AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR DEVELOPING A DIABETES MELLITUS COMPREHENSIVE CARE PLAN

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American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health-care 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.

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AACE Task Force for Developing a Diabetes Comprehensive Care Plan

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Abbreviations:
AACE = American Association of Clinical Endocrinologists; **BEL** = best evidence level; **CDE** = certified diabetes educator; **CGM** = continuous glucose monitoring; **CPG** = clinical practice guideline; **CSII** = continuous subcutaneous insulin infusion; **CVD** = cardiovascular disease; **DM** = diabetes mellitus; **DPP-4 inhibitor** = dipeptidyl-peptidase 4 inhibitor; **EL** = evidence level; **FDA** = US Food and Drug Administration; **FPG** = fasting plasma glucose; **GDM** = gestational diabetes mellitus; **GFR** = glomerular filtration rate; **GLP-1** = glucagonlike peptide 1; **A1C** = hemoglobin A_{1c}; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **MDI** = multiple daily injections; **NPH** = neutral protamine Hagedorn; **PPG** = postprandial glucose; **Q** = clinical question; **R** = recommendation; **RCT** = randomized controlled trial; **SMBG** = self-monitoring of blood glucose; **T1DM** = type 1 diabetes mellitus; **T2DM** = type 2 diabetes mellitus; **TZD** = thiazolidinedione

1. INTRODUCTION

These are clinical practice guidelines (CPGs) for developing a diabetes mellitus (DM) comprehensive care plan. The mandate for this CPG is to provide a practical guide for comprehensive care that incorporates an integrated consideration of microvascular and macrovascular risk rather than an isolated approach focusing merely on glycemic control.

This CPG will complement and extend existing CPGs available in the literature, as well as previously published American Association of Clinical Endocrinologists (AACE) DM CPGs. When a routine consultation is made for DM management, these new guidelines advocate that a comprehensive approach is taken 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 A_{1c} [A1C], postprandial glucose [PPG] excursions, fasting plasma glucose [FPG], glycemic variability) have an impact on cardiovascular disease (CVD) risk, mortality, and quality of life, other factors also affect clinical outcomes in persons with DM.

This document is organized into discrete clinical questions, with responses in the Executive Summary and an Appendix that provides the evidence base supporting these recommendations.

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 developed in 2011 addressing specific problems in DM care.
- A document that can eventually be implemented electronically in clinical practices to assist with decision-making for patients with DM.

This CPG focuses on comprehensive care and practical implementation strategies in a more concise format than could be achieved by an encyclopedic citation of all pertinent primary references. This latter strategy would create redundancy and overlap with other published CPGs and evidence-based reports related to DM. Therefore, although many highest evidence level (EL) 1 studies consisting of randomized controlled trials (RCTs), and meta-analyses of these trials 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).

2. METHODS

The AACE Board of Directors mandated a new CPG for the development of a DM comprehensive care plan. This CPG was developed in accordance with the AACE Protocol for Standardized Production of Clinical Practice Guidelines—2010 Update (1; see Figure 1; Tables 1-4]). Reference citations in the text of this document include the reference number, numerical descriptor (EL 1-4), and semantic descriptor (Table 1). Recommendations are assigned EL ratings on the basis of the quality of supporting evidence (Table 2), all of which have also been rated for strength (Table 3). The format of this CPG is based on specific and relevant clinical questions. All primary writers have made disclosures regarding multiplicities of interests and attested that they are not employed by industry. In addition, 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*.

Clinical questions are labeled "Q." Recommendations (labeled "R") 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 evidence level (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 (1 EL 4; CPG NE; see Figure 1; Tables 1-4]) There are 4 intuitive levels of evidence: 1 = strong, 2 = intermediate, 3 = weak, and 4 = no evidence (Table 3). Comments may be appended to the recommendation grade and BEL regarding any relevant subjective factors that

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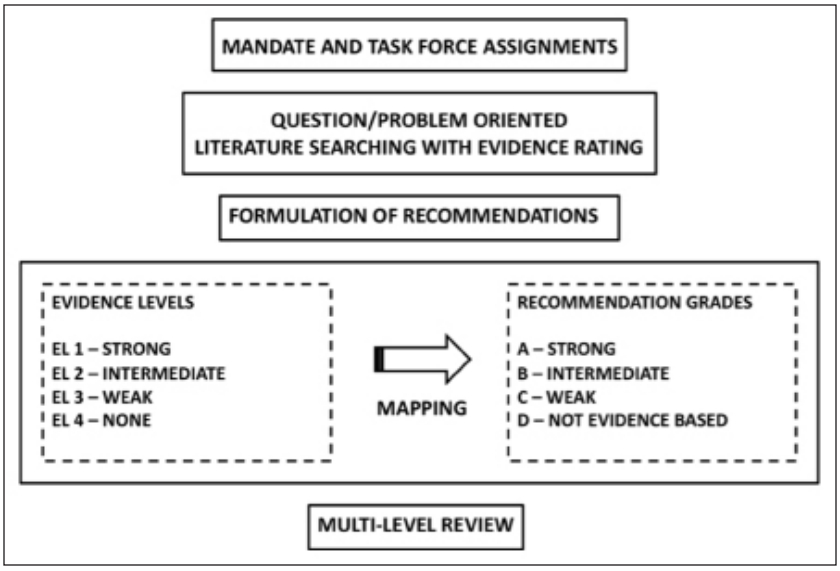

Fig. 1. 2010 American Association of Clinical Endocrinologists (AACE) Clinical Practice Guideline (CPG) methodology. Current AACE CPGs have a problem-oriented focus that results in a shortened production time line, middle-range literature searching, emphasis on patient-oriented evidence that matters,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

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, but rather it incorporates a complex expert integration of objective and subjective factors meant to reflect optimal real-life clinical decision-making and to enhance patient care. Where appropriate, multiple recommendations are provided, so that the reader has management options. This document represents only a guideline. Individual patient circumstances and presentations differ, and the ultimate clinical management is based on what is in the best interest

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 reference 1: *Endocr Pract*. 2010;16:270-283.
[b] 1 = strong evidence; 2 = intermediate evidence; 3 = weak evidence; and 4 = no evidence.

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 reference 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 reference 1: *Endocr Pract*. 2010;16:270-283.

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 reference 1: *Endocr Pract*. 2010;16:270-283.

of the individual patient, involving patient input and reasonable clinical judgment by the treating clinicians.

3. EXECUTIVE SUMMARY

3.Q1. How is DM Diagnosed and Classified?

3.Q1.1. Diagnosis of DM

- **R1.** The following criteria may be used to diagnose DM (Table 5) (**Grade A; BEL 1**):
  - FPG concentration (after 8 or more hours of no caloric intake) of 126 mg/dL or greater, *or*
  - Plasma glucose concentration of 200 mg/dL or greater 2 hours after ingesting 75-g oral glucose load in the morning after an overnight fast of at least 8 hours, *or*
  - Symptoms of uncontrolled hyperglycemia (eg, polyuria, polydipsia, polyphagia) and a random (casual, nonfasting) plasma glucose concentration of 200 mg/dL or greater, *or*
  - A1C level of 6.5% or higher.

In the absence of unequivocal hyperglycemia or severe metabolic stress, the same test (glucose or A1C measurement) should be repeated on a different day to confirm the diagnosis of DM (**Grade D; BEL 4**). Screening should be considered in the presence of risk factors for DM (Table 5) (**Grade D; BEL 4**).

- **R2.** There is a continuum of risk for poor patient outcomes in the progression from normal glucose tolerance to overt type 2 DM (T2DM) (**Grade D; BEL 4**). Prediabetes can be identified by the presence of impaired glucose tolerance, which is an oral glucose tolerance test glucose value of 140 to 199 mg/dL, 2 hours after ingesting 75 g of glucose, and/or impaired fasting glucose, which is a fasting glucose value of 100 to 125 mg/dL (Table 5) (**Grade D; BEL 4**). A1C values between 5.5% and 6.4% should be a signal to do more specific glucose testing (**Grade D; BEL 4**). A1C testing should be used as a screening tool only; FPG measurement or an oral glucose tolerance test should be used for definitive diagnosis (**Grade D; BEL 4**). Metabolic syndrome based on National Cholesterol Education Program IV Adult Treatment Panel III criteria is a prediabetes equivalent (**Grade C; BEL 3**).
- **R3.** In pregnancy, elevated plasma glucose levels (FPG concentration >92 mg/dL; 1-hour postchallenge glucose value ≥180 mg/dL; or 2-hour value ≥153 mg/dL) satisfy the criteria for a diagnosis of gestational DM (GDM) (**Grade C; BEL 3**). All pregnant women should be screened for GDM at 24 to 28 weeks' gestation, using a 75-g (glucose), 2-hour oral glucose tolerance test.

3.Q1.2. Classification of DM

DM represents a group of heterogeneous metabolic disorders that develop when insulin secretion is insufficient to maintain normal plasma glucose levels.

- **R4.** T2DM is the most common form of DM, accounting for more than 90% of cases. It is typically identified in patients older than 30 years who are overweight or obese and/or have a positive family history, but do not have autoantibodies characteristic of type 1 DM (T1DM). Most persons with T2DM have evidence of insulin resistance (such as high triglycerides or low high-density lipoprotein cholesterol [HDL-C]) (**Grade A; BEL 1**).
- **R5.** T1DM is usually characterized by absolute insulin deficiency and may be confirmed by the presence of autoantibodies to glutamic acid decarboxylase, pancreatic islet β cells (tyrosine phosphatase IA-2), and/or insulin (**Grade A; BEL 1**). Some forms of T1DM have no evidence of autoimmunity and have been termed idiopathic. T1DM or monogenic DM can also occur in obese children and adolescents. Therefore, documenting the levels of insulin and C-peptide and the presence or absence of immune markers and obtaining a careful family history in addition to the clinical presentation may be useful in establishing the correct diagnosis, determining treatment, and helping to distinguish between T1DM and T2DM in children (**Grade A; BEL 1**).
- **R6.** GDM is a condition in which women without previously diagnosed DM exhibit elevated plasma glucose levels (see R3 above) (**Grade C; BEL 3**).

Table 5
Glucose Testing and Interpretation

Test	Result	Diagnosis
Fasting plasma glucose, mg/dL	≤99	Normal
	100-125	Impaired fasting glucose
	≥126	Diabetes, confirmed by repeating the test on a different day
Glucose, mg/dL (oral glucose tolerance test, 2 hours after ingestion of 75-g glucose load)	≤139	Normal
	140-199	Impaired glucose tolerance
	≥200	Diabetes, confirmed by repeating the test on a different day
Hemoglobin A_{1c}, % (as a screening test)	≤5.4	Normal
	5.5-6.4	High risk/prediabetes; requires screening by glucose criteria
	≥6.5	Diabetes, confirmed by repeating the test on a different day

- **R7.** Evaluation for monogenic DM (formerly maturity-onset diabetes of the young) is recommended for any child with an atypical presentation, course, or response to therapy. Diagnostic likelihood is strengthened by a family history over 3 generations suggesting autosomal dominant inheritance. This type of DM can occur in the child before appearing in the parent or other relatives (**Grade A; BEL 1**).

3.Q2. How Can DM Be Prevented?

- **R8.** T2DM can be prevented or at least delayed by intervening in persons who have prediabetes (see Table 6 for prediabetes risk factors suggesting a need for screening) (2). Monitoring of patients with prediabetes to assess their glycemic status should include at least annual measurement of FPG and/or an oral glucose tolerance test (Table 5) (**Grade D; BEL 4**). A1C should be for screening use only (**Grade D; BEL 4**). CVD risk factors (especially elevated blood pressure and/or dyslipidemia) and excessive weight should be addressed and monitored at regular intervals (**Grade D; BEL 4**).
- **R9.** Persons with prediabetes should modify their lifestyle, including initial attempts to lose 5% to 10% of body weight if overweight or obese and participation in moderate physical activity (eg, walking) at least 150 minutes per week (**Grade D; BEL 4**). Organized programs with follow-up appear to benefit these efforts (**Grade A; BEL 1**).
- **R10.** In addition to lifestyle measures, metformin or perhaps thiazolidinediones (TZDs) should be considered for younger patients who are at moderate to high risk for developing DM; for patients with additional CVD risk factors including hypertension, dyslipidemia, or polycystic ovarian syndrome; for patients with a family history of DM in a first-degree relative; and/or for patients who are obese (**Grade A; BEL 1**).
- **R11.** Obesity is a major risk factor for T2DM and for CVD. Lifestyle modification (primarily calorie reduction and appropriately prescribed physical activity) is the cornerstone in the control of obesity in T2DM (**Grade A; BEL 1**). Pharmacotherapy for weight loss may be considered when lifestyle modification fails to achieve the targeted goal in patients with T2DM and a body mass index greater than 27 kg/m^2 (**Grade D; BEL 4**). Consideration may be given to laparoscopic-assisted gastric banding in patients with T2DM who have a body mass index greater than 30 kg/m^2 or Roux-en-Y gastric bypass for patients with a body mass index greater than 35 kg/m^2 to achieve at least short-term weight reduction (**Grade A; BEL 1**). Patients with T2DM who undergo Roux-en-Y gastric bypass must have meticulous metabolic postoperative follow-up because of a risk of vitamin and mineral deficiencies and hypoglycemia (**Grade D; BEL 4**).

3.Q3. What is the Role of a DM Comprehensive Care Plan?

- **R12.** Every patient with documented DM requires a comprehensive treatment program, which takes into account the patient's unique medical history, behaviors

and risk factors, ethnocultural background, and environment (**Grade A; BEL 4**; upgraded by unanimous consensus as prime importance in this CPG).

3.Q3.1. Multidisciplinary Team Approach

- **R13.** An organized multidisciplinary team may best deliver care for patients with DM. Members of such a team can include a primary care physician, endocrinologist, physician assistant, nurse practitioner, registered nurse, certified diabetes educator (CDE), dietitian, exercise specialist, and mental health care professional. The educational, social, and logistical elements of therapy and the variation in successful care delivery associated with age and maturation present additional complexity when caring for children with DM (**Grade D; BEL 4**).

3.Q3.2. DM Self-Management Education

- **R14.** Persons with DM should receive comprehensive DM self-management education at the time of DM diagnosis and subsequently as appropriate. Therapeutic lifestyle management must be discussed with all patients with DM and prediabetes at the time of diagnosis and throughout their lifetime. This includes medical nutrition therapy (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 quantity and quality of sleep (**Grade D; BEL 4**).

[See Appendix for Q4: What is the Imperative for Education and Team Approach in DM Management?]

3.Q5. What Are the Comprehensive Treatment Goals for Persons With DM?

3.Q5.1. Glycemic and A1C Goals

3.Q5.1.1. Outpatient Glucose Targets for Nonpregnant Adults

- **R15.** Glucose targets should be individualized and take into account residual life expectancy, duration of disease, presence or absence of microvascular and macrovascular complications, CVD risk factors, comorbid conditions and risk for severe hypoglycemia. Glucose targets should also be formulated in the context of the patient's psychological, social, and economic status (**Grade A; BEL 1**). In general, therapy should target a A1C level of 6.5% or less for most nonpregnant adults, if it can be achieved safely (**Grade D, BEL 4**) (Table 7) (3,4). To achieve this target A1C level, FPG should usually be less than 110 mg/dL and the 2-hour postprandial glucose concentration should be less than 140 mg/dL (**Grade B, BEL 2**) (Table 7) (3).

In adults with recent onset of T2DM and no clinically significant CVD, glycemic control aimed at normal (or near-normal) glycemia may be considered, with the aim of preventing the development of microvascular (**Grade A; BEL 1**) and macrovascular complications over a lifetime, if it can be achieved without substantial hypoglycemia or other unacceptable adverse consequences. Although it is uncertain that the clinical course of established CVD is improved by strict glycemic control, the progression of microvascular complications clearly is benefitted (**Grade A; BEL 1**). In certain patients, a less stringent goal may be considered (A1C 7%-8%) (**Grade A; BEL 1**). Such individuals those with history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing DM in which the general goal has been difficult to attain despite intensive efforts (**Grade A; BEL 1**).

3.Q5.1.2. Inpatient Glucose Targets for Nonpregnant Adults

- **R16.** For most hospitalized persons with hyperglycemia, a glucose range of 140 to 180 mg/dL is recommended, provided these targets can be safely achieved (Table 7) (4) (**Grade D; BEL 4**).

3.Q5.1.3. Outpatient Glucose Targets for Pregnant Women

- **R17.** For women with GDM, treatment goals are a preprandial glucose concentration of 95 mg/dL or lower and either a 1-hour postmeal glucose value of 140 mg/dL or less or a 2-hour postmeal glucose value of 120 mg/dL or less (**Grade D; BEL 4**). For women with preexisting T1DM or T2DM who become pregnant, glycemic goals are a premeal, bedtime, and overnight glucose values of 60 to 99 mg/dL; a peak postprandial glucose value of 100 to 129 mg/dL; and a A1C value of 6.0% or less—only if they can be achieved safely (**Grade D; BEL 4**).

3.Q5.2. CVD Risk Reduction Targets

- **R18.** CVD is the primary cause of death for most persons with DM; therefore a DM comprehensive care plan should include modification of CVD risk factors **(Grade A; BEL 1)**. Cardiovascular risk reduction targets are summarized in Table 7 (5-10).

3.Q5.2.1. Blood Pressure

- **R19.** The blood pressure goal for persons with DM or prediabetes is less than 130/80 mm Hg (Table 7) (**Grade D; BEL 4**).

3.Q5.2.2. Lipids

- **R20.** Treatment targets for dyslipidemia are based on established CVD risk reduction recommendations. In persons with DM or prediabetes and no CVD or minimal CV risk, the low-density lipoprotein cholesterol (LDL-C) goal of less than 100 mg/dL is the primary target for therapy. The goal for non–HDL-C is less than 130 mg/dL. The highest-risk patients are those with established CVD or more than 2 major CVD risk factors. For these patients, LDL-C remains the primary target for therapy with a goal of less than 70 mg/dL. The non–HDL-C treatment goal is less than 100 mg/dL (Table 7) (**Grade A; BEL 1**). HDL-C values greater than 40 mg/dL in men and greater than 50 mg/dL in women are desirable. If the triglyceride concentration is 200 mg/dL or greater, non–HDL-C becomes a secondary target (**Grade C; BEL 3**).

3.Q6. How Can DM Comprehensive Care Plan Guideline Targets Be Achieved?

3.Q6.1. Therapeutic Lifestyle Changes

- **R21.** Medical nutritional therapy must be individualized, and this generally means evaluation and teaching by a trained nutritionist/registered dietitian or knowledgeable physician (**Grade D; BEL 4**). Insulin dosage adjustments to match carbohydrate intake (eg, use of carbohydrate counting), sucrose-containing or high glycemic index food limitations, adequate protein intake, "heart healthy" diet use, weight management, and sufficient physical activity are recommended.
- **R22.** Regular physical activity, both aerobic and strength training, are important to improve a variety of CVD risk factors, decrease risk of falls and fractures, improve functional capacity and sense of well-being, and improve glucose control in persons with T2DM. Increased physical activity is also a major component in weight loss and weight maintenance programs. The current recommendations of at least 150 minutes per week of moderate-intensity exercise, such as brisk walking or its equivalent, are now well accepted and part of the nationally recommended guidelines. For persons with T2DM, it is also recommended to incorporate flexibility and strength training exercises. 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 their goals and exercise limitations. Physical activity programs should begin slowly and build up gradually (**Grade D; BEL 4**).

3.Q6.2. Antihyperglycemic Pharmacotherapy

The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 AACE/ACE Diabetes Algorithm for Glycemic Control (**Grade D; BEL 4**).

- **R23.** Insulin is required in all patients with T1DM, and it should be considered for patients with T2DM 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**).
- **R24.** Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or PPG levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making. TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (dipeptidyl-peptidase 4 inhibitors [DPP-4 inhibitors]) also favorably affect FPG. When insulin therapy is indicated in patients with T2DM to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia (**Grade A; BEL 1**). The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose (SMBG).
- **R25.** When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered (**Grade A; BEL 1**). Incretin-based therapy (DPP-4 inhibitors and glucagonlike peptide 1 [GLP-1] receptor agonists, especially short-acting GLP-1 agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia (**Grade A; BEL 1**). Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, A1C, and weight (**Grade A; BEL 1**).
- **R26.** Premixed insulin (fixed combination of shorter- and longer-acting components) analogue therapy may

be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared with basal insulin or basal-bolus insulin (**Grade D; BEL 4**). Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy (**Grade B; BEL 3**).

- **R27.** Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained (**Grade D; BEL 4**). Most patients with an initial A1C level greater than 7.5% will require combination therapy using agents with complementary mechanisms of action (**Grade D; BEL 4**). The AACE algorithm outlines treatment choices on the basis of the current A1C level (**Grade D; BEL 4**).

3.Q7. What Are Some Special Considerations for Treatment of Hyperglycemia?

3.Q7.1. Treatment of Hyperglycemia in T1DM

- **R28.** Physiologic insulin regimens, which provide both basal and prandial insulin, are recommended for most patients with T1DM (**Grade A; BEL 1**). These regimens include (a) use of multiple daily injections (MDI), which usually provide 1 or 2 injections daily of basal insulin to control glycemia between meals and overnight and injections of prandial insulin before each meal to control meal-related glycemia; (b) the use of continuous subcutaneous insulin infusion (CSII) to provide a more physiologic way to deliver insulin, which may improve glucose control while reducing risks of hypoglycemia; and (c) for other patients (especially if hypoglycemia is a problem), the use of insulin analogues (**Grade A; BEL 1**).

3.Q7.2. CSII (Insulin Pump Therapy)

- **R29.** CSII is useful in motivated and DM-educated patients with T1DM and in certain insulinopenic patients with T2DM who are unable to achieve optimal glycemic control with MDI. Thorough education and periodic reevaluation of CSII users, as well as CSII expertise of the prescribing physician, is necessary to ensure patient safety (**Grade D; BEL 4**). Sensor-augmented CSII should be considered in patients in whom it is deemed appropriate (**Grade B; BEL 2**).

3.Q7.3. Treatment of Hyperglycemia in Children and Adolescents

- **R30.** The pharmacologic treatment of any form of DM in children does not, at this stage of our knowledge, differ in substance from treatment in adults (**Grade D; BEL 4**). In children or adolescents with T1DM, insulin regimens should be MDI or CSII (**Grade D; BEL 4**), but injection frequencies may become problematic in some school settings. Higher insulin to carbohydrate ratios may be needed during puberty (**Grade D; BEL 4**). In children or adolescents with T2DM, diet and lifestyle modification are implemented first; addition of metformin and/or insulin should be considered when glycemic targets are not achievable with lifestyle measures alone (**Grade C; BEL 3**). 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 Web site (11) (http://www.ispad.org/FileCenter.html?CategoryID=5).

3.Q7.4. Treatment of Hyperglycemia in Pregnancy

- **R31.** All women with preexisting DM (T1DM, T2DM, 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**). Regular or rapid-acting insulin analogues are the preferred treatment for postprandial hyperglycemia in pregnant women. Basal insulin needs can be provided by using rapid-acting insulin via CSII or by using long-acting insulin (eg, NPH; US Food and Drug Administration [FDA] pregnancy category B) (**Grade B; BEL 2**). Although insulin is the preferred treatment approach, metformin and glyburide have been shown to be effective alternatives and without adverse effects in some women.

3.Q7.5. Treatment of Hyperglycemia in Hospitalized Patients

- **R32.** Insulin can rapidly control hyperglycemia and, therefore, is the drug of choice for hospitalized patients with hyperglycemia (**Grade D; BEL 4**). Subcutaneous insulin orders should be specified as "basal," "prandial," or "correction" (**Grade D; BEL 4**). Insulin dosing should be synchronized with provision of enteral or parenteral nutrition (**Grade D; BEL 4**). Exclusive use of "sliding scale insulin" should be discouraged (**Grade D; BEL 4**). Oral antihyperglycemic agents have a limited role in acute care settings, and practitioners should consider discontinuing them in favor of insulin during acute illness that might reasonably be expected to affect glucose levels and/or increase the risk for medication-related adverse events (**Grade D; BEL 4**). Regular insulin is acceptable for intravenous administration, but insulin analogues are preferred for subcutaneous administration. Intravenous insulin is preferred for critically ill patients.

Table 6
Prediabetes Risk Factors Suggesting a Need for Screening (2 [EL 4; consensus NE])

Family history of diabetes mellitus
Cardiovascular disease
Being overweight or obese
Sedentary lifestyle
Nonwhite ancestry
Previously identified impaired glucose tolerance, impaired fasting glucose, and/or metabolic syndrome
Hypertension
Increased levels of triglycerides, low concentrations of high-density lipoprotein cholesterol, or both
History of gestational diabetes mellitus
Delivery of a baby weighing more than 4 kg (9 lb)
Polycystic ovary syndrome
Antipsychotic therapy for schizophrenia and/or severe bipolar disease

3.Q8. When and How Should Glucose Monitoring Be Used?

- **R33.** 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**).
- **R34.** SMBG should be performed by all patients using insulin (minimum of twice daily and ideally at least before any injection of insulin) (**Grade D; BEL 4**). 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 symptoms (**Grade D; BEL 4**). 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 (**Grade D; BEL 4**). Although still early in its development, continuous glucose monitoring (CGM) can be useful for many patients to improve A1C levels and reduce hypoglycemia (**Grade D; BEL 4**).

3.Q9. How Should Hypoglycemia Be Prevented, Identified, and Managed in Patients With DM?

- **R35.** Hypoglycemia treatment requires oral administration of rapidly absorbed glucose (**Grade D; BEL 4**). If the patient is unable to swallow, parenteral glucagon may be given by a trained family member or by medical personnel (**Grade D; BEL 4**). In unresponsive patients, intravenous glucose should be given (**Grade D; BEL 4**). Patients may need to be hospitalized for observation if a sulfonylurea or a very large dose of insulin is the cause of the hypoglycemia because prolonged hypoglycemia can occur (**Grade D; BEL 4**). If the patient has hypoglycemic unawareness and hypoglycemia-associated autonomic failure, several weeks of hypoglycemia avoidance may reduce the risk or prevent the recurrence of severe hypoglycemia (**Grade A; BEL 1**). In patients with T2DM who become hypoglycemic and have been treated with an α-glucosidase inhibitor in addition to insulin or an insulin secretagogue, oral glucose must be given because α-glucosidase inhibitors inhibit the breakdown and absorption of complex carbohydrates and disaccharides (**Grade D; BEL 4**).

3.Q10. How Should Microvascular and Neuropathic Disease Be Prevented, Diagnosed, and Treated in Patients With DM?

Microvascular and neuropathic complications are most closely associated with glycemic status; the risk for and progression of these complications are reduced by improving glycemic control.

3.Q10.1. Diabetic Nephropathy

- **R36.** Beginning 5 years after diagnosis in patients with T1DM and at diagnosis in patients with T2DM, an annual assessment of serum creatinine to estimate the glomerular filtration rate (GFR) and urine albumin excretion should be performed to identify, stage, and monitor progression of diabetic nephropathy (**Grade D; BEL 4**). Patients with diabetic nephropathy should be counseled regarding the increased need for optimal glycemic control, blood pressure control, dyslipidemia control, and smoking cessation (**Grade A; BEL 1**). When therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers is initiated, renal function and serum potassium levels must be closely monitored (**Grade A; BEL 1**).

Table 7
Comprehensive Diabetes Care Treatment Goals

Parameter	Treatment Goal	Reference (evidence level and study design)
Glucose		
Hemoglobin A_{1c}, %	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"	(3 [EL 4; position NE])
Fasting plasma glucose, mg/dL	<110	
2-Hour postprandial glucose, mg/dL	<140	
Inpatient hyperglycemia: glucose, mg/dL	140-180	(4 [EL 4; consensus NE]) (BEL 4; Grade D)
Lipids		
Low-density lipoprotein cholesterol, mg/dL	≤70 highest risk; <100 high risk	(5 [EL 4; consensus])
Non–high-density lipoprotein cholesterol, mg/dL	<100 highest risk; <130 high risk	
Apolipoprotein B, mg/dL	<80 highest risk; <90 high risk	
High-density lipoprotein cholesterol, mg/dL	>40 in men; >50 in women	(5 [EL 4; consensus])
Triglycerides, mg/dL	<150	
Blood pressure		
Systolic, mm Hg	<130	(6 [EL 4; CPG NE])
Diastolic, mm Hg	<80	
Weight		
Weight loss	Reduce weight by at least 5%-10%; avoid weight gain	(3 [EL 4; position NE])
Anticoagulant Therapy		
Aspirin	For secondary cardiovascular disease prevention or primary prevention for patients at very high risk[a]	(7 [EL 1; MRCT but small sample sizes and event rates], 8 [EL 1; MRCT], 9 [EL 1; MRCT], 10 [EL 2, PCS])

Abbreviations: BEL, best evidence level; CPG, clinical practice guideline; EL, evidence level; MRCT, meta-analysis of randomized controlled trials; NE, no evidence (theory, opinion, consensus, review, or preclinical study); PCS, prospective cohort study.
[a] High risk = diabetes mellitus without cardiovascular disease; highest risk = diabetes mellitus plus cardiovascular disease.

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3.Q10.2. Diabetic Retinopathy

- **R37.** At the time of diagnosis, patients with T2DM should be referred to an experienced ophthalmologist or optometrist for annual dilated eye examination (**Grade D; BEL 4**). In patients with T1DM, a referral should be made within 5 years of diagnosis (**Grade B; BEL 2**). Women who are pregnant and have DM should be referred for frequent/repeated eye examinations during pregnancy and 1 year postpartum (**Grade C; BEL 3**). Patients with active retinopathy should have examinations more frequently than once a year, as should patients receiving vascular endothelial growth factor therapy (**Grade D; BEL 4**). Optimal glucose, blood pressure, and lipid control should be implemented to slow the progression of retinopathy (**Grade D; BEL 4**).

3.Q10.3. Diabetic Neuropathy

- **R38.** Diabetic painful neuropathy is diagnosed clinically and must be differentiated from other painful conditions (**Grade D; BEL 4**). Interventions that reduce oxidative stress, improve glycemic control, and/or improve dyslipidemia and hypertension might have a beneficial effect on diabetic neuropathy (**Grade A; BEL 1**). Exercise and balance training may also be beneficial (**Grade C; BEL 3**). Tricyclic antidepressants, anticonvulsants, and serotonin and norepinephrine reuptake inhibitors are useful treatments (**Grade A; BEL 1**). Large-fiber neuropathies are 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 as needed (**Grade A; BEL 1**). Small-fiber neuropathies are managed with foot protection (eg, padded socks), supportive shoes with orthotics if necessary, regular foot and shoe inspection, prevention of heat injury, and use of emollient creams; however, for pain management, the medications mentioned above must be used (**Grade A; BEL 1**).

3.Q11. How Should Macrovascular Disease Be Prevented, Diagnosed, and Treated in Patients With Prediabetes or DM?

3.Q11.1. Antiplatelet Therapy

- **R39.** The use of low-dosage aspirin (75-162 mg daily) is recommended for secondary prevention of CVD (**Grade A; BEL 1**). For primary prevention of CVD, its use may be considered for those at high risk (10-year risk >10%) (**Grade D; BEL 4**).

3.Q11.2. Hypertension

- **R40.** Therapeutic recommendations for hypertension should include lifestyle modification to include DASH diet (Dietary Approaches to Stop Hypertension), in particular reduced salt intake, physical activity, and, as needed, consultation with a registered dietician and/or CDE (**Grade A; BEL 1**). Pharmacologic therapy is used to achieve targets unresponsive to therapeutic lifestyle changes alone. Initially, antihypertensive agents are selected on the basis of their ability to reduce blood pressure and to prevent or slow the progression of nephropathy and retinopathy; angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are considered the preferred choice in patients with DM (**Grade D; BEL 4**). The use of combination therapy is likely required 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.Q11.3. Dyslipidemia

- **R41.** All patients with DM should be screened for dyslipidemia (**Grade A; BEL 1**). Therapeutic recommendations should include therapeutic lifestyle changes and, as needed, consultation with a registered dietitian and/or CDE (**Grade A; BEL 1**). Pharmacologic therapy is used to achieve targets unresponsive to therapeutic lifestyle changes alone. LDL-C is the primary target for therapy. Statins are the treatment of choice in the absence of contraindications. Combinations of statins (**Grade A; BEL 1**) with bile acid sequestrants, niacin, and/or cholesterol absorption inhibitors should be considered in situations of inadequate goal attainment. These agents may be used instead of statins in cases of statin-related adverse events or intolerance (**Grade A; BEL 2**). In patients with LDL-C at goal, but with triglyceride concentrations of 200 mg/dL or higher or low HDL-C (<35 mg/dL), treatment protocols including the use of fibrates or niacin are used to achieve non–HDL-C goal (<100 mg/dL when at highest risk; <130 mg/dL when at high risk) (**Grade A; BEL 1**). Apolipoprotein B targets are less than 80 mg/dL in patients with CVD and less than 90 mg/dL in patients without CVD.

3.Q11.4. Asymptomatic Coronary Artery Disease

- **R42.** Measurement of coronary artery calcification or coronary imaging may be used to assess whether a patient is a reasonable candidate for intensification of

glycemic, lipid, and/or blood pressure control (**Grade C; BEL 3**). Screening for asymptomatic coronary artery disease with various stress tests in patients with T2DM has not been clearly demonstrated to improve cardiac outcomes and is therefore not recommended (**Grade D; BEL 4**).

3.Q12. How Should Other Common Comorbidities of DM Be Addressed?

3.Q12.1. Sleep-Related Problems

- **R43.** Obstructive sleep apnea is common and should be screened for in adults with T2DM, especially in men older than 50 years (**Grade D; BEL 4**). Continuous positive airway pressure should be considered for treating patients with obstructive sleep apnea (**Grade A; BEL 1**). This condition can be diagnosed by history or by home monitoring, but referral to a sleep specialist should be considered in patients suspected of having obstructive sleep apnea or restless leg syndrome (**Grade D; BEL 4**).

3.Q12.2. Depression

- **R44.** Routine depression screening is recommended for adults with DM. Untreated comorbid depression can have serious clinical implications for patients with DM (**Grade A; BEL 1**).

4. APPENDIX: EVIDENCE BASE

In the Appendix, evidence is presented and discussed that supports the specific recommendations provided in the Executive Summary.

4.Q1. How is DM Diagnosed and Classified?

4.Q1.1. Diagnosis of DM

DM refers to a group of metabolic disorders that result in hyperglycemia, regardless of the underlying process. DM is diagnosed by using any of 3 established criteria (Table 5) (12 [EL 4; consensus NE]).

An International Expert Committee has recommended that a A1C level of greater than 6.5% be used as a criterion for diagnosis of DM (13 [EL 4; Consensus NE]). Subsequent analyses of the fidelity of DM diagnosis using A1C vs FPG or 2-hour oral glucose tolerance test (Table 5) have questioned this (14 [EL 3; SS]). Moreover, A1C is known to be affected by nonglycemic factors, such as changes in red 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 (15 [EL 3; SS], 16 [EL 4; review NE]). 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 the variability of glucose levels may be such that a substantial number of persons would be misclassified (17). On the basis of these limitations, A1C measurement cannot be recommended as a primary method for diagnosing DM. A1C can be used as a screening test, but the diagnosis of DM is best confirmed by 1 of the 3 established direct measures of plasma glucose. When A1C is used to diagnose DM, it is recommended to follow-up with a glucose level when possible because glucose levels, not A1C, are used for proper home glucose monitoring.

4.Q1.2. Classification of DM

DM is classified into T1DM, T2DM, GDM, and other less common causes such as rare insulin resistance and mitochondrial syndromes. T1DM accounts for less than 10% of all DM cases, occurs more commonly in younger persons, 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 T1DM, evidence for autoimmunity is lacking and the etiology of islet destruction is unclear. The severe insulinopenia predisposes patients with T1DM to diabetic ketoacidosis. Diabetic ketoacidosis can occur in patients with T2DM as well (18 [EL 3; SS]). T2DM accounts for more than 90% of all cases of DM; it remains undiagnosed for years in many affected persons they are asymptomatic. As a result, up to 25% of patients with T2DM have already developed 1 or more microvascular complication by the time of diagnosis (19 [EL 1; RCT]). Insulin resistance and concurrent relative insulin deficiency and glucagon excess underlie the pathophysiology of T2DM (20 [EL 2; PCS]).

4.Q2. How Can DM Be Prevented?

Prediabetes is a condition defined by an increased risk to develop DM and CVD. Prediabetes can be identified by the presence of impaired glucose tolerance (oral glucose tolerance test glucose value of 140-199 mg/dL 2 hours after ingesting 75 g of glucose), impaired fasting glucose (FPG value of 100-125 mg/dL), or A1C value of 5.7% to 6.4% (Table 5). Metabolic syndrome based on National Cholesterol Education Program IV Adult Treatment Panel III criteria may be considered a prediabetes equivalent. Polycystic ovary syndrome is also a prediabetes condition (2 [EL 4; consensus NE]). Risk factors suggesting a need for screening are listed in Table 6 (2 [EL 4; consensus NE]).

Prevention of T2DM depends upon systematic lifestyle modification, including caloric intake reduction (eg, 500 kcal deficit per day) and regular daily exercise (30 minutes aerobic work) to lose greater than 7% body weight (3

[EL 4; position NE]). Lifestyle management alone may be adequate for low-risk states and will reduce DM incidence by as much as 58% (3 [EL 4; position NE]). Pharmacologic assistance with orlistat may be helpful (120 mg 3 times daily) (21 [EL 1; RCT]).

For patients in whom lifestyle modification after 3 to 6 months has failed to produce necessary improvement, pharmacologic intervention may be appropriate. No medications are approved by the FDA for the management of prediabetes and/or the prevention of T2DM. Metformin (22 [EL 1; RCT]) and acarbose (23 [EL 1; RCT], 24 [EL 1; RCT], 25 [EL 4; opinion NE]) might be appropriate for certain patients. TZDs are effective in preventing DM (26 [EL 1; RCT], 27 [EL 1; RCT]) in 62% to 72% of high-risk patients; however, because of their potentially 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 (2 [EL 4; consensus NE]). Metformin is an antidiabetic drug that is not approved for obesity. However, it reduces the risk of developing DM in persons with impaired glucose tolerance as demonstrated in the Diabetes Prevention Program (22 [EL 1; RCT], 28 [EL 1; RCT, follow-up study]). In 3 studies, orlistat reduced conversion to DM (21 [EL 1; RCT], 29 [EL 1; RCT], 30 [EL 1; MRCT]). One of these studies reported a reduction from 10.9% to 5.2% ($P = .041$) in the conversion rate to DM (29 [EL 1; RCT]). Orlistat therapy is also associated with decreases in A1C; in one study, A1C decreased by 1.1% in the orlistat group and by 0.2% in the control group. Orlistat therapy also resulted in a mean weight loss of 5% (31 [EL 2; MNRCT]).

Obesity

The cornerstone for controlling obesity in prediabetes and DM is lifestyle modification, particularly calorie reduction and appropriately prescribed physical activity. Older drugs approved by the FDA have not been systematically tested in patients with DM. One review of 28 studies comparing orlistat and placebo (32 [EL 1; MRCT]), found a 3.86-kg weight loss favoring orlistat in patients at low risk for CVD, a 2.50-kg weight loss favoring orlistat in patients with DM, and a 2.04-kg weight loss favoring orlistat in patients at high risk for CVD. Orlistat also improves most cardiometabolic risk factors (29 [EL 1; RCT], 33 [EL 1; MRCT]).

Surgical intervention in obesity significantly reduces the risk of DM and the risk of future mortality (34 [EL 2; RCT (controls were those who declined surgery)], 35 [EL 3; SS, retrospective cohort], 36 [EL 3; SS, retrospective review of prospectively collected data]) and is cost effective (37 [EL 2; RCCS], 38 [EL 3; SS], 39 [EL 2; retrospective cohort study], 40 [EL 3; SS]). Excess weight loss at 1 year was 26% greater with gastric bypass (19%-34%) (41 [EL 2; MNRCT]). In the highest-quality study reviewed in a meta-analysis, the loss of excess body weight was 76% with Roux-en-Y gastric bypass vs 48% with gastric banding. DM resolved in 78% of the gastric bypass group compared with 50% in the gastric banding group, but perioperative complications were more common with gastric bypass (9% vs 5%), and long-term reoperation rates were lower with gastric bypass (16% vs 24%) (41 [EL 2; MNRCT]).

The beneficial effect of surgery on reversal of existing DM and prevention of its development has been confirmed in a number of studies (42 [EL 3; RCCS], 43 [EL 2; PCS], 44 [EL 2; PCS], 45 [EL 3; CCS], 46 [EL 2; MNRCT]). The percentage of reversal is related to the degree of weight loss, which is consistent with improvements in insulin sensitivity (44 [EL 2; PCS]). The Swedish Obese Subjects study reported improvement in DM with bariatric surgery (47 [EL 2; PCS]). After 2 years of follow-up, the DM incidence was 8% in the control group and 1% in the surgical group. After 10 years, the DM incidence in the control group was 24% compared with only 7% in the group of patients who underwent operation. The incidence rate was related to the amount of weight lost (48 [EL 4; review NE]). Roux-en-Y and other gastric bypass procedures may contribute to improvement in DM beyond the weight loss (49 [EL 4; consensus, NE], 50 [EL 1, RCT], 51 [EL 4; consensus]).

4.Q3. What is the Role of a DM Comprehensive Care Plan?

The overarching expert opinion of the Task Force that wrote this CPG, based on the cumulative experience and extant clinical evidence, is that all patients with DM should have a DM comprehensive care plan formulated and then implemented. On the basis of unanimous consensus and prime importance, this is upgraded to evidence level Grade A.

4.Q4. What is the Imperative for Education and Team Approach in DM Management?

A team must be involved in DM care. Working with different health care providers 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. It is important to use other providers' skills and specialties to ensure the patient has the best care and understanding of their condition. Often, problems may be apparent to one health care provider, 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.

Certified Diabetes Educators

A CDE is generally a nurse or registered dietician, but could be another health care 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.

Registered Dietitians

Following a healthful diet is necessary to maintain good health in everyone. However, persons with DM need to especially follow their prescribed meal plan and physical activity program as an integral part of their therapy. Registered dieticians 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 physiological and psychosocial problems. These issues may not be identified during physician office visits.

Registered Nurses

Registered nurses 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. Physician time can be saved when the nurse fields phone calls related to medication administration, assessment of medication tolerability, and other related DM management issues.

Nurse Practitioners and Physician Assistants

A patient may see these "mid-level" providers in conjunction with the physician. These providers 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. Also, these providers often take over some treatment decisions, thus freeing the physician to concentrate on other health care issues.

Primary Care Physicians

It is important that a patient has a primary care physician. It is critical that a primary care physician 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 health care team. It is important for patients to see the appropriate specialist as part of their care.

4.Q5. What Are the Comprehensive Treatment Goals for Patients With DM?

4.Q5.1. Glycemic and A1C Goals

4.Q5.1.1. Outpatient Glucose Targets for Nonpregnant Adults

There is no dispute that elevated glucose levels are associated with microvascular and macrovascular complications of DM. Similarly, it has been accepted that strategies aimed at lowering glucose concentrations can lead to lower rate of microvascular and, perhaps in some instances, of macroangiopathic complications (52 [EL 1; RCT], 53 [EL 3; SS], 54 [EL 1; RCT, posttrial monitoring], 55 [EL 3; SS], [56 [EL 1; RCT]). What has remained the subject of multiple debates, are the specific targets for glucose control in patients with DM.

Healthy persons do not exhibit preprandial plasma glucose concentrations above 99 mg/dL or above 120 mg/dL after meals. Indeed, there was a progressively increased risk of T2DM in men with FPG levels above 87 mg/dL in 1 study (57 [EL 3; SS]) and above 94 mg/dL in another study based on long-term follow-up (58 [EL 3; SS]). Similarly, standardized DCCT (Diabetes Control and Complications)–aligned A1C levels remain under 6.0% in healthy persons. Epidemiologic evidence shows a continuous relationship between A1C and CVD and all-cause mortality with lowest rates at A1C levels below 5% (59 [EL 2; PCS]).

Logically, one should aim for "normal" levels when treating patients with DM. However, it is unknown whether treating patients with DM—some with preexisting diabetic complications—using complicated regimens to force their glucose concentrations into the normal range actually prevents or delays those complications. 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 (60 [EL 1; RCT], 61 [EL 1; RCT], 62 [EL 1; RCT], 63 [EL 1; RCT]).

There are still no RCTs that establish optimal glycemic targets. In view of this situation, professional organizations have relied on results from existing interventional trials achieving improved A1C levels and epidemiologic analyses of various studies to arrive at consensus statements or expert opinions regarding these targets. Thus, some (3 [EL 4; position NE]) have recommended general target A1C level at or below 6.5%, while others have recommended a general target of less than 7% (64 [EL 4; NE], 65 [EL 4; CPG NE]). In all cases, it has been recognized that potential risks of intensive glycemic control may outweigh its benefits, especially in patients with history of frequent severe hypoglycemia, hypoglycemia unawareness, or very long duration of DM, particularly in the presence of established, advanced atherosclerosis, advanced age, and terminal illness.

In patients with DM, a A1C level above 7% is associated with increased risk of microvascular and macrovascular complications (55 [EL 3; SS], 56 [EL 1; RCT], 66 [EL 1; RCT], 67 [EL 1; RCT]). Strategies aimed at lowering glycemic levels (as evidenced by A1C lowering) have decreased microvascular complications and, in some cases, macrovascular complications. The target A1C can be achieved, given today's pharmacotherapy. To achieve the target A1C levels, fasting and preprandial glucose levels should be below 110 mg/dL. The evidence for having a PPG target is predominantly based on cross-sectional and prospective epidemiologic studies with few RCTs (3 [EL 4; position NE], 68 [EL 2; PCS]).

4.Q5.1.2. Inpatient Glucose Targets for Nonpregnant Adults

Glycemic targets for intensive care unit intensive insulin therapy have been debated recently, primarily because of the findings of the real-world NICE-SUGAR study (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) (69 [EL 1; RCT]) and recently published meta-analyses (70 [EL 1; MRCT], 71 [EL 1, MRCT], 72 [EL 2; MNRCT], 73 [EL 1; MRCT]), which challenged the findings of the 2 earlier proof-of-concept Leuven studies (74 [EL 1; RCT], 75 [EL 1; RCT]). The real-world study and meta-analysis studies (61 [EL 1; RCT], 72 [EL 2; MNRCT], 73 [EL 1; MRCT]) found increased mortality in various intensive care unit settings at multiple centers with tighter intensive insulin therapy glycemic targets that were associated with a higher rate of severe hypoglycemia. The first Leuven study demonstrated outcome benefits with glycemic targets of 80 to 110 mg/dL in primarily cardiothoracic surgical patients (74 [EL 1; RCT]). This study was conducted in a highly controlled intensive care unit environment that also provided uniform standards of nutrition support. The second Leuven study demonstrated outcome benefit in medical intensive care unit patients with prolonged critical illness receiving intensive insulin therapy with glycemic targets of 80 to 110 mg/dL (75 [EL 1; RCT]). The AACE/American Diabetes Association consensus statement on inpatient glycemic control (4 [EL 4; consensus NE]) outlines the argument in favor of more relaxed glycemic targets, as high as 140 to 180 mg/dL, especially in settings that do not have documented experience with respect to low rates of hypoglycemia with tighter glycemic targets. If uniform glucose monitoring and insulin protocols, safety, low rates of hypoglycemia, standardized nutrition support, and documented reductions in mortality exist in a specific setting, then lower intensive insulin therapy glycemic targets may be considered (74 [EL 1; RCT], 75 [EL 1; RCT]). 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 below 110 mg/dL are no longer recommended.

Additionally, minimizing glycemic variability, independent of levels, is associated with better intensive care unit patient outcomes and less hypoglycemia and less insulin required (intensive care unit/non–intensive care unit) (76 [EL 2; PCS, retrospective review of data], 77 [EL 3; SS]).

4.Q5.2. CVD Risk Reduction Targets

4.Q5.2.1. Blood Pressure

Blood pressure goals for most patients with DM and prediabetes are less than 130/80 mm Hg (Table 7). Epidemiologic analyses demonstrate increased CVD events for blood pressure greater than 115/75 mm Hg. However, interventional RCTs have led to less clear results. Patients achieving blood pressure less than 140/80 mm Hg realize benefits (especially fewer strokes, less nephropathy, and CVD events). Whether reducing systolic to 130 mm Hg or less will lead to further reduction in CVD events remains to be demonstrated (62 [EL 1; RCT], 78 [EL 1; RCT, posthoc analysis]).

4.Q5.2.2. Lipids

Treatment targets for dyslipidemia in DM are based on the presence of CVD risk factors; serum levels of LDL-C; and serum levels of other lipids, lipoproteins, or lipoprotein components (Table 7). In patients at highest risk for CVD, including those known to have CVD or those with DM plus 1 or more additional major CVD risk factor(s), the goals for LCL-C, non–HDL-C, and apolipoprotein B should be less than 70 mg/dL, less than 100 mg/dL, and less than 80 mg/dL, respectively. In patients at high risk, which would include those without DM or known clinical CVD but with more than 2 major CVD risk factors (including smoking, hypertension, or family history of premature coronary artery disease), the goals for LCL-C, non–HDL-C, and apolipoprotein B should be less than 100 mg/dL, less than 130 mg/dL, and less than 90 mg/dL, respectively (79 [EL 4; CPG NE], 80 [EL 3; SS]). Other targets are an HDL-C concentration greater than 40 mg/dL in men and greater than 50 mg/dL in women and a triglyceride concentration less than 150 mg/dL (79 [EL 4; CPG NE]).

4.Q6. How Can DM Comprehensive Care Plan Guideline Targets Be Achieved?

4.Q6.1. Therapeutic Lifestyle Changes

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

The role of nutritional medicine in a DM comprehensive care plan consists of counseling about general healthful eating, medical nutritional therapy, and nutrition support when appropriate. 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 essentially the same as for patients without DM (Table 8) (3 [EL 4; position NE], 81 [EL 3, SS], 82 [EL 3; SS], 83 [EL 4; position NE], 84 [EL 4; position NE], 85 [EL 4; review NE], 86 [EL 3, SS], 87 [EL 1; RCT], 88 [EL 4; review NE], 89 [EL 4; review NE], 90 [EL 4; review NE], 91 [EL 4; review NE], 92 [EL 4; NE review], 93 [EL 4, review NE], 94 [EL 4; review NE], 95 [EL 2; MNRCT], 96 [EL 2; PCS; data may not be generalizable to patients with DM already], 97 [EL 4, CPG NE], 98 [EL 4; review NE], 99 [EL 4; CPG NE]). These recommendations should be discussed, in plain language, initially and then periodically during follow-up office visits with the physician or with a registered dietician (3 [EL 4; position NE]). These components are related to broad, nontechnical comments about foods that can promote health vs foods that may promote disease or complications from disease and are suitable for the general population, including those patients without DM. Physician discussions should include specific foods, dishes, meal planning, grocery shopping, and dining-out strategies. The components

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	Regular meals and snacks; avoid fasting to lose weight 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 Informal physician-patient discussions Use mild cooking techniques instead of high-heat cooking	(84 [EL 4; position NE]) (85 [EL4; review NE]) (86 [EL 3; SS]) (81 [EL 3; SS]) (82 [EL 3; SS]) (83 [EL 4; position NE]) (87 [EL 1; RCT])
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, pulses, 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	(88 [EL 4; review NE]) (89 [EL 4; review NE]) (84 [EL 4; position NE]) (90 [EL 4; review NE]) (91 [EL 4; review NE]) (92 [EL4; NE review]) (93 [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; no- or low-fat dairy products	(94 [EL 4; review NE]) (98 [EL 4; review NE]) (99 [EL 4; CPG NE])
Protein	Consume protein in foods preferably with low saturated fats (fish, egg whites, beans); there is no need to avoid animal protein Avoid or limit processed meats	(84 [EL 4; position NE]) (95 [EL 2; MNRCT], 96 [EL 2; PCS; data may not be generalizable to patients with diabetes already])
Micronutrients	Routine supplementation is not necessary Specifically, chromium, vanadium, magnesium, vitamins A, C, and E, and CoQ10 are not recommended for glycemic control Supplementation to avoid insufficiency or deficiency in at-risk patients A healthful eating meal plan can generally provide sufficient micronutrients	(97 [EL 4; CPG NE])

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

of medical nutritional therapy address the metabolic needs of patients with DM (100 [EL 4; CPG NE]). These recommendations should also be discussed and implemented by the physician or a registered dietician in all patients with DM. Medical nutritional therapy involves a more detailed discussion, usually in terms of calories, grams, and other metrics, and intensive implementation effort of dietary recommendations aimed at optimizing glycemic control and reducing the risk for complications.

All patients should be advised how to achieve and maintain a healthful weight, corresponding to a normal range body mass index of 18.5 to 24.9 kg/m^2. The key to adopting the principles given in Tables 7 and 8 are to personalize the recommendations on the basis of a patient's specific medical conditions, lifestyle, and behavior. Patients unable to accomplish this should be referred to a registered dietician or weight-loss program that has a proven success rate. In areas underserved by registered dieticians, physicians should take on more responsibility with nutritional counseling and reinforcement of healthful eating patterns during patient encounters.

A review and position paper on medical nutritional therapy for both T1DM and T2DM has recently been published (101 [EL 4; consensus NE]). Twenty-nine specific recommendations address issues affecting glucose control, reduction of CVD risk factors, and weight management. Key recommendations address the need for consistency in day-to-day carbohydrate intake, adjusting insulin doses to match carbohydrate intake (eg, use of carbohydrate counting), limitation of sucrose-containing or high-glycemic index foods, adequate protein intake, "heart healthy" diets, weight management, exercise, and increased glucose monitoring. The bottom line is that medical nutritional therapy must be personalized and this generally means evaluation and teaching by a registered dietician or knowledgeable physician.

There is now good evidence that regular physical activity improves glucose control in persons with T2DM (102 [EL 1; RCT], 103 [EL 2; NRCT], 104 [EL 2; NRCT], 105 [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, some good studies on exercise alone show improved glucose control (106 [EL 1; RCT], 107 [EL 4; commentary NE], 108 [EL 1; RCT]). There is no question that regular physical exercise, both aerobic exercise and strength training, are 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 (107 [EL 4; commentary NE]). Physical activity is also a main component in weight loss and maintenance programs and is particularly important in the weight maintenance phase. The current recommendations of at least 150 minutes per week of moderate-intensity exercise such as brisk walking or its equivalent are now well accepted and part of the nationally recommended guidelines. For persons with T2DM, recommendations include flexibility and strength training exercises with aerobic exercise. A recent study makes a good point for combining both aerobic and strength exercise in a program for patients with T2DM (106 [EL 1; RCT]).

Key points are that patients must be evaluated initially for contraindications and/or limitations to increased physical activity, that an exercise prescription be developed for each patient according to both goals and limitations, and that additional physical activity should be started slowly and built up gradually.

4.Q6.2. Antihyperglycemic Pharmacotherapy

The goal of glycemic treatment of persons with T2DM 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 agents. In achieving control, all currently available oral glucose-lowering agents are more or less similar in their glucose-lowering potency (109 [EL 1; MRCT], 110 [EL 3; CSS]). The apparent greater efficacy of agents brought to market in the past, compared with efficacy of newer agents, is probably because of higher baseline glucose levels (3 [EL 4; position NE]).

There are, however, differences between various classes of glucose-lowering agents. The duration of glycemic control with TZDs appears to be maintained over periods up to 5 to 6 years, while with sulfonylureas, glucose lowering is maximal at 6 months and glucose levels return towards baseline at about 3 years; metformin appears intermediate in durability (111 [EL 1; RCT]). Metformin is sometimes associated with weight loss, but may lead to gastrointestinal adverse effects (eg, dyspepsia, loose stools, or diarrhea) in a significant subset of patients, and it can be associated with the development of vitamin B_{12} deficiency over time (112 [EL 1; RCT]). Although the monotherapy UKPDS (United Kingdom Prospective Diabetes Study) metformin substudy (113 [EL 1; RCT]) showed a reduction in cardiovascular events, the metformin plus sulfonylurea UKPDS substudy (114 [EL 1; RCT]) actually showed an increase in such events, leading to uncertainty as to whether the drug can be regarded as having positive, negative, or neutral cardiovascular effects. The addition of a sulfonylurea to metformin is associated with a greater than 5-fold increase in likelihood of hypoglycemia over that seen with metformin alone or when a sulfonylurea is administered in conjunction with a TZD, DPP-4 inhibitor, or nateglinide (115 [EL 1; MRCT]). The average weight gain with sulfonylurea is comparable to that with TZDs (116 [EL 2; MNRCT]), an important potential adverse effect not widely appreciated.

DPP-4 inhibitors do not cause weight gain, they can be administered in patients with renal insufficiency with appropriate dosing adjustment, they lack significant gastrointestinal adverse effects (117 [EL 4; opinion NE]), and they have been associated with reduction in cardiovascular events in analyses of registration trials (118 [EL 1; MRCT]), although they have not yet been specifically studied in trials addressing CVD effects.

Colesevelam and α-glucosidase inhibitors are infrequently used in the United States, perhaps because of gastrointestinal adverse effects, but they are worth consideration in selected patients. Colesevelam lowers LDL-C, for which it was originally developed, and both agents are not systemically absorbed and hence are less likely to have systemic adverse effects.

TZDs increase HDL-C (and pioglitazone lowers triglycerides), lower blood pressure, reduce markers of inflammation, reduce hepatic steatosis (119 [EL 4; review NE]), decrease carotid and coronary artery thickening (120 [EL 1; RCT]), and prevent restenosis after percutaneous transluminal coronary angioplasty (121 [EL 1; MCRT]), and they may help prevent central nervous system insulin resistance–related cognitive dysfunction (122 [EL 2; PCS]). However, TZDs can have adverse effects such as fluid retention, to some extent explaining the weight gain associated with their use. Because of this, TZDs should be used with caution in patients with peripheral vascular disease, both venous and arterial. TZDs are contraindicated in patients with New York Heart Association class 3 and 4. The average weight gain with sulfonylureas is comparable to that with TZDs (116 [EL 2; MNRCT]). TZDs can also reduce bone mineralization and are associated with nonosteoporotic bone fractures. The TZD rosiglitazone has been withdrawn from use in Europe and severely restricted in the United States because of concerns over a possible increase in CVD risk (123 [EL 4; review NE]).

In 2009, bromocriptine mesylate was approved for treatment of T2DM. It is unclear how this drug improves glycemic control, but it reduces A1C by ~0.5%. Bromocriptine is a potent agonist at dopamine D_2 receptors and various serotonin receptors. It also inhibits the release of glutamate by reversing the glutamate GLT-1 transporter (124).

In general, all oral antihyperglycemic agents appear to be similar in glucose-lowering potential over the short-term at a given baseline A1C (125 [EL 4; review NE]). Sulfonylureas have moderate hypoglycemia risk, both in monotherapy and in combinations, while none of the other oral glucose-lowering agents intrinsically cause this deleterious effect. Gastrointestinal symptoms can occur with metformin, colesevelam, and α-glucosidase inhibitors. These agents should be used with caution in persons with renal insufficiency: metformin use is contraindicated in stage 4 and 5 chronic kidney disease, sulfonylureas are more likely to cause hypoglycemia, TZDs are more likely to cause fluid retention, and DPP-4 inhibitor dosage reduction is required in patients with clinically significant renal impairment.

It is appropriate to consider combining several such agents in the treatment regimen because many patients do not achieve adequate glycemic control with oral agent monotherapy (AACE/ACE glycemic algorithm) (3 [EL 4; position NE]). Sulfonylureas are particularly problematic when used in such combinations. Key benefits of incretin-mediated treatment include the avoidance of hypoglycemia and weight gain; these benefits will not be seen when DPP-4 inhibitors are administered with sulfonylureas. Similarly, sulfonylureas eliminate the weight loss benefit and can cause hypoglycemia when administered with metformin or TZDs (116 [EL 2; MNRCT]). Metformin, in contrast, is quite effective when administered in combination with the other agents, as long as one avoids its use in patients with renal insufficiency (GFR <60 mL/min) (3 [EL 4; position NE]) or gastrointestinal intolerance.

Several years of clinical trials and treatment with DPP-4 inhibitors and GLP-1 receptor agonists have provided insight into their clinical usefulness and their potential adverse effects. Increases in GLP-1 activity up to 2- to 3-fold above physiologic levels increase insulin and decrease glucagon secretion only when the plasma glucose levels are elevated (126 [EL 4; review NE], 127 [EL 4; review]). In patients with T2DM, this lowers fasting and postprandial hyperglycemia and is associated with minimal risk of hypoglycemia (128 [EL 1; MRCT]). These levels do not increase satiety. The administration of pharmacologic quantities of GLP-1 receptor agonists to achieve plasma GLP-1 activities that are 5- to 7-fold higher than physiologic activities may produce the additional effects of delayed gastric emptying, increased satiety, decreased food intake, and a modest mean weight loss of 4% to 5% of the body weight (128 [EL 1; MRCT], 129 [EL 2; RCT, only 9 patients studied (downrated from EL 1), 130 [EL 4; review NE]).

As monotherapy, DPP-4 inhibitors decrease mean A1C by 0.4% to 0.8% (118 [EL 1; MRCT]). When combined with metformin, the mean decrease can be as high as 1.2% to 1.4% (118 [EL 1; MRCT]). Although DPP-4 inhibitors are currently more expensive than sulfonylureas, they have the advantage that they do not cause hypoglycemia or weight gain. In contrast to sulfonylureas, they improve the inappropriate hyperglucagonemia of DM. The oral DPP-4 inhibitors are of particular benefit in patients who need an increase in endogenous insulin secretion, but who would be at high risk for hypoglycemia from sulfonylureas.

The GLP-1 receptor agonists are given by subcutaneous injection. They are most useful as add-on therapy for patients with inadequately controlled DM on oral monotherapy (131 [EL 1; RCT], 132 [EL 1; RCT follow-up study], 133 [EL 1; RCT], 134 [EL 1; RCT, 135 [EL 1; RCT], 136 [EL 4; animal study NE], 137 [EL 1; RCT], 138

[EL 1; RCT], 139 [EL 1; RCT]). Several clinical trials have compared the effects of adding a GLP-1 receptor agonist (exenatide twice daily or liraglutide once daily) with adding insulin (glargine insulin or mixed insulin twice daily) in patients with inadequately controlled DM on oral agents (140 [EL 1; RCT], 141 [EL 1; RCT], 142 [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 hypoglycemia.

The main adverse effects noted with DPP-4 inhibitors are a small increase in upper respiratory tract viral infections and a rare hypersensitivity reaction (128 [EL 1; MRCT]). The main adverse effects with GLP-1 receptor agonists are nausea and vomiting (128 [EL 1; MRCT]). These adverse effects usually diminish over time. GLP-1 receptor agonist therapy is initiated with a lower initial dosage that is uptitrated over 3 to 4 weeks or longer if needed. In 5% to 10% of patients, the nausea and vomiting are sufficiently severe that they cannot tolerate the drug. In rodents, GLP-1 receptor agonists may increase the frequency of benign and malignant C-cell neoplasms; neither acute pancreatitis nor medullary thyroid carcinoma in humans has been convincingly shown to be caused by incretin-based therapies (143 [EL 4; NE]). GLP-1 receptor agonists should be discontinued in patients who develop acute pancreatitis. Liraglutide use is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2. The FDA has stated that patients on therapy do not need to be monitored for medullary thyroid carcinoma (eg, with calcitonin levels). If they are at risk for medullary thyroid carcinoma, this treatment should not be started (143 [EL 4; NE]).

Longer-acting GLP-1 receptor agonists, such as liraglutide, have a greater effect in lowering A1C than the shorter-acting exenatide twice daily (144 [EL 1; RCT], 145 [EL 1; RCT]). In recent head-to-head comparator trials, both exenatide long-acting release and liraglutide, when added to the treatment regimen of patients with T2DM inadequately controlled on metformin, decreased A1C significantly more than addition of a DPP-4 inhibitor (146 [EL 1; RCT], 147 [EL 1; RCT]). Liraglutide was more effective than a sulfonylurea as monotherapy (148).

Usually insulin therapy is initiated in T2DM when combination oral agent therapy, with or without GLP-1 receptor agonist therapy, fails to achieve the glycemic goal or when a patient, whether drug naïve or on a treatment regimen, presents with a A1C level greater than 9.0% and symptomatic hyperglycemia (3 [EL 4; position NE]). The traditional postponement of insulin therapy for years after prolonged lifestyle and oral agent efforts 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 (149 [EL 4; NE]).

Insulin therapy is initiated as a basal, basal-bolus, prandial, or premixed regimen. Most commonly, basal insulin is introduced in combination with approved oral agents. Approved agents for use with insulin include metformin, sulfonylureas, glinides, DPP-4 inhibitors, and TZDs. Sulfonylurea and glinides raise the potential for hypoglycemia with insulin, the latter class especially with prandial insulins; TZDs can be associated with weight gain, edema, and potential for congestive heart failure in combination with insulin.

Long-acting basal insulin is the initial choice for initiation of insulin therapy. The long-acting insulin analogues glargine and detemir are preferred over intermediate-acting NPH insulin because they do not have pronounced peak, they have more prolonged activity (up to 24 hours), they are associated with less weight gain, and they have less day-to-day variability within and between patients, resulting in both fewer symptoms and less nocturnal hypoglycemia (150 [EL 1; RCT], 151 [EL 1; MRCT], 152 [EL 4; CPG NE], 153 [EL 1; RCT], 154 [EL 1; MRCT]). The onset of NPH insulin is approximately 2 to 4 hours, peak action is between 4 and 10 hours, and duration of action is between 12 and 18 hours. Absorption among patients and within the same patient is variable (155 [EL 4; opinion NE]). NPH insulin, which offers a cost advantage over the basal analogues, may be maintained if good glycemic control has been achieved in the absence of hypoglycemia (especially nocturnal) and unacceptable glycemic excursions. Basal insulin therapy with analogues is usually initiated with 10 units or 0.1 to 0.2 unit/kg once daily. Several titration algorithms are published in the literature (150 [EL 1; RCT], 156 [EL 1; RCT]). Many patients can perform this titration on their own, following clear instructions, with good results (150 [EL 1; RCT], 156 [EL 1; RCT]).

Prandial or short-acting insulins are available as regular human insulin and rapid-acting insulin analogues (lispro, aspart, and glulisine). The insulin analogues are preferred if available (3 [EL 4; position NE]). Regular human insulin should be administered 30 to 45 minutes before meals—often a difficult challenge for patients—because of slow absorption and delayed onset of action (30-60 minutes) that does not match normal insulin release in response to a meal. Regular human insulin is associated with variable absorption resulting in variable peak activity (2-4 hours), inconsistent PPG control, a 6- to 8-hour duration of action, and possibly delayed hypoglycemia. Compared with regular human insulin, rapid-acting insulin analogues have a more rapid onset and shorter duration of action (4-5 hours) (157 [EL 4; review NE]). When given at mealtime, rapid-acting insulin analogues have been shown to be more effective than regular human insulin in lowering PPG, which is most likely related to their more rapid onset of action (158 [EL 1; MRCT]). Rapid-acting insulin analogues are associated with a lower risk of hypoglycemia, especially severe hypoglycemia, than regular human insulin (159 [EL 1; MRCT]).

The amylin analogue pramlintide is the only other medication approved for the treatment of T1DM. It is administered along 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 insulin dosage (160 [EL 1; RCT], 161 [EL 1; RCT], 162 [EL 1; RCT], 163 [EL 1; MRCT]), although this is usually attenuated in T2DM because of insulin resistance.

Premixed insulins are available as 70% NPH/30% regular, 70% insulin aspart protamine/30% insulin aspart, 75% insulin lispro protamine/25% insulin lispro, or 50% insulin lispro protamine/50% insulin lispro. These mixtures provide elements of both postprandial and intermediate-release glucose control. The analogue premixed insulins are preferred over human 70/30 given the faster onset of action, more consistent PPG control, and less variability in activity. Premixed insulin may be administered at the largest meal once daily or at the 2 largest meals twice daily. Adjustments are made on the basis of the predinner glucose level if administered prebreakfast and the fasting blood glucose level if administered predinner. Some patients are more suitable for this less complex regimen, and their DM can be well controlled with 2 injections of premixed insulin. However, the fixed doses of this regimen lack flexibility for specific titration of each insulin component based on SMBG. Premixed insulins are somewhat limited in their ability to reach glycemic targets unless given more frequently or in higher doses, which increases the potential for hypoglycemia and weight gain (164 [EL 1; RCT]).

Basal-bolus insulin therapy involves 4 injections a day combining basal insulin and prandial insulin before meals. Basal-bolus insulin therapy provides flexibility and is well suited for patients with varied food intake or irregular meal patterns (3 [EL 4; position NE]). Another advantage of basal-bolus insulin therapy is the ability to adjust insulin doses at each meal depending on the size of the meal (carbohydrate content). On the basis of SMBG, independent adjustments of the prandial and basal components can be made. Basal insulin adjustments are described above. Premeal prandial insulin doses can be initiated at 5 units per meal or about 7% of the basal insulin dose or 1 unit per 15 g carbohydrate (ie, 1 carbohydrate exchange). Doses may vary considerably on the basis of body weight and degree of insulin resistance and the amount of carbohydrate consumed at each meal. Titration of premeal prandial insulin is made with small changes weekly on the basis of 2-hour postmeal glucose levels or, if these are not available, the premeal glucose level at the subsequent meal. If the premeal glucose is elevated, supplemental doses of rapid-acting insulin can be added to the mealtime dose (correction dose), and if premeal glucose is below target, the mealtime dose can be decreased. Adjustments of basal and prandial insulins should be made independently to achieve target A1C levels, waking euglycemia, and physiologic PPG excursions without excessive hypoglycemia.

4.Q7. What Are the Special Considerations for Treatment of Hyperglycemia?

4.Q7.1. Treatment of Hyperglycemia in T1DM

Insulin therapy is necessary for life in all patients with T1DM (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 a RCT against nonphysiologic insulin regimens (once or twice daily insulin). Rather, physiologic insulin regimens have been formally studied as one component of a comprehensive treatment strategy for patients with T1DM.

There have been numerous RCTs comparing basal insulin analogues with NPH insulin in addition to rapid-acting analogues with regular human insulin. With insulin analogues, no additional improvements of mean glucose as measured by A1C have been shown, but there is a consistent reduction of hypoglycemia (157 [EL 4; review NE]). In comparisons of MDI and CSII for T1DM, there have been small but consistent improvements in A1C, as well as substantial reductions in severe hypoglycemia (165 [EL 1; MRCT], 166 [EL 1; MRCT]).

4.Q7.2. CSII (Insulin Pump Therapy)

Insulin pumps have been used for more than 30 years (167 [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 T1DM and less than 1% of insulin-treated patients with T2DM use CSII (168 [EL 3; SS]). The FDA estimates that the number of US patients with T1DM using CSII was ~375 000 in 2007, up from approximately 130 000 in 2002 (169 [EL 4; review NE]).

The American Diabetes Association published a position statement in 2004 (170 [EL 4; review NE]). The American Association of Diabetes Educators published its Guidelines for Successful Outcomes in 2009 (171 [EL 4; CPG NE]). The American Academy of Pediatrics published its position statement in 2006 (172 [EL 4; position NE]). Lastly, the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes have published a joint consensus statement regarding the use of insulin pumps in children (173 [EL 4; consensus NE]). AACE has its own consensus statement on insulin pump management (174 [EL 4; consensus]).

Table 9 presents a summary of important clinical research findings on CSII efficacy and safety in patients

with T1DM; included in the table are the results of key meta-analyses covering clinical research on insulin pump therapy published after 2003 (166 [EL 1; MRCT], 175 [EL 1; MRCT], 176 [EL 1; MRCT], 177 [EL 1; MRCT], 178 [EL 1; MRCT], 179 [EL 1; MRCT]).

Based on this evidence and other currently available data, CSII appears to be justified for basal-bolus insulin therapy in appropriately selected patients with T1DM who have inadequate control with MDI. The ideal CSII candidate is a patient with T1DM or absolutely insulin-deficient T2DM who currently performs 4 or more insulin injections daily and assesses the blood glucose levels 4 or more times daily, is motivated to achieve tighter plasma glucose 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 the use of a CGM device. 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 health care team, in particular their pump-supervising physician.

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 T1DM. Table 10 summarizes the key assumptions and findings of 5 recent representative cost-effectiveness analyses comparing CSII with MDI in specific patient populations (180 [EL 3; SS], 181 [EL 3; SS], 182 [EL 3; SS], 183 [EL 3; retrospective review SS], 184 [EL 3; SS]).

4.Q7.3. Treatment of Hyperglycemia 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. 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 diabetic ketoacidosis 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 (185 [EL 3; SS]) the potassium channel protein Kir6.2 in β cells and in the *ABCC8* gene encoding the sulfonylurea receptor protein SUR1 (186 [EL 3; SS]). Other causes have also been defined, including mutations in the insulin gene (187 [EL 3; SS]). Recognizing these disorders and distinguishing them from T1DM 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 (188 [EL 2; PCS]). Excellent reviews are available (189 [EL 4; review NE], 190 [EL 4; guidelines NE]).

Monogenic DM, initially called MODY (191 [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 forms of DM result from compromised insulin secretion, in one 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 (192 [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 1α (*HNF1A*) (193 [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 T1DM, T2DM (194 [EL 4; review NE]), or GDM (195 [EL 3; SS]). Making the correct diagnosis is important for genetic counseling and for 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).

T1DM is the most common form of DM occurring in children and adolescents, and its incidence is increasing in most populations in the world. The types of insulin used and administration regimens in older patients are also used in children. Most physicians treating DM in children use MDI regimens, and when appropriate, CSII (196 [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 and whose care is improved and facilitated for parents by using pumps (197 [EL 2; PCS]). In adolescents, the main problems with glycemic control often involve social and behavioral complications (198 [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 T2DM has been reported in preschool children, one must be cautious making this diagnosis in preadolescent children, taking care to exclude T1DM by assessing immune markers and monogenic DM by careful family history and genetic testing. Guidelines for differentiating T1DM from T2DM in children have been published (190 [EL 4; guidelines NE]), but several reports have demonstrated that these are imperfect and that phenotypic overlap

Table 9
Meta-Analyses of Continuous Subcutaneous Insulin Infusion Studies Published Since 2003

Reference (evidence level and study design)	Meta-analysis objectives	Number/types of studies included in meta-analysis	Clinical findings
(175 [EL 1; MRCT)	Investigation of metabolic and psychosocial impact of CSII therapy vs other treatment modalities (eg, MDI, conventional therapy) in children, adolescents, and adults (n = 1547)	2483 studies identified; 61 met initial criteria; final review consisted of 52 studies (37 paired, 4 randomized crossover, and 11 parallel) published between 1979-2001	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
(176 [EL 1; MRCT)	Comparison of effects of CSII vs MDI on glycemic control, hypoglycemic risk, insulin requirements, and adverse events in adults with T1DM (n = 908), children with T1DM (n = 74), and patients with T2DM (n = 234)	673 studies identified; final review consisted of 22 RCTs (17 T1DM, 2 T2DM, 3 pediatric) published through March 2007	A1C reduction greater and insulin requirements lower with CSII than MDI in adults and adolescents with T1DM; risk of hypoglycemia comparable among adult patients (data unavailable for adolescent patients) No conclusive CSII benefits seen for patients with T2DM
(177 [EL 1; MRCT)	Comparison of effects of CSII and MDI on glycemic control and hypoglycemia in adults and children with T1DM (n = 669) or T2DM (n = 239)	107 studies identified; final review consisted of 15 RCTs published between 2002 and March 2008	In patients with T1DM, A1C was mildly decreased with CSII vs MDI; CSII affect on hypoglycemia unclear CSII and MDI outcomes were similar among patients with T2DM *Notes:* CSII efficacy in patients with hypoglycemia unawareness or recurrent severe hypoglycemia inconclusive because of lack of data
(178 [EL 1; MRCT])	Examination of CSII and MDI effects on glycemic control and incidence of severe hypoglycemia in patients with T1DM (n = 1414); focused on studies with ≥6 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 diabetes 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
(179 [EL 1; MRCT])	Comparison of glycemic control and hypoglycemic incidence with short-acting, analogue-based CSII (n = 444) vs MDI (n = 439) therapy of ≥12 weeks' duration in patients with T1DM	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: CSII, continuous subcutaneous insulin infusion; EL, evidence level; A1C, hemoglobin A_{1c}; MDI, multiple daily injections; MRCT, meta-analysis of randomized controlled trials; RCT, randomized controlled trial; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

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Table 10
Summary Data From Cost-effectiveness Analyses Comparing Continuous Subcutaneous Insulin Infusion With Multiple Daily Injections in Adults and Children With Type 1 Diabetes Mellitus

Reference	Study objective, perspective, data source	QALYs gained	Cost per QALY (ICER)	Additional key findings
(180 [EL 3; SS])	To estimate long-term (60-year) cost-effectiveness of CSII compared with MDI in adults and children with T1DM US 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 diabetes complications including PDR, ESRD, PVD The NNT for PDR was 9 (ie, only 9 patients need to be treated with CSII to avoid 1 case of PDR)
(181 [EL 3; SS])	To evaluate the long-term (60-year) cost-effectiveness of CSII compared with MDI in adult patients with T1DM 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	…
(182 [EL 3; SS])	Assessment report to examine the clinical and cost-effectiveness of using CSII to treat diabetes (T1DM and during pregnancy) NICE, United Kingdom Systematic review and economic evaluation (74 studies included)	NA	NA	CSII is cost-effective for T1DM in both children and adults No evidence that CSII is better than MDI in pregnancy
(184 [EL 3; SS])	To project the long-term (60-year) costs and outcomes of CSII compared with MDI in patients with T1DM 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 diabetes-related complications For patients with T1DM, CSII represents good value on the basis on current UK standards

Abbreviations: 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 (UK); 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; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

between these disorders in children is common. T2DM remains a diagnosis of exclusion in adolescents. Diet and lifestyle modification are always the first treatment choice, but their effectiveness in children has not been extensively studied. Treatment of this disease in children does not differ appreciably from its treatment in adults. Metformin has been studied (199 [EL 1; RCT]) and remains the only oral medication approved by the FDA for use in children with T2DM. Insulin is effective and used widely alone or in combination with metformin.

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 Web site (11 [EL 4; CPG NE]).

4.Q7.4. Treatment of Hyperglycemia in Pregnancy

Abnormal glucose tolerance develops at higher rates and at younger ages among offspring of diabetic women. Maternal DM is one of the strongest risk factors for the development of T2DM among Pima Indian children (200 [EL 2; PCS], 201 [EL 3; CCS], 202 [EL 3; SS]). By the time these offspring themselves reach childbearing age, they are very likely to be obese and have DM, thereby perpetuating a vicious cycle (202 [EL 3; SS]). That this is not simply a genetic predisposition is inferred from the finding of lower rates of DM in offspring of women who were born before their mothers developed DM (203 [EL 3; SS])this is even true among sibling pairs whose birth dates straddle the onset of their mother's DM (200 [EL 2; PCS]) Thus, all women with DM in the childbearing years should have preconception care and guidance to bring their blood glucose concentrations to less than 100 mg/dL, which is on average, equivalent to a A1C level of less than 6.1% (204 [EL 4; CPG NE]). In T1DM, optimal care may necessitate CGM and CSII. The rapid-acting insulin analogues for pump therapy that have been studied in pregnancy include lispro and aspart (205 [EL 2; NRCT], 206 [EL 3; retrospective study SS], 207 [EL 3; retrospective study SS], 208 [EL 1; RCT]). The data that detemir is safe in pregnancy are convincing (209 [EL 3; SCR], 210 [EL 3; retrospective study SS]). However, even though glargine is widely used, there are still no conclusive reports on its safety. Although insulin is the preferred treatment approach, metformin and glyburide have been shown to be effective alternatives without adverse effects in some women. Metformin crosses the placenta and is classified as category B for pregnancy; sulfonylureas do not cross the placenta. Regardless, the optimal therapy for women with GDM or T2DM who are not able to maintain normoglycemia with a carbohydrate-restricted diet is insulin (204 [EL 4; CPG NE]).

The HAPO study (Hyperglycemia and Adverse Pregnancy Outcomes) (211 [EL 2; PCS]) confirmed findings in the Pima Indians (200 [EL 2; PCS]) that, even among offspring of women without GDM as it is currently defined (212 [EL 4; CPG NE], 213 [EL 4; consensus NE], 214 [EL 4; review NE], 215 [EL 3; PCS], 216 [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. The diabetic pregnancy and even maternal obesity itself (213 [EL 4; consensus NE]) set the stage for a vicious cycle with offspring of women with DM during pregnancy being more likely to become obese and to develop DM at younger ages (215 [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 the offspring. Low birth weight, as well as high birth weight, is associated with higher rates of DM (216 [EL 3; SS]). Abnormal birth weight not only directly affects the offspring, but leads to higher rates of GDM eventually in the offspring, thereby adding to the vicious cycle. Early diagnosis and treatment, careful preparation of diabetic women for pregnancy, and meticulous control of glucose abnormalities throughout pregnancy are currently our best hope to break this cycle and prevent the myriad of problems (217 [EL 4; review NE]).

4.Q7.5. Treatment of Hyperglycemia in Hospitalized Patients

Patients with T2DM are hospitalized more frequently than patients without DM, and multiple hospitalizations are common among patients with DM (218 [EL 3; SS]). Hyperglycemia in hospitalized patients, with or without a previous diagnosis of DM, is associated with poor clinical outcomes. This topic has been reviewed in the recent AACE/American Diabetes Association Consensus Statement on Inpatient Hyperglycemia and the 2009 American Diabetes Association standards of medical care in DM (4 [EL 4; consensus NE], 204 [EL 4; CPG NE]).

The management of hyperglycemia in the hospital setting presents multiple challenges including variations in the patient's nutritional status and altered level of consciousness and monitoring limitations of glycemia. Given the paramount importance of patient safety, reasonable glucose targets in the hospital setting should be set at modestly higher levels than in patients with DM in the outpatient setting. For most patients, a glucose concentration range of 140 to 180 mg/dL (7.8 to 10 mmol/L) has been recommended, provided these targets can be safely achieved. More stringent targets may be appropriate in stable patients with previous tight glycemic control. Less stringent targets may be appropriate in terminally ill patients or in patients who have extensive comorbidities (4 [EL 4; consensus NE]). Both overtreatment and undertreatment of hyperglycemia should be avoided.

Insulin therapy is the preferred method of glycemic control in most hospitalized patients because of its rapid

half-life, its powerful glucose-lowering ability, and the ease by which it can be titrated to adjust to the changing medical status of hospitalized patients. In the intensive care units, intravenous infusion of insulin is the preferred route of administration. Outside of critical care units, subcutaneous insulin administration is a more common method of insulin delivery. Scheduled subcutaneous insulin should consist of basal, nutritional, and correction components (with the latter 2 being administered before meals). Prolonged use of sliding scale insulin as the sole method of glucose control is discouraged (4 [EL 4; consensus NE], 204 [EL 4; CPG NE], 219 [EL 4; review NE])

Each of the major classes of noninsulin glucose-lowering drugs has substantial limitations for inpatient use and thus, they are generally not recommended. These agents provide little flexibility or opportunity for titration in a setting where acute changes in patient status often demand such action. Despite the shortcomings for use of these agents in the inpatient setting, for patients whose glycemia was well controlled on oral agents before admission, transition to oral agents in the day or two before discharge is often necessary.

4.Q8. 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 or exercise) or medication dose (most often insulin), or 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-day 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 cell (120 days), but it should be appreciated that 50% of A1C is determined by glycemia during the 1 month preceding measurement. Currently, 99% of laboratories in the United States use standardized and certified assay traced to the DCCT (Diabetes Control and Complications Trial). 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 (eg, hemolysis, splenomegaly, or use of epoetin alfa), alterations in the hemoglobin molecule (hemoglobinopathies), iron status, or recent blood transfusion (17).

Glucose meters for use by patients in the home are fast (5 seconds), require small amounts of blood (generally less than 5 μL), and are reasonably accurate. As of this writing, the international standard for accuracy (ISO 15197) is that 95% of the time, patient-based glucose meters need to have accuracy of ±20% for plasma glucose readings above 75 mg/dL and ±15% for plasma glucose readings below 75 mg/dL. Each of the meter chemistries has its own set of interferences, the one with the most recent attention being glucose dehydrogenase pyrroloquinoline quinone chemistry that can result in a maltose interference with glucose, causing falsely high glucose readings (220 [EL 4; opinion NE]). The FDA has asked the manufacturers of these strips to use different chemistries. SMBG has not been studied on its own, but rather as one component of a comprehensive treatment strategy (66 [EL 1; RCT]). SMBG frequency (in a retrospective analysis) has been shown to be predictive of A1C levels (221 [EL 3; SS]). Patient adherence is the greatest predictor of success. When used appropriately, CGM can lower A1C and reduce hypoglycemic exposure (222 [EL 1; RCT], 223 [EL 1; RCT]). CGM currently uses interstitial fluid glucose as an alternative to plasma glucose. All 3 systems currently approved use of glucose oxidase embedded on the sensor. With today's technology, there is usually a 7- to 15-minute "lag time" between the plasma and interstitial glucose, and then receiver display. Accuracy of the current generation of CGM devices is not yet deemed sufficient by the FDA to recommend them for routine use.

4.Q9. How Should Hypoglycemia Be Prevented, Identified, and Managed in Patients With DM?

Hypoglycemia in DM is defined as low glucose levels, accompanied by typical symptoms of hypoglycemia, that are relieved by the ingestion of glucose (Whipple triad) (224 [EL 4; review NE]). For patients with T2DM, hypoglycemia is typically recognized in association with use of insulin and sulfonylureas. Hypoglycemia can be a difficult condition to quantitatively measure because there is no consensus as to what constitutes low plasma glucose levels. Although symptoms of severe hypoglycemia are generally recognizable, mild-to-moderate hypoglycemia may remain asymptomatic and unreported in patients with T2DM. Asymptomatic hypoglycemia may also be prevalent and can reduce awareness of subsequent hypoglycemia by causing autonomic failure, subsequently causing a cycle of recurrent hypoglycemia. Hypoglycemia triggers hunger and may lead to undesireable weight gain. Certain hypoglycemia-related responses (psychomotor function) are altered in elderly patients compared with younger patients. Hypoglycemia is associated with more short-term disability and higher health care costs. Hypoglycemia manifests

as neurogenic and/or neuroglycopenic symptoms. The risk of hypoglycemia in patients with T2DM is related to the duration of disease. Certain populations may have reduced awareness and response to hypoglycemia. Severe and prolonged hypoglycemia may be associated with severe consequences such as seizure, coma, ECG abnormalities, and arrhythmia.

The risk of hypoglycemia is greater in older patients, those with longer DM duration, and those with lesser insulin reserve and perhaps the drive for strict glycemic control (225 [EL 4; NE]). Hypoglycemia is the rate-limiting factor in glycemic management. Therapeutic agents such as exogenous insulin, sulfonylureas (especially glyburide) (226 [EL 1; MRCT]), and glinides may induce hypoglycemia in T2DM, which may be mild, moderate, or severe. In severe cases, hypoglycemia is associated with neuroglycopenic symptoms, which could lead to coma, and, possibly, sudden death (60 [EL 1; RCT]).

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) (227 [EL 4; review NE]). Hypoglycemic unawareness is especially prominent in patients who have marked swings in glucose levels and can be reversed by a period of intensive therapy that dampens glycemic excursions (228 [EL 3; SCR], 229 [EL 2; NRCT]). Hyperinsulinemia, increased alcohol intake, starvation, and organ failure may be aggravating factors for hypoglycemia.

Normal plasma glucose concentrations are above 65 mg/dL. In general, symptoms of hypoglycemia occur when the plasma glucose levels fall to 60 mg/dL. Symptoms can occur with normal glucose levels in a patient who has very high glucose levels that drop quickly. SMBG can be helpful, but not necessarily diagnostic because of glucose meter inaccuracy.

Hypoglycemia is an important consideration in the treatment strategy for T1DM and T2DM. It remains a significant barrier in terms of treatment adherence and achievement of glycemic goals.

In adults with T2DM, treatment strategies should avoid therapeutic agents that can produce severe hypoglycemia. Many classes of pharmaceutical agents, used alone or in combination, are not associated with severe hypoglycemia and are reviewed in the AACE algorithm for T2DM (3 [EL 4; position NE]).

4.Q10. How Should Microvascular and Neuropathic Disease Be Prevented, Diagnosed, and Treated in Patients With DM?

4.Q10.1. Diabetic Nephropathy

Microalbuminuria (defined as excretion of 30 to 299 mg of albumin per day or an albumin-to-creatinine ratio of 30 to 299 mg/g in a random urine specimen) precedes albuminuria (defined as the excretion of 300 mg/24 h or more of albumin or an albumin-to-creatinine ratio of 300 mg/g or higher in a random urine specimen) by several years in both T1DM and T2DM. Microalbuminuria develops between approximately 5 and 15 years after the onset of DM, and it progresses to albuminuria over ~10 years (230 [EL 4; review NE]). Microalbuminuria may be the earliest clinical manifestation of diabetic nephropathy in persons with T1DM, and it may appear within 5 years of diagnosis. In comparison, microalbuminuria is often present at diagnosis in persons with T2DM and may reflect underlying cardiovascular disease. In addition to its relation to renal disease, microalbuminuria is an important risk factor for CVD and early cardiovascular mortality in patients with and without DM and/or hypertension. Once albuminuria develops, progression to end-stage kidney disease occurs rapidly over ~5 years. Annual screening for microalbuminuria should be performed from the outset in patients with T2DM and beginning at puberty or 5 years after diagnosis in patients with T1DM. Measurement of the albumin-to-creatinine ratio (normal <30 mg albumin/g creatinine) in a random urine sample is acceptable for screening and obviates the need for the more cumbersome 24-hour or timed urine collections (231 [EL 4; CPG NE]). Screening with a spot urine albumin level, if assessed by immunoassay or dipstick without the simultaneous measurement of urine creatinine, is suboptimal and fraught with errors. Albumin excretion can be increased by exercise, febrile illness, urinary tract infection, hematuria, severe hypertension, heart failure, and even high-grade hyperglycemia. Therefore, it is prudent to confirm albuminuria status with repeated testing before establishing a firm basis for therapeutic intervention for diabetic nephropathy.

The National Kidney Foundation classification is based on GFR and the presence of kidney damage, as evidenced by abnormalities on pathologic, urine, blood, or imaging tests. The National Kidney Foundation classification differs from that based on albuminuria (232 [EL 4; review NE]). The GFR (mL/min per 1.73 m^2 body surface area)-based classification is as follows:

Stage	Description
Stage 1	Kidney damage with normal or increased GFR >90 mL/min
Stage 2	Kidney damage with mildly decreased GFR 60-89 mL/min
Stage 3	Moderately decreased GFR 30-59 mL/min
Stage 4	Severely decreased GFR 15-29 mL/min
Stage 5	Kidney failure, GFR <15 mL/min or dialysis (231 [EL 4; CPG NE])

The finding that GFR may decline in adult patients with T2DM without concurrent increase in albumin excretion

(233 [EL 3; CSS]) provides strong rationale for the use of GFR in screening for nephropathy. The GFR can be estimated from the measured serum creatinine level, using one of the standard formulas such as that from the Modification of Diet in Renal Disease (234 [EL 3; SS]). Thus, serum creatinine levels should be obtained and used for calculating the estimated GFR, at least annually, in all adults with DM, including those without evidence of albuminuria. Many laboratories now routinely report the estimated GFR, and the National Institutes of Health also has GFR calculators (http://www.nkdep.nih.gov).

Prevention of the development or progression of diabetic nephropathy includes optimal control of plasma glucose (A1C goal <7%) and blood pressure (blood pressure <130/80 mm Hg), inhibition of the renin-angiotensin-aldosterone system, and modification of other risk factors such as smoking and hyperlipidemia. Antihypertensive drugs that block the renin-angiotensin-aldosterone system provide adjunctive nephroprotective benefits besides their blood pressure–lowering effects. This property has been demonstrated for the angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in patients with T1DM and T2DM. In MICRO-HOPE (substudy of the Heart Outcomes Prevention Evaluation study), ramipril treatment resulted in a significant 24% reduction in the risk of progression from microalbuminuria to overt nephropathy (235 [EL 1; RCT]). Improved survival has also been demonstrated after renin-angiotensin-aldosterone system blockade in patients with DM (236 [EL 2; PCS]). In selected cases (such as patients with massive proteinuria), combination therapy with an angiotensin-converting enzyme inhibitor and an angiotensin II receptor blocker may produce additive effects on blood pressure control and reduction of albuminuria. Aliskiren, an orally active direct renin inhibitor, may have a role as part of combination therapy in patients with DM and persistent albuminuria, despite treatment with an angiotensin inhibitor (237 [EL 4; review NE], 238 [EL 4; review], 239 [EL 1; RCT], 240 [EL 1; RCT], 241 [EL 1; RCT]).

There are no randomized prospective studies to inform best practices on how often to measure albumin excretion during renin-angiotensin-aldosterone system–blocking therapy in patients with microalbuminuria. Follow-up data can help direct drug titration in patients with persistent microalbuminuria, as there is some suggestion that normalization (or near-normalization) of albumin excretion may decrease the risks of progressive nephropathy and CVD (235 [EL 1; RCT], 242 [EL 1; RCT]).

If the GFR continues to decrease despite excellent glycemic and blood pressure control, protein restriction may be of some benefit. The consensus recommendation is to prescribe a protein intake of approximately the adult recommended dietary allowance of 0.8 g/kg per day (approximately 10% of daily calories) in the patient with nephropathy. However, once the GFR begins to fall, further restriction to 0.6 g/kg per day may be beneficial in slowing the decline of GFR in selected patients (243 [EL 2; MNRCT]).

Referral to a nephrologist for the establishment of a firm diagnosis is indicated when the diagnosis of diabetic nephropathy is in doubt (eg, patients with nonclassic presentation, suspected IgA nephropathy, rapidly worsening nephropathy, active urinary sediment). Patients with advanced or severe kidney disease also should be cared for in consultation with a nephrologist. The timing of the referral to a nephrologist varies with the experience and comfort level of the DM caregiver in the management of kidney disease. The DM caregiver must be adept at delivering optimal management of risk factors for worsening nephropathy, such as hyperglycemia, hypertension, and dyslipidemia, to delay the progression of nephropathy for as long as possible. However, evidence suggests that referral of patients with stage 4 chronic kidney disease to a nephrologist is cost-effective and delays the time to dialysis treatment (244 [EL 4; opinion NE]).

Patients with stage 5 CKD require renal replacement therapy, and mortality while taking such therapy is higher in patients with DM than in patients without DM, largely because of CVD complications (245 [EL 3; SS]). Renal transplantation is the preferred replacement therapy for patient with DM who have end-stage kidney disease because long-term outcomes are superior to those achieved with dialysis. For patients with T1DM, the possibility of combined kidney-pancreas transplantation allows for considerably better outcomes (246 [EL 2; PCS]).

4.Q10.2. Diabetic Retinopathy

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 T1DM develop background retinopathy after 7 years, and most have some form of retinopathy after 20 years (247 [EL 4; review NE]). Similarly, diabetic retinopathy develops in most patients with T2DM after several years of poor glycemic control.

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 annual dilated eye examination is recommended (248 [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, point-of-care screening for retinopathy (249 [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 (250 [EL 3; SS]). However, the system is still under development and does not replace the current recommendation for annual dilated eye examination. Patients with T2DM should be referred for annual dilated eye examination by an ophthalmologist from the time of diagnosis because of the lag between onset and diagnosis of T2DM (251 [EL 3; CSS]). However, because 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 T1DM (252 [EL 3; SS]). Because pregnancy is a risk factor for progression of retinopathy, ophthalmologic examinations should be performed repeatedly during pregnancy and for 1 year postpartum (253 [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 followed up less frequently.

Optimization of glucose and blood pressure are proven strategies for primary prevention of diabetic retinopathy (52 [EL 1; RCT], 66 [EL 1; RCT], 236 [EL 2; PCS], 254 [EL 2; PCS]). Good control of glycemia and blood pressure also are effective in slowing the progression of preexisting background retinopathy.

Panretinal scatter laser photocoagulation is the treatment of choice for high-risk proliferative retinopathy (255 [EL 4; review NE]). For macular edema, a more focused approach is used, guided by fluorescein angiography (256 [EL 1; RCT]). Vitrectomy is reserved for patients with persistent vitreous hemorrhage or significant vitreous scarring and debris (255 [EL 4; review NE]).

4.Q10.3. Diabetic Neuropathy

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 (eg, carpal tunnel syndrome, proximal lumbosacral, thoracic, and cervical radiculoplexus neuropathies involving the proximal limb girdle) (257 [EL 4; NE], 258 [EL 4; review NE], 259 [EL 4; position NE], 260 [EL 4; NE]). The latter, for the most part, are inflammatory demyelinating conditions requiring immunotherapy. 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 (261 [EL 3; CSS], 262 [EL 2; PCS], 263 [EL 2; PCS]) factors. They may also be atypical variants such as small-fiber neuropathies, which present predominantly with pain and autonomic features (257 [EL 4; NE], 264 [EL 3; CSS]). Risk factors include metabolic syndrome (265 [EL 3; CSS]), impaired fasting glucose, and impaired glucose tolerance (266 [EL 2; PCS], 267 [EL 3; retrospective chart review SS]).

The scope of diabetic neuropathy is reviewed elsewhere (268 [EL 4; review NE]). Prevalence rates of neuropathy in DM are between 5% and 100%, depending on diagnostic criteria used (269 [EL 3; CSS], 270 [EL 3; CSS]). There are important 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 (271 [EL 4; review NE], 272 [EL 4; review 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 (273 [EL 4; review NE]).

Once diabetic neuropathy has been diagnosed, therapy should be initiated to reduce symptoms and prevent further progression. It is vitally important to improve strength and balance in the patient with large-fiber neuropathy to reduce the fall and fracture risk (274 [EL 2; PCS], 275 [EL 1; RCT], 276 [EL 1; RCT]). Patients with DM who have large-fiber neuropathies are incoordinate and ataxic and are 17 times more likely to fall than their nonneuropathic counterparts (277 [EL 2; RCCS]). Low-impact activities that emphasize muscular strength and coordination, and challenge the vestibular system, such as Pilates, yoga, and Tai Chi may also be particularly helpful.

Small-nerve fiber dysfunction usually occurs early and is often present without objective signs or electrophysiologic evidence of nerve damage (278 [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 small-fiber neuropathy with a strong (Level A) recommendation (279 [EL 4; consensus NE]). Intraepidermal nerve fiber density correlates inversely with both cold and heat detection thresholds (280 [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, impaired glucose tolerance, and impaired fasting glucose, suggesting early damage to small nerve fibers (281 [EL 3; CSS], 282 [EL 3; CSS]). Intraepidermal nerve fiber density is reduced in painful neuropathy compared with that observed in painless neuropathy (283 [EL 3; SS]); diet and exercise intervention in impaired glucose tolerance lead to increased intraepidermal nerve fiber density (284 [EL 2; PCS]). These data suggest that intraepidermal nerve fiber loss is an early feature of metabolic syndrome, prediabetes, and established DM, and the loss progresses with increasing neuropathic severity. There may be nerve regeneration with treatment.

Strategies for management of small-fiber neuropathy 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 development (285 [EL 2; PCS]). Patients should inspect the plantar surface of their feet with a mirror on a daily basis. Patients should test the bathwater with a part of the body that is not insensate before plunging a numb foot into the water. 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 (259 [EL 4; position NE]), is "pain arising as a direct consequence of abnormalities in the peripheral somatosensory system in people with diabetes." In the diabetic population, it has been estimated that between 3% and 25% of persons might experience neuropathic pain (286 [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 (287 [EL 4; review]) with hyperalgesia. There is frequently allodynia on examination (286 [EL 4; review NE], 287 [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 (286 [EL 4; review NE]), and other causes of neuropathic pain must be excluded. Outcome measures to assess response to therapy in clinical practice should include patient-reported improvements in the measures and numeric rating scales (288 [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 (289 [EL 3; SS]).

Physicians must be able to differentiate painful diabetic neuropathy from other unrelated or coexisting conditions in patients who have DM. The most common of these are claudication, Morton's neuroma, Charcot neuroarthropathy, fasciitis, osteoarthritis, and radiculopathy. The algorithm provided (see Figure 2) distinguishes between the different conditions that can produce pain and provides recommendations for their management. Level 1 evidence exists to support the use of tricyclic antidepressants (eg, amitriptyline; tricyclic antidepressants), the anticonvulsants gabapentin and pregabalin, and the serotonin and norepinephrine reuptake inhibitor, duloxetine (290 [EL 1; MRCT], 291 [EL 1; MRCT]). Preliminary evidence shows promise for topical treatment using a 5% lignocaine plaster applied to the most painful area (292 [EL 1; RCT]), although larger RCTs are required.

Cardiovascular autonomic neuropathy is significantly associated with overall mortality (293 [EL 4; review NE], 294 [EL 2; MNRCT]) and in some studies, but not all, with morbidity, such as silent myocardial ischemia, coronary artery disease, stroke, diabetic nephropathy progression, and perioperative morbidity. Some pathogenetic mechanisms may link cardiovascular autonomic neuropathy to cardiovascular dysfunction and diabetic complications (293 [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 intensive pharmacotherapeutic and lifestyle management of comorbid conditions. More recently, it has been shown that cardiovascular autonomic neuropathy may be useful for prediction of cardiovascular risk, and a combination of cardiovascular autonomic neuropathy (295 [EL 3; SS]) and symptoms of peripheral neuropathy increase the odds ratio to 4.55 for CVD and mortality (296 [EL 4; review NE]). Indeed, this is the strongest predictor of CVD risk, far greater than blood pressure, lipoprotein profile, and even adenosine scans (297 [EL 4; NE]). The reported prevalence of diabetic autonomic neuropathy varies widely (7.7%-90%) depending on the cohort studied and the methods used for the diagnosis (298 [EL 4; review NE], 299 [EL 4; review NE]). The most common clinical features, diagnostic methods, and treatment options are presented in Table 11 (261 [EL 3; CSS]).

Cardiovascular reflex tests are the criterion standard in clinical autonomic testing (300 [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 maneuver must not be performed 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 (301 [EL 4; NE]).

Patients with DM and features of cardiac autonomic dysfunction, such as unexplained tachycardia, orthostatic hypotension, and poor exercise tolerance, or with other symptoms of autonomic dysfunction, should be evaluated for the presence of cardiovascular autonomic neuropathy.

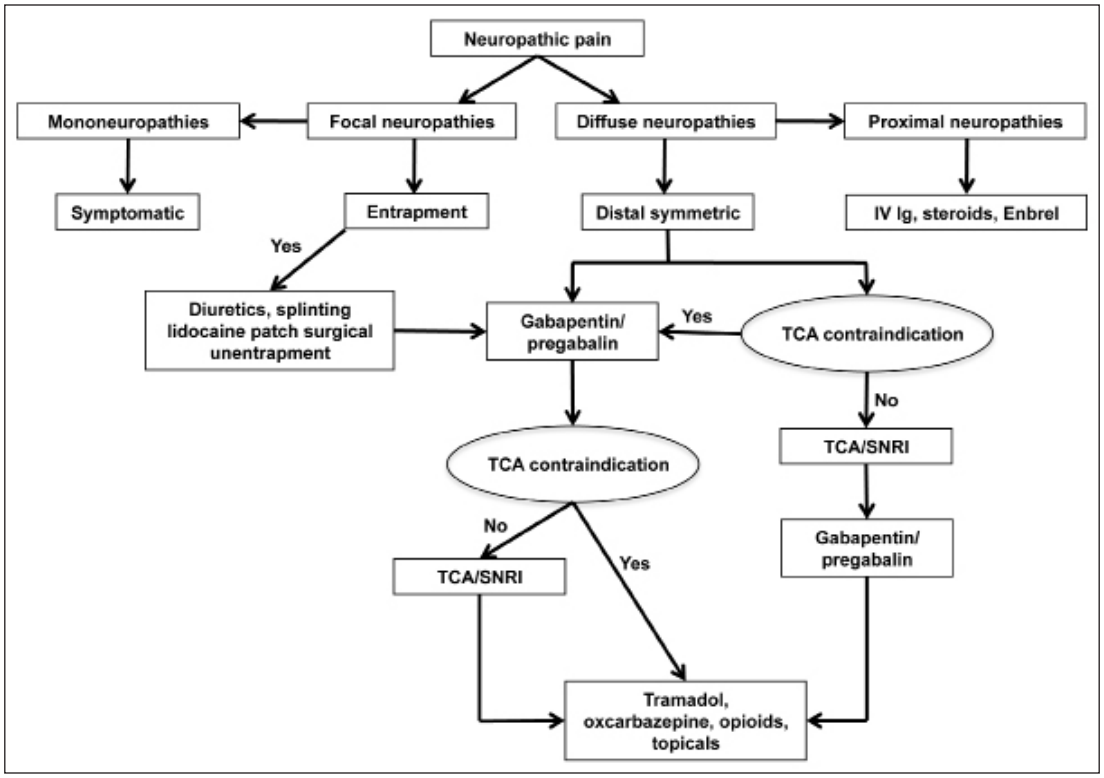

Fig. 2. Algorithm for treatment of neuropathic pain after exclusion of nondiabetic etiologies and stabilization of glycemic control (296 [EL 4; review NE]). IV Ig, intravenous immunoglobulin; TCA, tricyclic antidepressants; SNRI, serotonin-norepinephrine reuptake inhibitor.

Screening for cardiovascular autonomic neuropathy should be performed at diagnosis of T2DM and 5 years after the diagnosis of T1DM.

Retrospective and prospective studies have suggested a relationship between hyperglycemia and the development and severity of diabetic neuropathy and significant effects of intensive insulin treatment on prevention of neuropathy (302 [EL 4; review NE]). Treating oxidative stress may improve peripheral and autonomic neuropathy in adults with T2DM (303 [EL 1; RCT], 304 [EL 1; RCT], 305 [EL 1; RCT], 306 [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 (307 [EL 4; review NE], 308 [EL 1; RCT], 309 [EL 3; SS]). Fibrates and statins protect against peripheral nerve function decline in adults with T2DM (310 [EL 2; PCS], 311 [EL 2; PCS]). Older adults taking statins show a greater benefit than younger adults because of their higher attributable risk of CVD (312 [EL 4; review NE]).

Small studies in patients with DM found that aerobic exercise improved quantitative test results for peripheral nerve function and cardiac autonomic neuropathy (313 [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 (314 [EL 3; SS], 315 [EL 2; NRCT single-blinded]).

4.Q11. How Should Macrovascular Disease Be Prevented, Diagnosed, and Treated in Patients With Prediabetes or DM?

DM was usually, but now always, considered a CVD equivalent (316 [EL 1; MRCT]). 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 nondiabetic persons who had had a previous myocardial infarction at baseline and was almost 6-fold greater than the incidence of myocardial infarction in nondiabetic persons with no previous myocardial infarction at baseline (317 [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 nondiabetic persons who had had previous ischemic heart disease at baseline (318 [EL 3; SS]). A nationwide study of 3.3 million residents in Denmark followed-up for 5 years showed similar results (319 [EL 3; SS]).

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Table 11
Clinical Features, Diagnosis, and Treatment of Diabetic Autonomic Neuropathy (261 [EL 3; CSS])

Symptoms	Tests	Treatments
Cardiac		
Resting tachycardia, exercise intolerance	HRV, MUGA thallium scan, MIBG scan	Graded supervised exercise, angiotensin-converting enzyme inhibitors, β-adrenergic blockers
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, prokinetic agents (metoclopramide, domperidone, erythromycin)
Abdominal pain, early satiety, nausea, vomiting, bloating, belching	Endoscopy, manometry, electrogastrogram	Antibiotics, antiemetics, bulking agents, tricyclic antidepressants, pyloric Botox, gastric pacing
Constipation	Endoscopy	High-fiber diet, and 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, skin blood flow	Emollients and skin lubricants, scopolamine, glycopyrrolate, botulinum toxin, vasodilators
Pupillomotor and visceral dysfunction		
Vision blurring, impaired 1ight 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: H&P, history and physical; HRV, heart rate variability; MIBG, metaiodobenzylguanidine; MUGA, multigated radionuclide angiogram.

It is difficult to define quantitatively the factors responsible for DM being a CVD equivalent because insulin resistance, hypertension, lipid abnormalities, and procoagulant factors are all present in patients with T1DM and T2DM, as well as in those with hyperglycemia. Early epidemiologic studies indicated that the age-adjusted cardiovascular event rate for patients with DM was 2-fold greater than that of the nondiabetic individual at each identical level of systolic blood pressure from 105 to 195 mm Hg (320 [EL 4; review NE]). The 12-year follow-up of the MRFIT study (Multiple Risk Factor Intervention Trial) showed that at every level of total cholesterol, the rate of CVD-related death was 3-fold higher for patients with DM vs the rate in patients without DM (321 [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 (295 [EL 3; SS], 322 [EL 1; RCT]).

4.Q11.1. Glycemic Control

Hyperglycemia increases CVD both by its direct effects and indirectly by the effects of 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 (323 [EL 3; SS]); (324 [EL 2; PCS], 325 [EL 3; SS]). Intensive glycemic control reduces microvascular and macrovascular complications in patients with DM. The 2 large clinical trials of glycemic control in patients with diagnosed DM of only a few years' duration (DCCT [Diabetes Control and Complications Trial] and UKPDS [United Kingdom Prospective Diabetes Study]) both showed marked decreases in microvascular complications with intensive glycemic control compared with microvascular complications with ordinary glucose control (DCCT: 60%-70% [66 (EL 1; RCT)] and UKPDS: 25% reduction [(55 (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 (236 [EL 2; PCS], 326 [EL 1; RCT, questionnaires and other variables may have confounded]).

The beneficial effects of intensive glycemic control in reducing vascular complications are inversely related to the extent of vascular disease at the time it is initiated. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) (61 [EL 1; RCT]), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) (62 [EL 1; RCT]), and VADT (Veterans Affairs Diabetes Trial) (60 [EL 1; RCT]) trials investigated the effect of intensive glycemic control vs ordinary glycemic control on the development of new cardiovascular events in patients with T2DM and mean durations of diagnosed DM 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 a A1C level of 8% or less had a significant benefit from intensive glycemic control (327 [EL 1; RCT, posthoc analysis with other methodological limitations]). A subanalysis from the VADT trial indicated that patients who entered the trial with a duration of DM less than 15 years had a decrease in events with intensive glycemic control.

A randomized controlled substudy in the VADT trial investigated the utility of measuring coronary artery calcification in predicting subsequent clinical cardiovascular events (327 [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 (54 [EL 1; RCT, posttrial monitoring], 236 [EL 2; PCS], 326 [EL 1; RCT, questionnaires and other variables may have confoudned], 328 [EL 3; CSS]). In contrast, there is no such legacy effect of blood pressure control on cardiovascular risk (326 [EL 1; RCT, questionnaires and other variables may have confounded]).

4.Q11.2. 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 (7 [EL 1; MRCT but small sample sizes and event rates]). In patients with proven CVD, aspirin (75-162 mg daily) is generally indicated (7 [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.

The data from the many clinical trials and observational studies on the use of low-dose aspirin in the primary prevention of CVD in patients with DM continue to be controversial (322 [EL 1; RCT]). Several recent meta-analyses show no statistically significant benefit on either total cardiovascular outcomes or the individual events such as death, myocardial infarction, or stroke (8 [EL 1; MRCT]). An observational study in Chinese patients with T2DM reported that low-dosage aspirin was associated with a

paradoxical increase in CVD risk in primary prevention, and the risk of gastrointestinal bleeding was rather high (9 [EL 1; MRCT]). Occasional observational studies such as The Fremantle Diabetes Study report beneficial reduction in all-cause and CVD-related mortality with regular low-dosage aspirin use, particularly in men older than 65 years (10 [EL 2; PCS]). The controversial findings of the different studies may reflect the results of studies showing that patients with DM have an increased resistance to the effects of aspirin (329 [EL 1; MRCT]). This aspirin resistance has been linked in part to an effect of hyperglycemia (330 [EL 2; PCS]). Most studies (9 [EL 1; MRCT], 10 [EL 2; PCS], 329 [EL 1; MRCT]), but not all (330 [EL 2; PCS]), support the use of low-dosage aspirin in the secondary prevention of CVD in patients with DM.

4.Q11.3. Hypertension

At least 88% of persons with T2DM either have uncontrolled hypertension or are being treated for elevated blood pressure (331 [EL 3; SS]). Hypertension is not only more prevalent in persons with T2DM than in the general population, but it also predicts progression to DM. Once hypertension is diagnosed, an individual is 2.5 times more likely to receive a DM diagnosis within the next 5 years (332 [EL 2; PCS], 333 [EL 4; review NE]). The combination of hypertension and DM magnifies the risk of DM-related complications. Treatment of hypertension decreases both microvascular and macrovascular complications of DM (254 [EL 2; PCS]). The UKPDS found that with either an angiotensin-converting enzyme inhibitor (captopril) or a β-adrenergic blocker (atenolol), each 10 mm Hg decrease in systolic blood pressure 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 (52 [EL 1; RCT]).

Subsequent trials that have included large numbers of persons with DM, including the HOT trial (Hypertension Optimal Treatment) (334 [EL 1; RCT]), the HOPE study (Heart Outcomes Prevention Evaluation) (235 [EL 1; RCT]), the LIFE study (Losartan Intervention for Endpoint Reduction in Hypertension) (335 [EL 1; RCT]), and ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (336 [EL 1; RCT]), have demonstrated that blood pressure control improves cardiovascular outcomes when aggressive blood pressure targets are achieved. Numerous studies have also demonstrated a decrease in the progression of nephropathy and retinopathy. On the basis of these data, the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the American Diabetes Association, have recommended that blood pressure in DM be controlled to levels of 130/80 mm Hg (6 [EL 4; CPG NE], 337 [EL 4; NE]).

The target for blood pressure lowering remains somewhat controversial because the clinical trial data to support the level of 130/80 mm Hg are somewhat sparse. Epidemiologic data suggest that there is no evidence of a threshold for adverse outcomes, with a normal blood pressure level being below 115/75 mm Hg (338 [EL 4; review NE]). Clinical trial data show that intensifying therapy with blood pressure–lowering medications slows the progression of nephropathy and retinopathy (52 [EL 1; RCT], 254 [EL 2; PCS], 326 [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 less than 120 mm Hg, as compared with less than 140 mm Hg, reduces the standard composite outcome of fatal and nonfatal major cardiovascular events in persons with DM. Thus, there are no data from prospective RCTs that blood pressure targets below 130/80 mm Hg will affect cardiovascular outcomes. However, the data are clear that blood pressure lowering, once the diagnosis of hypertension is established, prevents microvascular and macrovascular complications associated with DM. While glucose and lipid management remain important, blood pressure lowering has the greatest and most immediate impact on morbidity and mortality (52 [EL 1; RCT], 326 [EL 1; RCT, questionnaires and other variables may have confounded]).

Accurate measurement of blood pressure remains fundamental to diagnosis and effective management of hypertension (6 [EL 4; CPG 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 provide 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 examination table), with feet on the floor, and arm supported at heart level. Caffeine, exercise, and smoking should be avoided for at least 30 minutes before 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.

Although 24-hour ambulatory blood pressure monitoring is not included as part of the diagnostic criteria for hypertension, it has become an important tool for guiding care of patients. Patients using ambulatory blood pressure monitoring whose 24-hour mean blood pressure values exceed 135/85 mm Hg are nearly twice as likely to have a cardiovascular event as those with 24-hour mean blood pressure values that remain below 135/85 mm Hg, irrespective of the level of the office blood pressure (339 [EL 4; review NE]). Routine use of ambulatory blood pressure

monitoring, 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.

The selection of medications can be guided by disease-specific considerations such as the presence of albuminuria, CVD, heart failure, postmyocardial infarction status, possible metabolic adverse effects, number of pills per day, adherence, and cost. Clinical trials with diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-adrenergic blockers, and calcium antagonists have a demonstrated benefit in the treatment of hypertension in both T1DM and T2DM (Table 12) (6 [EL 4; CPG NE], 235 [EL 1; RCT], 334 [EL 1; RCT], 335 [EL 1; RCT], 340 [EL 1; RCT, posthoc analysis]). The issue as to whether any one class is superior to another is no longer part of the decision-making process because most patients with DM need at least 2 to 4 drugs to achieve target blood pressure.

The UKPDS study group performed a 10-year posttrial monitoring observational study that demonstrated a loss of the benefit within 2 years if tight blood pressure control was not maintained (54 [EL1; RCT, posttrial monitoring]). 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 has facilitated patient adherence to 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 get to blood pressure goal while optimizing adherence to therapy. Ambulatory blood pressure monitoring should be used to guide blood pressure management because it allows assessment of a patient's blood pressure variability, thus facilitating medication adjustments to develop an appropriate personalized treatment regimen and avoid overtreatment.

4.Q11.3.1. Blood Pressure Management

Therapeutic recommendations for hypertension should include lifestyle modification to include the DASH diet (Dietary Approaches to Stop Hypertension) (341 [EL 1; RCT]), in particular reduced salt intake, increased physical activity, and, as needed, consultation with a registered dietician and/or CDE. Pharmacologic therapy is used to achieve targets unresponsive to therapeutic lifestyle changes alone. Hypertension is common in prediabetic states and, given the increased rates of CVD in prediabetes, should be managed as aggressively and with the same agents as in overt DM. Agents such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are preferred given their renal and/or CVD benefits. Other agents such as vasodilating β-adrenergic blockers, calcium channel blockers, diuretics, and centrally-acting agents should be used as necessary to achieve the same blood pressure targets as in overt DM (<130/80 mm Hg). Multiple agents may be necessary to achieve these targets (3 [EL 4; position NE]).

4.Q11.4. Dyslipidemia

In prediabetes and DM, there are multiple disturbances in lipoprotein metabolism resulting from various combinations of insulin deficiency, insulin resistance, and hyperglycemia. The dyslipidemia of T2DM is characterized by increased levels of triglyceride-rich lipoproteins

Table 12
Suggested Priority of Initiating Blood Pressure–Lowering Agents

Therapy	Reference (evidence level and study design)
Evidence based	
Renin-angiotensin-aldosterone system blockers (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker)	(235 [EL 1; RCT], 335 [EL 1; RCT])
Calcium channel blockers	(340 [EL 1; RCT, posthoc analysis])
Thiazide diuretic	(334 [EL 1; RCT])
β-Adrenergic blocker	(335 [EL 1; RCT])
Additional therapy	(6 [EL 4; CPG NE])
Aldosterone receptor blockers	
Direct renin inhibitor	
Selective α_1-adrenergic blockers	
Central α_2 agonists	
Direct vasodilators	

(very low-density lipoprotein, intermediate-density lipoprotein, and remnant particles), low levels of HDL-C, and increased levels of small, dense LDL-C particles (342 [EL 4; review NE]). Contributing to these quantitative and qualitative abnormalities are the suppressed activity of lipoprotein lipase, increased activity of hepatic lipase, and an enhanced activity of cholesterol-ester transfer protein, the latter being responsible for transfer of triglycerides and cholesterol esters from very low-density lipoprotein and intermediate-density lipoprotein to LDL-C and HDL-C particles. The hypertriglyceridemia is thus indirectly linked with changes in the HDL-C and LDL-C composition that are conducive to accelerated atherogenesis (343 [EL 4; review NE]).

4.Q11.4.1. Screening and Follow-Up (79 [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 profile should be repeated more frequently after initiation of treatment.
- If LDL-C is at goal, but triglyceride concentration is greater than 200 mg/dL, calculate non–HDL-C (total cholesterol – HDL-C), or check the apolipoprotein B level.
- Other tests of uncertain significance at diagnosis, but that may improve risk stratification in follow-up include C-reactive protein, lipoprotein(a), lipoprotein-associated phospholipase A_2, LDL particle number, and LDL size.

4.Q11.4.2. Therapeutic Recommendations

All patients should receive information about physical activity recommendations, a meal plan designed to improve glucose and lipids, and risk reduction strategies. Consultation with a CDE is desirable (79 [EL 4; CPG NE], 344 [EL 1; RCT]). In patients with CVD, a statin should be started along with therapeutic lifestyle changes if the LDL-C concentration is greater than 100 mg/dL (79 [EL 4; CPG NE], 345 [EL 1; MRCT]). Lipids should be rechecked within 6 to 8 weeks. If the LDL-C concentration remains greater than 70 mg/dL, then the statin dosage should be titrated with the goal of lowering the LDL-C to less than 70 mg/dL or by ~30% to 40% if the goal is not achieved by maximally tolerated statin therapy (79 [EL 4; CPG NE]). Alternatively, the combination of a statin with another lipid-lowering agent may be required to achieve this goal. In patients without known CVD, treatment should begin with therapeutic lifestyle changes for an initial 6- to 8-week trial. If the LDL-C is 100 mg/dL or greater, age is 40 years or older (346 [EL 1; RCT], 347 [EL 1; RCT]), or age is younger than 40 years and there are multiple risk factors (212 [EL 4; CPG NE], 344 [EL 1; RCT]), then statin therapy should be initiated with the goal of lowering LDL-C to less than 100 mg/dL or by ~30% to 40%. If the LDL-C concentration is less than 100 mg/dL, then consider statin therapy if age is older than 40 years and 1 more CVD risk factor is present (hypertension, smoking, albuminuria, or family history of premature CVD) (212 [EL 4; CPG NE], 344 [EL 1; RCT], 346 [EL 1; RCT], 347 [EL 1; RCT]). In patients with statin intolerance or unacceptable adverse events, a bile acid sequestrant (348 [EL 1; RCT]), niacin (349 [EL 1; RCT], 350 [EL 4; review NE], 351 [EL 1; RCT]), or cholesterol absorption inhibitor should be considered alone or in combination (352 [EL 1; RCT], 353 [EL 1; RCT]).

In patients with LDL-C at goal, but a fasting triglyceride concentration of 150 mg/dL or greater or low HDL-C (≤40 mg/dL in men, ≤50 mg/dL in women), the following actions should be implemented:

- Optimize glycemic control and emphasize weight loss (if indicated) (5 [EL 4; consensus], 344 [EL 1; RCT]).
- Modify any medications that may contribute to hypertriglyceridemia.
- In patients with fasting triglyceride concentrations of 200 to 499 mg/dL, calculate non–HDL-C (total cholesterol – HDL-C) and consider starting or titrating a statin if the non–HDL-C or apolipoprotein B is above goal (79 [EL 4; CPG NE], 80 [EL 3; SS], 354 [EL 2; PCS]).
- Consider adding fibrate or niacin if the fasting triglyceride concentration is greater than 200 mg/dL and/or HDL-C is low after the non–HDL-C or apolipoprotein B goal is achieved (355 [EL 4; consensus], 356 [EL 4; review NE], 357 [EL 3; SS], 358 [EL 1; RCT], 359 [EL 3; SS]).
- If the fasting triglyceride concentration is 500 mg/dL or greater, initiate treatment with very low-fat diet and initiate omega fatty acids and/or fibrates for prophylaxis against acute pancreatitis; rule out other secondary causes and reassess lipid status when the triglyceride concentration is less than 500 mg/dL (350 [EL 4; review NE]).
- If the fasting triglyceride concentration remains 500 mg/dL or greater after initiation of fibrates and/or niacin, consider the addition of fish oil (to provide 2-4 g of omega-3 fatty acids daily) (360 [EL 4; review NE]).

4.Q11.4.3. Lipid Management in Prediabetes

The primary goal should be to be to reduce the LDL-C concentration to less than 100 mg/dL for patients without CVD and to less than 70 mg/dL for patients with CVD (79 [EL 4; CPG NE]). High-potency statins, and possibly those combined with absorption inhibitors or bile acid–binding resins, are effective and preferred (79 [EL 4; CPG NE]). Modification of triglycerides with proliferator-activated receptor-α agonists,

such as fenofibrate, has failed to reduce CVD events in 2 separate trials (357 [EL 3; SS], 361 [EL 1; RCT]). However, at very high concentrations (>500 mg/dL), triglyceride reduction with fish oils and fibrates may be necessary to prevent pancreatitis. Use of gemfibrozil is discouraged owing to its interaction with statin clearance and risk for severe rhabdomyolysis. Low HDL-C is common in prediabetes. Nicotinic acid is effective in raising HDL-C, but it increases insulin resistance and may accelerate the appearance of overt DM. There are no randomized interventional trials of prediabetes with CVD events as outcome measures.

4.Q11.5. Asymptomatic Coronary Artery Disease

Although screening for asymptomatic coronary artery disease in patients with T2DM 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.

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 been supportive (322 [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 (327 [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.Q12. How Should Other Common Comorbidities of DM Be Addressed?

4.Q12.1. Sleep-Related Problems

Daytime drowsiness is the most obvious symptom of a sleep disorder and has been shown to cause an increased risk of accidents and increased errors in judgment and performance (362 [EL 3; SS]). Sleep deprivation raises the major risk factors for heart disease. Restless leg syndrome is increasingly being recognized as a medical cause of sleep disturbance, and medication can be quite successful in relieving it (363 [EL 3; CSS]). When sleep apnea 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, but many sleep disturbances can be diagnosed with home tests after a careful history and physical.

Sleep deprivation from any cause, and sleep apnea in particular, aggravates insulin resistance, hypertension, hyperglycemia, dyslipidemia, and inflammatory cytokines. Sleep apnea is especially common in adults with DM, occurring in approximately 2 of 3 of men with DM older than 65 years (364 [EL 4; review NE]).

Sleep apnea refers to numerous episodes during sleep where the individual stops breathing and is then awakened by the need for oxygen. The most common type of sleep apnea is obstructive sleep apnea caused by physical obstruction of the airway during sleep. Obstructive sleep apnea is more common in obese persons, in men, and in elderly persons (365 [EL 3; CSS], 366 [EL 3; CSS]). Treatment of obstructive sleep apnea in persons with DM can lower FPG, PPG, and A1C levels as much or more than any oral agents (367 [EL 3; CSS], 368 [EL 3; SS]). There is improvement in cardiovascular outcomes in patients with sleep apnea who are successfully treated compared with those who are not (369 [EL 2; PCS], 370 [EL 1; RCT single-blind], 371 [EL 1; RCT single-blind]). The usual treatment of obstructive sleep apnea is continuous positive airway pressure. Patients with newly diagnosed sleep apnea should persevere through the initial phase of continuous positive airway pressure therapy. When continuous positive airway pressure is successful, it can dramatically improve a person's quality of life (372 [EL 2; CPS]). Because of recent improvements in the technology, this treatment should be reevaluated for those patients in whom continuous positive airway pressure failed in the past. For certain subgroups with obstructive sleep apnea, surgery to widen the airway or devices that reposition the jaw may be appropriate.

4.Q12.2. Depression

Routine depression screening of 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 (373 [EL 1; meta-analysis]). Depression and DM also are associated with a significantly increased all-cause and CVD-related mortality rate (374 [EL 2; PCS]). Continuing use of antidepressant medication is associated with an increased relative risk of T2DM, although the elevation in absolute risk is modest (375 [EL 3; SS]).

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DISCLOSURE

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Dr. Yehuda Handelsman reports that he has received speakers' bureau honoraria from AstraZeneca, Bristol-Myers Squibb/AstraZeneca, Daiichi Sankyo, Inc, GlaxoSmithKline plc, Merck & Co, Inc, and Novartis AG; consultant honoraria from Bristol-Myers Squibb/AstraZeneca, Daiichi Sankyo, Inc, Gilead, Genentech, Inc, GlaxoSmithKline plc, Merck & Co, Inc, XOMA, Tethys Bioscience, Inc, and Tolerx, Inc; and research grant support from Daiichi Sankyo, Inc, GlaxoSmithKline plc, Novartis AG, NovoNordisk A/S, Takeda Pharmaceuticals North America, Inc, sanofi-aventis U.S., LLC, XOMA, and Tolerx, Inc.

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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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