aged 19 to 59 years be vaccinated against HBV as soon as possible after DM diagnosis, and HBV vaccination should be considered for individuals age ≥60 years after assessment of risk and the likelihood of an adequate immune response. The differential age recommendations are based on economic models that yielded age-stratified calculations. The incremental cost per quality-adjusted life-year (QALY) saved was $75,100 for adults up to 59 years, but costs per QALY saved increased substantially with greater age after this point because of other causes of mortality, as well as declining immune responses to the vaccine in older adults (615 [EL 4; NE]).

4.Q22. How Should Depression be Managed in the Context of Diabetes?

Routine screening for depression in adults with DM is recommended. Untreated comorbid depression can have serious clinical implications for patients with DM because depression contributes to poor self-care, less treatment-related adherence, and poor glycemic control (616 [EL 1; meta-analysis]). In addition, depression may be a risk factor for developing DM (617 [EL 2; MNRCT]). Depression and DM also are associated with a significantly increased all-cause and CVD-related mortality rate (618 [EL 2; PCS]). Chronic use of antidepressant medication is associated with a modestly increased relative risk of T2D (619 [EL 3; SS]). This may reflect the association of DM with depression rather than suggest an adverse effect of these agents (620 [EL 2; PCS]). The impact of the newer agents for treating depression is yet to be established, especially if they contribute to weight gain (621 [EL 2; NRCT]).

Collaboration with mental health professionals skilled in treating patients with DM can improve glycemic control and psychological well-being (622 [EL 1; RCT, single-blinded]). Patients with depression or DM-related distress should be referred to mental health professionals who are integrated into the DM care team (212 [EL 4; NE]).

4.Q23. What is the Association Between Diabetes and Cancer?

Epidemiologic evidence suggests increased risks of cancer and cancer mortality in patients with obesity and DM (623 [EL 3; SS]; 624 [EL 2; PCS]; 625 [EL 2; PCS]). Whether antihyperglycemic therapy increases cancer risk remains unknown due to limited and conflicting data, although the latest analyses do not support increased cancer risk for any given treatment. Readers should consult the AACE/ACE Consensus Statement on Diabetes and Cancer for a complete discussion (626 [EL 4; NE]).

Increased BMI (>25 kg/m^2) is associated with an increased risk of a wide variety of cancers. The strongest associations appear to be for endometrial, gall bladder, esophageal (adenocarcinoma), renal, thyroid, ovarian, breast, and colorectal cancer, with weaker but still statistically significant associations for leukemia, malignant and multiple melanoma, pancreatic cancer, and non-Hodgkin lymphoma (627 [EL 2; MNRCT]; 628 [EL 2; MNRCT]; 629 [EL 2; MNRCT]; 630 [EL 2; MNRCT]; 631 [EL 2; MNRCT]). Increased BMI may, however, be protective for lung, esophageal (squamous) (628 [EL 2; MNRCT]), and prostate cancer (632 [EL 3; SS]) in males, although more aggressive prostate cancers seem to be more common in males who are overweight or obese (633 [EL 4; NE]). In females, increased BMI may be protective for premenopausal breast and lung cancer (628 [EL 2; MNRCT]). As noted in the 2013 AACE/ACE Consensus Statement on Diabetes and Cancer, a higher BMI is also closely associated with increased levels of endogenous insulin, insulin-like growth factors, inflammatory cytokines, and other factors that can have downstream procancer growth effects (626 [EL 4; NE]). These and other potential mechanisms have been recently reviewed (634 [EL 4; NE]).

DM also significantly increases the risk of various common cancers, including endometrial, breast, hepatic, bladder, pancreatic, and colorectal cancers. As with increased BMI, the risk of prostate cancer appears to be decreased among males with DM (635 [EL 2; MNRCT]; 636 [EL 2; MNRCT]; 637 [EL 2; MNRCT]; 638 [EL 2; MNRCT]; 639 [EL 2; MNRCT]; 640 [EL 2; MNRCT]).

In addition to the other obesity-related mechanisms noted above, hyperinsulinemia appears strongly connected to the development of cancer in patients with DM. Animal models suggest that increased activation of insulin and insulin growth factor 1 (IGF-1) receptor leads to increased tumor volume (641 [EL 4; NE]; 642 [EL 4; NE]; 643 [EL 4; NE]). Whether hyperglycemia contributes to cancer development is less clear. Energy for tumor cell growth and proliferation comes from glucose but also from amino acids such as glutamine (644 [EL 4; NE]). In fact, cancer cells can thrive using nonglycemic energy sources due to genetic mutations in tumor cells, as well changes to intracellular signaling stimulated by activation of growth factor receptors (644 [EL 4; NE]; 645 [EL 4; NE]; 646 [EL 4; NE]).

The evidence for the effects of specific antihyperglycemic agents on cancer risk is limited and confounded by factors such as the indications for specific drugs, effects on other cancer risk factors such as body weight and hyperinsulinemia, and the complex progressive nature of hyperglycemia and pharmacotherapy in T2D. Metformin may have a neutral effect or modestly decrease cancer incidence and mortality, particularly colorectal, hepatocellular, and lung cancer (647 [EL 2; PCS]; 648 [EL 2; MNRCT]; 649 [EL 1; MRCT]; 650 [EL 2; MNRCT]). The effect of metformin on cancer outcomes is currently being explored in prospective trials. Pioglitazone may be associated with a very small, nonsignificant risk of bladder cancer, although recent evidence from a large population study suggests there is no significant association (127 [EL 4; NE]; 128 [EL 3; SS]). TZD therapy in general is not associated with other cancers.

The risk of cancer with incretin therapies has garnered much attention since the publication of a meta-analysis finding an increased incidence of pancreatic disease in individuals taking these medications (651 [EL 3; SS]). However, a thorough review of available data conducted by the FDA and the European Medicines Agency (EMA) has not uncovered evidence to support a causal association (652 [EL 4; NE]). In particular, results from a pooled analysis of sitagliptin data (653 [EL 1; MRCT]), as well as from the SAVOR (Saxagliptin Assessment of Vascular

Outcomes Recorded) (146 [EL 1; RCT]) and EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) trials (145 [EL 1; RCT]) did not show any increased incidence of pancreatic disease among patients taking these agents. Results from 2 retrospective cohort studies indicate no risk of pancreatitis with exenatide (654 [EL 3; SS]; 655 [EL 3; SS]), while 1 study reported an increased risk for past users but not for recent or current users (656 [EL 2; PCS]). An increase in thyroid carcinoma occurred in preclinical trials of liraglutide; in liraglutide clinical trials, 1.3 cases of thyroid cancer per 1,000 patient-years occurred in patients taking liraglutide versus 1.0 cases per 1,000 patient-years in those receiving placebo (657 [EL 4; NE]).

Contrary to preliminary evidence suggesting that exogenous insulin may be associated with an increased cancer risk, recent studies have not substantiated this risk, including the large-scale ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial, which involved >6,000 patients receiving glargine over a median trial duration of 6 years. In ORIGIN, use of insulin glargine was not associated with an increased risk of any cancer (HR, 1.0; 95% CI, 0.88 to 1.13) or cancer death (HR, 0.94; 95% CI, 0.77 to 1.15) (658 [EL 1; RCT]).

Among the SGLT2 inhibitors, more cases of bladder cancer occurred among dapagliflozin-treated than control-treated patients in clinical trials, and the product labeling indicates that this agent should not be used in patients with active bladder cancer and should be used with caution in patients with a history of bladder cancer (659 [EL 4; NE]). An increased incidence of bladder cancer was not observed in clinical trials with canagliflozin (660 [EL 4; NE]).

4.Q24. Which Occupations Have Specific Diabetes Management Requirements?

The licensing and certification of various occupations, including commercial drivers and pilots, anesthesiologists, and commercial or recreational divers, is restricted for persons with insulin-treated DM because of the potential risk hypoglycemia may pose to the patient and others.

4.Q24.1. Risk of Accidents

An area of great concern has been whether DM might lead operators of commercial vehicles (e.g., 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 the various forms of retinopathy and cataract, is of course a potential cause of impaired driving ability, and there is general consensus that ascertainment of the visual acuity of commercial motor vehicle drivers or airline pilots is a reasonable measure for measuring such risk. Similarly, coronary artery disease, CVD, musculoskeletal conditions, and diabetic neuropathy might in various ways impair safe driving or piloting ability. The U.S. Federal Motor Carrier Safety Administration and Federal Aviation Administration both require medical certification for operating commercial motor vehicles (used in interstate commerce) and airplanes; these are based on a medical examination including vision, audiometric, and cardiac assessments, as well as standard history and physical examination. Both organizations cite the use of insulin for glycemic control as a criterion for disqualification. Although an insulin-waiver program exists for drivers, this is a complex undertaking, leading many to refuse the treatment even if medically needed. It should be noted that individual states might have separate regulations governing commercial drivers' licenses (661 [EL 4; NE]). For commercial pilots, insulin treatment is an absolute disqualification (662 [EL 4; NE]).

4.Q24.2. Hypoglycemia and Antihyperglycemic Treatments

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 addressed a set of key questions relevant to this topic (663 [EL 4; NE]):

1. Are individuals with DM at increased risk for a motor vehicle crash compared with individuals who do not have DM?
2. Is hypoglycemia an important risk factor for a motor vehicle crash among individuals with DM?
3. What risk factors are associated with an increased incidence of severe hypoglycemia, and what is the incidence of severe hypoglycemia with different treatments and treatment modalities (e.g., use of insulin and injectable noninsulin drugs such as GLP-1 receptor agonists)?
4. How effective is hypoglycemia awareness training in preventing the consequences of hypoglycemia?

The authors of the report performed a set of meta-analyses of existing publications to address these 4 questions. They showed evidence that, 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 U.S. showed a 25% increase in risk of accidents, while studies conducted outside the U.S. showed no increased risk. This was particularly true when non-U.S. and U.S. cohorts of insulin-treated persons were compared. The analysis of the 2 available U.S. studies showed a 2.75-fold greater risk of motor vehicle accident when insulin-treated persons were compared with individuals without DM (P = .001), while studies from outside the U.S. demonstrated no significant difference in accident risk. In contrast, a meta-analysis restricted to U.S. studies of persons with DM not

using pharmacologic treatment or using oral antihyperglycemic agents did not show a significant increase in risk of accidents. In the individual studies included in the analysis, sulfonylurea use did not significantly increase the risk of accident (664 [EL 2; RCCS]; 665 [EL 2; RCCS]; 666 [EL 2; RCCS]).

The applicability of these studies to the current population of persons with DM in the U.S. is limited because recommended treatment goals and approaches have changed dramatically since the follow-up periods of most of the cited studies. First, the studies of insulin users involved mostly patients 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 (667 [EL 1; RCT, not blinded]). Second, sulfonylurea treatment is associated with a greater likelihood of hypoglycemia than all other noninsulin antihyperglycemic agents (metformin, TZDs, α-glucosidase inhibitors, DPP-4 inhibitors, and GLP-1 receptor agonists) and carries a nearly a twofold greater likelihood of hypoglycemia than basal insulin (668 [EL 1; MRCT]). Unfortunately, reliable large population studies of motor vehicle accidents involving patients 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). Finally, and perhaps most importantly, the role of SMBG in preventing episodes of hypoglycemia was not well addressed in the available studies.

4.Q24.3. Commercial Drivers and Lifestyle

Over the past 2 decades, the prevalence of obesity among commercial motor vehicle operators has risen even faster than in the general population. Commercial drivers may be away from home for long periods of time with infrequent stops, usually driving for long periods. At times they have limited control over their work environment, and little time for exercise. Meals tend be irregular, and dining choices are often limited. A population-based survey of 1,265 U.S. long-haul truck drivers, 76% of whom were physically inactive, showed that 69% were obese compared to 31% in the age-matched U.S. adult working population, and 51% versus 19% were smokers (669 [EL 3; SS]). Obesity, hypertension, and DM in turn increase the risk of OSA among drivers (670 [EL 2; RCCS]), which is not only a risk factor for accidents but also may contribute to worsening of glycemia and other cardiovascular risk factors. Although the details differ, commercial car drivers represent another large group with similar health concerns (671 [EL 3; SS]).

Because commercial vehicle operators (particularly drivers) exhibit a variety of lifestyle issues that put them at high risks of DM and associated comorbidities, this group would particularly benefit from improved healthcare access with a focus on measures to reduce obesity.

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*Note: All reference sources are followed by an evidence level (EL) rating of 1, 2, 3, or 4 and the study design. The strongest evidence levels (**EL 1** and **EL 2**) appear in red for easier recognition.*

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