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

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

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

# AACE TASK FORCE
# FOR DEVELOPING A DIABETES COMPREHENSIVE CARE PLAN
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**Abbreviations:**

**A1C** = hemoglobin A1c; **AACE** = American Association of Clinical Endocrinologists; **ACCORD** = Action to Control Cardiovascular Risk in Diabetes; **ACE** =

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

# 1. INTRODUCTION

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

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

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

The objectives of this CPG are to provide the following:

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

To achieve these goals, this CPG includes an executive summary consisting of 67 clinical practice recommendations organized within 24 questions covering the spectrum of DM management. The recommendations provide brief, accurate answers to each question, and an extensively referenced appendix organized according to the same list of questions provides supporting evidence for each recommendation. The format is concise and does not attempt to present an encyclopedic citation of all pertinent primary references, which would create redundancy and overlap with other published CPGs and evidence-based reports related to DM. Therefore, although many highest evidence level (EL) studies—consisting of randomized controlled trials (RCTs) and meta-analyses of these trials

(EL 1)—are cited in this CPG, in the interest of conciseness, there is also a deliberate, preferential, and frequent citation of derivative EL 4 publications that include many primary evidence citations (EL 1, EL 2, and EL 3). Thus, this CPG is not intended to serve as a DM textbook but rather to complement existing texts as well as other DM CPGs available in the literature including previously published AACE DM CPGs.

## 2. METHODS

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

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

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

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

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

## 3. EXECUTIVE SUMMARY

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

- Q1. How is diabetes screened and diagnosed?
- Q2. How is prediabetes managed?
- Q3. What are the glycemic treatment goals of DM?
- Q4. How are glycemic targets achieved for type 2 diabetes (T2D)?
- Q5. How should glycemia in type 1 diabetes (T1D) be managed?
- Q6. How is hypoglycemia managed?
- Q7. How is hypertension managed in patients with diabetes?
- Q8. How is dyslipidemia managed in patients with diabetes?
- Q9. How is nephropathy managed in patients with diabetes?
- Q10. How is retinopathy managed in patients with diabetes?

- Q11. How is neuropathy diagnosed and managed in patients with diabetes?
- Q12. How is CVD managed in patients with diabetes?
- Q13. How is obesity managed in patients with diabetes?
- Q14. What is the role of sleep medicine in the care of the patient with diabetes?
- Q15. How is diabetes managed in the hospital?
- Q16. How is a comprehensive diabetes care plan established in children and adolescents?
- Q17. How should diabetes in pregnancy be managed?
- Q18. When and how should glucose monitoring be used?
- Q19. When and how should insulin pump therapy be used?
- Q20. What is the imperative for education and team approach in DM management?
- Q21. Which vaccinations should be given to patients with diabetes?
- Q22. How should depression be managed in the context of diabetes?
- Q23. What is the association between diabetes and cancer?
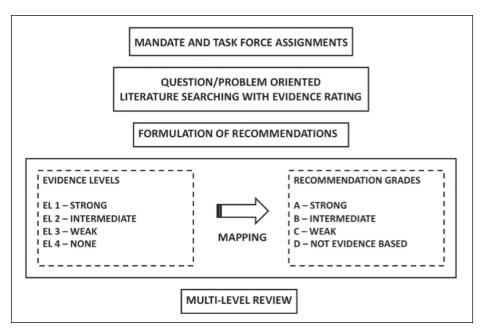- Q24. Which occupations have specific diabetes management requirements?



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

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

**3.Q1.    How is diabetes screened and diagnosed?**
- **R1.**  There is a continuum of risk for poor health outcomes in the progression from normal glucose tolerance to overt T2D. Screening should be considered in the presence of risk factors for DM (Table 5) (**Grade C; BEL 3**). Individuals at risk for DM whose glucose values are in the normal range should be screened every 3 years; clinicians may consider annual screening for patients with 2 or more risk factors (**Grade C; BEL 3**).
- **R2.**  The following criteria may be used to diagnose DM (Table 6) (**Grade B; BEL 3**):
  - FPG concentration (after 8 or more hours of no caloric intake) ≥126 mg/dL, *or*
  - Plasma glucose concentration ≥200 mg/dL 2 hours after ingesting a 75-g oral glucose load in the morning after an overnight fast of at least 8 hours, *or*
  - Symptoms of hyperglycemia (e.g., polyuria, polydipsia, polyphagia) and a random (casual, nonfasting) plasma glucose concentration ≥200 mg/dL, *or*
  - A1C level ≥6.5%

    Glucose criteria (i.e., FPG or 2-h glucose after a 75-g oral glucose load) are preferred for the diagnosis of DM. The same test—plasma glucose or A1C measurement—should be repeated on a different day to confirm the diagnosis of DM. However, a glucose level ≥200 mg/dL in the presence of DM symptoms does not need to be confirmed (**Grade B; BEL 3**).

- **R3.**  Prediabetes may be identified by the presence of impaired glucose tolerance (IGT), which is a plasma glucose value of 140 to 199 mg/dL 2 hours after ingesting 75 g of glucose, and/or impaired fasting glucose (IFG), which is a fasting glucose value of 100 to 125 mg/dL (Table 6) (**Grade B; BEL 2**). A1C values between 5.5 and 6.4% inclusive should be a signal to do more specific glucose testing (**Grade D; BEL 4**). For prediabetes, A1C testing should be used only as a screening tool; FPG measurement or an oral glucose tolerance test (OGTT) should be used for definitive diagnosis (**Grade B; BEL 2**). Metabolic syndrome based on National Cholesterol Education Program IV Adult Treatment Panel III criteria should be considered a prediabetes equivalent (**Grade C; BEL 3**).
- **R4.**  Pregnant females with DM risk factors should be screened at the first prenatal visit for undiagnosed T2D using standard criteria (**Grade D; BEL 4**). At 24 to 28 weeks' gestation, all pregnant subjects should be screened for gestational

| | |
|---|---|
| **Table 1** <br> **2010 American Association of Clinical Endocrinologists Protocol for** <br> **Production of Clinical Practice Guidelines—Step I: Evidence Rating[a]** | |
| **Numerical descriptor (evidence level)[b]** | **Semantic descriptor (reference methodology)** |
| 1 | Meta-analysis of randomized controlled trials (MRCT) |
| 1 | Randomized controlled trials (RCT) |
| 2 | Meta-analysis of nonrandomized prospective or case-controlled trials (MNRCT) |
| 2 | Nonrandomized controlled trial (NRCT) |
| 2 | Prospective cohort study (PCS) |
| 2 | Retrospective case-control study (RCCS) |
| 3 | Cross-sectional study (CSS) |
| 3 | Surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modeling of database) (SS) |
| 3 | Consecutive case series (CCS) |
| 3 | Single case reports (SCR) |
| 4 | No evidence (theory, opinion, consensus, review, or preclinical study) (NE) |

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

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

- **R5.** DM represents a group of heterogeneous metabolic disorders that develop when insulin secretion is insufficient to maintain normal plasma glucose levels. T2D is the most common form of DM, accounting for more than 90% of cases, and is typically identified in patients who are overweight or obese and/or have a family history of DM, a history of GDM, or meet the criteria for metabolic syndrome. Once DM glucose criteria have been satisfied, T2D should be diagnosed based on patient history, phenotype, and lack of autoantibodies characteristic of T1D (**Grade A; BEL 1**). Most persons with T2D have evidence of insulin resistance (such as elevated fasting or postprandial plasma insulin and/or elevated C-peptide concentrations), high triglycerides, and/or low high-density lipoprotein cholesterol [HDL-C]).

- **R6.** T1D is usually characterized by absolute insulin deficiency and should be confirmed by the presence of autoantibodies to glutamic acid decarboxylase, pancreatic islet β cells (tyrosine phosphatase IA-2), zinc transporter (ZnT8), and/or insulin (**Grade A; BEL 1).** Some forms of T1D have no evidence of autoimmunity and have been termed idiopathic. T1D can also occur in people who are overweight or obese. Therefore, documenting the levels of insulin and C-peptide and the presence or absence of immune markers in addition to the clinical presentation may

help establish the correct diagnosis to distinguish between T1D and T2D in children or adults and determine appropriate treatment (**Grade B; BEL 2**).

- **R7.** Any child or young adult with an atypical presentation, course, or response to therapy may be evaluated for monogenic DM (formerly maturity-onset diabetes of the young); diagnostic likelihood is strengthened by a family history over 3 generations, suggesting autosomal dominant inheritance (**Grade C; BEL 3**).

### 3.Q2. How is Prediabetes Managed?

- **R8.** T2D can be prevented or at least delayed by intervening in persons who have prediabetes (see Table 6 for glucose criteria) (**Grade A, BEL 1**). Frequent measurement of FPG and/or an OGTT may be used to assess the glycemic status of patients with prediabetes (**Grade C; BEL 3**). The clinician should manage CVD risk factors (especially elevated blood pressure and/or dyslipidemia) and excessive weight, and monitor these risks at regular intervals (**Grade C; BEL 3**).

- **R9.** Persons with prediabetes should modify their lifestyle, including initial attempts to lose 5 to 10% of body weight if overweight or obese and participate in moderate physical activity (e.g., walking) at least 150 minutes per week (**Grade B; BEL 3**). Physicians should recommend patients participate in organized lifestyle change programs with follow-up, where available, because behavioral support will benefit weight-loss efforts (**Grade B; BEL 3**).

- **R10.** In addition to lifestyle modification, medications including metformin, acarbose, or

| Table 2<br>2010 American Association of Clinical Endocrinologists Protocol for Production of<br>Clinical Practice Guidelines—Step II: Evidence Analysis and Subjective Factors[a] | | |
|---|---|---|
| **Study design** | **Data analysis** | **Interpretation of results** |
| Premise correctness | Intent-to-treat | Generalizability |
| Allocation concealment (randomization) | Appropriate statistics | Logical |
| Selection bias | | Incompleteness |
| Appropriate blinding | | Validity |
| Using surrogate end points (especially in "first-in-its-class" intervention) | | |
| Sample size (beta error) | | |
| Null hypothesis vs. Bayesian statistics | | |
| [a] Reprinted from (1): *Endocr Pract.* 2010;16:270-283. | | |

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

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

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

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

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

**3.Q3.1.  *Outpatient Glucose Targets for Nonpregnant Adults***
- **R11.** Glucose targets should be individualized and take into account life expectancy, disease duration, presence or absence of micro- and macrovascular complications, CVD risk factors, comorbid conditions, and risk for hypoglycemia, as well as the patient's psychological status (**Grade A; BEL 1**). In general, the goal of

therapy should be an A1C level ≤6.5% for most nonpregnant adults, if it can be achieved safely (Table 7) (**Grade D; BEL 4**). To achieve this target A1C level, FPG may need to be <110 mg/dL, and the 2-hour PPG may need to be <140 mg/dL (Table 7) (**Grade B, BEL 2**).

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

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

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

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

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

- **R13.** For females with GDM, the following glucose goals should be considered: preprandial glucose concentration ≤95 mg/dL and either a 1-hour postmeal glucose value ≤140 mg/dL or a 2-hour postmeal glucose value ≤120 mg/dL (**Grade D; BEL 4**). For females with pre-existing T1D or T2D who become pregnant, glucose should be controlled to meet the following goals (but only if they can be safely achieved): premeal, bedtime, and overnight glucose values between 60 and 99 mg/dL; a peak PPG value between 100 and 129 mg/dL; and an A1C value ≤6.0% (**Grade D; BEL 4**).

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

### 3.Q4.1. *Therapeutic Lifestyle Changes*

- **R14.** Medical nutrition therapy (MNT) is recommended for all people with prediabetes or DM, including T1D, T2D, GDM, and other less common forms of DM. MNT must be individualized, generally via evaluation and teaching by a trained nutritionist or registered dietitian or a physician knowledgeable in nutrition (**Grade D; BEL 4**). The goals of MNT are to improve overall health by teaching patients to eat a diet containing a variety of foods in appropriate amounts to help manage body weight, glucose, lipids, and blood

pressure (Table 8). Nutritional recommendations should take into account personal and cultural preferences, as well as the individual's knowledge of nutrition, willingness to change eating habits, and barriers to change. For people on insulin therapy, insulin dosage adjustments should match carbohydrate intake (e.g., with use of carbohydrate counting).

- **R15.** Patients should engage in at least 150 minutes per week of moderate-intensity exercise such as brisk walking (15- to 20-minute mile) or its equivalent (**Grade B; BEL 2**). Persons with T2D should also incorporate flexibility and strength-training exercises (**Grade B; BEL 2**). Patients must be evaluated initially for contraindications and/or limitations to physical activity, and then an exercise prescription should be developed for each patient according to both goals and activity limitations. Physical activity programs should begin slowly and build up gradually (**Grade D; BEL 4**). Patients with T1D should also exercise regularly; however, individuals requiring insulin therapy should be educated about the acute and chronic effects of exercise on blood glucose levels and learn how to adjust insulin dosages and food intake to maintain good glucose control before, during, and after exercise to avoid significant hypo- or hyperglycemia (**Grade D; BEL 4**).

### 3.Q4.2. *Antihyperglycemic Pharmacotherapy for T2D*

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

| Table 4 2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step IV: Examples of Qualifiers[a] |
| --- |
| Cost-effectiveness |
| Risk-benefit analysis |
| Evidence gaps |
| Alternative physician preferences (dissenting opinions) |
| Alternative recommendations ("cascades") |
| Resource availability |
| Cultural factors |
| Relevance (patient-oriented evidence that matters) |
| [a] Reprinted from (1): *Endocr Pract*. 2010;16:270-283. |

| Table 5 |
|---|
| **Risk Factors for Prediabetes and T2D: Criteria for Testing for Diabetes in Asymptomatic Adults** |
| Age ≥45 years without other risk factors |
| CVD or family history of T2D |
| Overweight or obese[a] |
| Sedentary lifestyle |
| Member of an at-risk racial or ethnic group: Asian, African American, Hispanic, Native American (Alaska Natives and American Indians), or Pacific Islander |
| HDL-C <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L) |
| IGT, IFG, and/or metabolic syndrome |
| PCOS, acanthosis nigricans, NAFLD |
| Hypertension (BP >140/90 mm Hg or on therapy for hypertension) |
| History of gestational diabetes or delivery of a baby weighing more than 4 kg (9 lb) |
| Antipsychotic therapy for schizophrenia and/or severe bipolar disease |
| Chronic glucocorticoid exposure |
| Sleep disorders in the presence of glucose intolerance (A1C >5.7%, IGT, or IFG on previous testing), including OSA, chronic sleep deprivation, and night-shift occupation |
| Abbreviations: A1C = hemoglobin A1C; BP = blood pressure; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NAFLD = nonalcoholic fatty liver disease; OSA = obstructive sleep apnea; PCOS = polycystic ovary syndrome.<br>[a] Testing should be considered in all adults who are obese (BMI ≥30 kg/m$^2$), and those who are overweight (BMI 25 to <30 kg/m$^2$) and have additional risk factors. At-risk BMI may be lower in some ethnic groups, in whom parameters such as waist circumference and other factors may be used. |

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

- **R17.** Details about the effects of and rationale for available antihyperglycemic agents can be found in the 2015 AACE Comprehensive Diabetes Management Algorithm Consensus Statement (4). The AACE recommends initiating therapy with metformin, a glucagon-like peptide 1 (GLP-1) receptor agonist, a dipeptidyl peptidase 4 (DPP-4) inhibitor, a sodium glucose cotransporter 2 (SGLT2) inhibitor, or an α-glucosidase inhibitor for patients with an entry A1C of <7.5% (**Grade C; BEL 3**). A TZD, sulfonylurea, or glinide may be considered as alternative therapies but should be used with caution due to side-effect profiles (**Grade C; BEL 3**). For patients with entry A1C levels >7.5%, the AACE recommends initiating treatment with metformin (unless contraindicated) plus a second agent, with preference given to

agents with a low potential for hypoglycemia that are weight neutral or associated with weight loss (**Grade C; BEL 3**). This includes GLP-1 receptor agonists, SGLT2 inhibitors, or DPP-4 inhibitors as the preferred second agents; TZDs and basal insulin may be considered as alternatives. Colesevelam, bromocriptine, or an α-glucosidase inhibitor have limited glucose-lowering potential but also carry a low risk of adverse effects and may be useful for glycemic control in some situations (**Grade C; BEL 3**). Sulfonylureas and glinides are considered the least desirable alternatives due to the risk of hypoglycemia (**Grade B; BEL 2**). For patients with an entry A1C >9.0% who have symptoms of hyperglycemia, insulin therapy alone or in combination with metformin or other oral agents is recommended (**Grade A; BEL 1**). Pramlintide and the GLP-1 receptor agonists can be used as adjuncts to prandial insulin therapy to reduce postprandial hyperglycemia, A1C, and weight (**Grade B; BEL 2**). The long-acting GLP-1 receptor agonists also reduce fasting glucose.

- **R18**. Insulin should be considered for T2D when noninsulin antihyperglycemic therapy

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

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

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

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

### 3.Q6.  How is Hypoglycemia Managed?

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

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**Table 6**
**Glucose Testing and Interpretation**

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

Abbreviations: A1C = hemoglobin A1C; FPG = fasting plasma glucose; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; PG = plasma glucose.
[a] A1C should be used only for screening prediabetes. The diagnosis of prediabetes, which may manifest as either IFG or IGT, should be confirmed with glucose testing.
[b] Glucose criteria are preferred for the diagnosis of DM. In all cases, the diagnosis should be confirmed on a separate day by repeating glucose or A1C testing. When A1C is used for diagnosis, follow-up glucose testing should be done when possible to help manage DM.

| Table 7 Comprehensive Diabetes Care Treatment Goals | | |
|---|---|---|
| **Parameter** | **Treatment goal** | **Reference (evidence level and study design)** |
| Glucose | | |
| A1C, % | Individualize on the basis of age, comorbidities, duration of disease; in general ≤6.5 for most; closer to normal for healthy; less stringent for "less healthy" | (4 [EL 4; NE]) |
| FPG, mg/dL | <110 | |
| 2-h PPG, mg/dL | <140 | |
| Inpatient hyperglycemia: glucose, mg/dL | 140-180 | (5 [EL 4; consensus NE]) |
| Blood pressure | Individualize on the basis of age, comorbidities, and duration of disease, with general target of: | (8 [EL 4; NE]) |
| Systolic, mm Hg | ~130 | |
| Diastolic, mm Hg | ~80 | |
| Lipids | | |
| LCL-C, mg/dL | <100, moderate risk <br> <70, high risk | (4 [EL 4; NE]) |
| Non-HDL-C, mg/dL | <130, moderate risk <br> <100, high risk | |
| Triglycerides, mg/dL | <150 | |
| TC/HDL-C ratio | <3.5, moderate risk <br> <3.0, high risk | |
| ApoB, mg/dL | <90, moderate risk <br> <80, high risk | |
| LDL particles | <1,200 moderate risk <br> <1,000 high risk | |
| Weight | | |
| Weight loss | Reduce weight by at least 5 to 10%; avoid weight gain | (4 [EL 4; NE]) |
| Anticoagulant therapy | | |
| Aspirin | For secondary CVD prevention or primary prevention for patients at very high risk[a] | (9 [EL 1; MRCT but small sample sizes and event rates]; 10 [EL 1; MRCT]; 11 [EL 1; MRCT]; 12 [EL 2; PCS]) |

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

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

| | Table 8 American Association of Clinical Endocrinologists Healthful Eating Recommendations for Patients With Diabetes Mellitus | |
|---|---|---|
| **Topic** | **Recommendation** | **Reference (evidence level and study design)** |
| General eating habits | Eat regular meals and snacks; avoid fasting to lose weight Consume plant-based diet (high in fiber, low calories/glycemic index, and high in phytochemicals/antioxidants) Understand Nutrition Facts Label information Incorporate beliefs and culture into discussions Use mild cooking techniques instead of high-heat cooking Keep physician-patient discussions informal | (71 [EL 3; SS]; 72 [EL 4; position NE]; 73 [EL 4; position NE]; 74 [EL 4; review NE]; 75 [EL 3; SS]; 76 [EL 1; RCT]; 86 [EL 3; SS]) |
| Carbohydrate | Explain the 3 types of carbohydrates—sugars, starch, and fiber—and the effects on health for each type Specify healthful carbohydrates (fresh fruits and vegetables, legumes, whole grains); target 7-10 servings per day Lower-glycemic index foods may facilitate glycemic control (glycemic index score <55 out of 100: multigrain bread, pumpernickel bread, whole oats, legumes, apple, lentils, chickpeas, mango, yams, brown rice), but there is insufficient evidence to support a formal recommendation to educate patients that sugars have both positive and negative health effects | (73 [EL 4; position NE]; 77 [EL 4; review NE]; 78 [EL 4; review NE]; 79 [EL 4; review NE]; 80 [EL 4; NE review]; 81 [EL 4; review NE]; 89 [EL 4; review NE]) |
| Fat | Specify healthful fats (low mercury/contaminant-containing nuts, avocado, certain plant oils, fish) Limit saturated fats (butter, fatty red meats, tropical plant oils, fast foods) and *trans* fat; choose fat-free or low-fat dairy products | (82 [EL 4; review NE]; 87 [EL 4; review NE]; 88 [EL 4; NE review]) |
| Protein | Consume protein in foods with low saturated fats (fish, egg whites, beans); there is no need to avoid animal protein Avoid or limit processed meats | (73 [EL 4; position NE]; 83 [EL 2; MNRCT]; 85 [EL 2; PCS, data may not be generalizable to patients with diabetes already]) |
| Micronutrients | Routine supplementation is not necessary; a healthful eating meal plan can generally provide sufficient micronutrients Specifically, chromium; vanadium; magnesium; vitamins A, C, and E; and CoQ10 are not recommended for glycemic control Vitamin supplements should be recommended to patients at risk of insufficiency or deficiency | (84 [EL 4; CPG NE]) |
| Abbreviations: BEL = best evidence level; CPG = clinical practice guideline; EL = evidence level; MNRCT = meta-analysis of non-randomized prospective or case-controlled trials; NE = no evidence (theory, opinion, consensus, review, or preclinical study); PCS = prospective cohort study; RCT = randomized controlled trial. | | |

**Table 9**
**Effects of Diabetes Drug Action[a]**

| | Met | GLP1RA | SGLT2I | DPP4I | TZD | AGI | Coles | BCR-QR | SU/Glinide | Insulin | Pram |
|---|---|---|---|---|---|---|---|---|---|---|---|
| FPG lowering | **Moderate** | **Mild to moderate**[b] | **Moderate** | Mild | **Moderate** | Neutral | Mild | Neutral | **SU: moderate** Glinide: mild | **Moderate to marked (basal insulin or premixed)** | Mild |
| PPG lowering | Mild | **Moderate to marked** | Mild | **Moderate** | Mild | **Moderate** | Mild | Mild | **Moderate** | **Moderate to marked (short/ rapid-acting insulin or premixed)** | **Moderate to marked** |
| NAFLD benefit | Mild | Mild | Neutral | Neutral | **Moderate** | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral |
| Hypoglycemia | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral | *SU: moderate to severe Glinide: mild to moderate* | *Moderate to severe, especially with short/rapid-acting or premixed* | Neutral |
| Weight | **Slight loss** | *Loss* | *Loss* | Neutral | *Gain* | Neutral | Neutral | Neutral | *Gain* | *Gain* | *Loss* |
| Renal impairment/ GU | *Contraindicated in stage 3B, 4, 5 CKD* | *Exenatide contraindicated CrCl <30 mg/ mL* | *GU infection risk* | Dose adjustment may be necessary (except linagliptin) | *May worsen fluid retention* | Neutral | Neutral | Neutral | *Increased hypoglycemia risk* | *Increased risks of hypoglycemia and fluid retention* | Neutral |
| GI adverse effects | *Moderate* | *Moderate (caution in PIs about pancreatitis)* | Neutral | Neutral *(caution in PIs about pancreatitis)* | Neutral | *Moderate* | Mild | *Moderate* | Neutral | Neutral | *Moderate* |
| CHF | Neutral | Neutral | Neutral | Neutral *(caution: possibly increased CHF hospitalization risk in CV safety trial)* | *Moderate* | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral |
| CVD | Possible benefit | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral | Safe | ? | Neutral | Neutral |
| Bone | Neutral | Neutral | *Bone loss* | Neutral | *Moderate bone loss* | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral |

Abbreviations: AGI = α-glucosidase inhibitors; BCR-QR = bromocriptine quick release; CHF = congestive heart failure; CKD = chronic kidney disease; Coles = colesevelam; CrCl = creatinine clearance; CV = cardiovascular; DPP4I = dipeptidyl peptidase 4 inhibitors; FPG = fasting plasma glucose; GI = gastrointestinal; GLP1RA = glucagon-like peptide 1 receptor agonists; GU = genitourinary; Met = metformin; NAFLD = nonalcoholic fatty liver disease; PI = prescribing information; PPG = postprandial glucose; SGLT2I = sodium-glucose cotransporter 2 inhibitors; SU = sulfonylureas; TZD = thiazolidinediones.
[a] Boldface type highlights a benefit or potential benefit; italic type highlights adverse effects.
[b] Mild: albiglutide and exenatide; moderate: dulaglutide, exenatide extended release, and liraglutide.

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

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

- **R22.** The blood pressure goal for persons with DM or prediabetes should be individualized and should generally be about 130/80 mm Hg (Table 7) (**Grade B; BEL 2**). A more intensive goal (e.g., <120/80 mm Hg) should be considered for some patients, provided this target can be reached safely without adverse effects from medication (**Grade C; BEL 3**). More relaxed goals may be considered for frail patients with complicated comorbidities or those who have adverse medication effects (**Grade D; BEL 4**).

- **R23.** Therapeutic lifestyle modification for hypertension should include dietary interventions that emphasize reduced salt intake such as DASH (Dietary Approaches to Stop Hypertension), physical activity, and, as needed, consultation with a registered dietitian and/or certified diabetes educator (CDE) (**Grade A; BEL 1**). Pharmacologic therapy should be used to achieve targets unresponsive to therapeutic lifestyle changes alone (**Grade A; BEL 1**). The clinician should select antihypertensive agents on the basis of their ability to reduce blood pressure and prevent or slow the progression of nephropathy and retinopathy; angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are preferred in patients with DM (**Grade C; BEL 3**). Combination therapy should be used when needed to achieve blood pressure targets, including calcium channel antagonists, diuretics, combined α/β-adrenergic blockers, and newer-generation β-adrenergic blockers in addition to agents that block the renin-angiotensin system (**Grade A; BEL 1**).

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

- **R24.** All patients with DM should be screened for dyslipidemia (**Grade B; BEL 2**). Therapeutic recommendations should include lifestyle changes and, as needed, consultation with a registered dietitian and/or CDE (**Grade B; BEL 2**).

- **R25.** Because macrovascular disease may be evident prior to the diagnosis of DM, lipid levels of patients with prediabetes should be managed in the same manner as those of patients with DM (**Grade D; BEL 4**).

- **R26.** In persons with DM or prediabetes and no atherosclerotic CVD (ASCVD) or major cardiovascular risk factors (i.e., moderate CVD risk), treatment efforts should target a low-density lipoprotein cholesterol (LDL-C) goal of <100 mg/dL and a non-HDL-C goal of <130 mg/dL (**Grade B; BEL 2**). In high-risk patients (those with DM and established ASCVD or at least 1 additional major ASCVD risk factor such as hypertension, family history, low HDL-C, or smoking), a statin should be started along with therapeutic lifestyle changes regardless of baseline LDL-C level (**Grade A; BEL 1**). In these patients, an LDL-C level <70 mg/dL and a non-HDL-C treatment goal <100 mg/dL should be targeted (Table 7) (**Grade B; BEL 2**). If the triglyceride concentration is ≥200 mg/dL, non-HDL-C may be used to predict ASCVD risk (**Grade C; BEL 3**). Secondary treatment goals may be considered, including apolipoprotein B (ApoB) <80 mg/dL and low-density lipoprotein particles (LDL-P) <1,000 nmol/L in patients with ASCVD or at least 1 major risk factor, and <90 mg/dL or <1,200 nmol/L in patients without ASCVD and no additional risk factors, respectively (**Grade D; BEL 4**).

- **R27.** Pharmacologic therapy should be used to achieve lipid targets unresponsive to therapeutic lifestyle changes alone (**Grade A; BEL 1**). Statins are the treatment of choice in the absence of contraindications. Statin dosage should always be adjusted to achieve LDL-C and non-HDL-C goals (Table 7) unless limited by adverse effects or intolerance (**Grade A; BEL 1**). Combining the statin with a bile acid sequestrant, niacin, and/or cholesterol absorption inhibitor should be considered when the desired target cannot be achieved with the statin alone; these agents may be used instead of statins in cases of statin-related adverse events or intolerance (**Grade C; BEL 3**). In patients who have LDL-C levels at goal but triglyceride concentrations ≥200 mg/dL and

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

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

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

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

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

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

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

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

**Fig. 2.** GFR and albuminuria grid illustrating the risk of progression by color intensity. The number in each box suggests the frequency of monitoring (number of times per year). Green indicates stable disease with annual follow-up measurements if CKD is present; yellow indicates caution and calls for ≥1 measurement per year; orange requires 2 measurements per year; red calls for 3 measurements per year, and deep red may require close monitoring at a frequency of 4 times or more per year (at least every 1-3 months). These general parameters are based on expert opinion and must take into account underlying comorbid conditions and disease state, as well as the likelihood of a change in management for any individual patient. *CKD* = chronic kidney disease; *GFR* = glomerular filtration rate. Frequency of recommendations from the KDIGO CKD Workgroup (263 [EL 4; NE]; 266 [EL 4; NE]). Modified and reprinted with permission from Macmillan Publishers Ltd: *Kidney International* 2011;80(1):17-28, copyright 2011.

- **R33.** Controlling glucose to individual target levels is recommended to prevent the onset of neuropathy (**Grade A; BEL 1**). Although nothing has been shown to reverse neuropathy once it is established, there is speculation that interventions that reduce oxidative stress, improve glycemic control, and/or improve dyslipidemia and hypertension might have a beneficial effect on established diabetic neuropathy.
- **R34.** Tricyclic antidepressants, anticonvulsants, and serotonin and norepinephrine reuptake inhibitors should be considered for the treatment of painful neuropathy (**Grade A; BEL 1**).
- **R35.** Large-fiber neuropathies should be managed with strength, gait, and balance training; pain management; orthotics to treat and prevent foot deformities; tendon lengthening for pes equinus from

Achilles tendon shortening; and/or surgical reconstruction and full-contact casting for foot ulcers, as needed (**Grade B; BEL 2**).
- **R36.** SFNs should be managed with foot protection (e.g., padded socks), supportive shoes with orthotics if necessary, regular foot and shoe inspection, prevention of heat injury, and use of emollient creams. For pain management, the medications mentioned in R34 should be considered (**Grade B; BEL 2**).

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

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

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

- **R38.** The use of low-dosage aspirin (75 to 162 mg daily) is recommended for secondary prevention of CVD (**Grade A; BEL 1**). Some patients may benefit from higher doses (**Grade B; BEL 2**). For primary prevention of CVD, aspirin use may be considered for those at high cardiovascular risk (10-year risk >10%) (**Grade D; BEL 4**).

- **R39.** Measurement of coronary artery calcification or coronary imaging may help assess whether a patient is a reasonable candidate for intensification of glycemic, lipid, and/or blood pressure control (**Grade B; BEL 2**). Screening for asymptomatic coronary artery disease with various stress tests in patients with T2D has not been clearly demonstrated to improve cardiac outcomes and is therefore not recommended (**Grade A; BEL 1**).

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

- **R40.** Obesity should be diagnosed according to body mass index (BMI) (**Grade B; BEL 2**). Individuals with a BMI $\geq$30 kg/m$^2$ are classified as obese, and those with a BMI of 25 to <30 kg/m$^2$ are overweight. For Southeast Asians and Asian Indians, lower BMI cutpoints may be appropriate. Measurement of waist circumference may be considered for individuals with a BMI between 25 and 35 kg/m$^2$ (**Grade D; BEL 4**). Those with waist circumference values >102 cm (40 in) for males and > 88 cm (35 in) for females are at higher risk for metabolic disease. In addition to these anthropometric measures, patients should be evaluated for obesity-related complications, including other components of metabolic syndrome, sleep apnea, and osteoarthritis to determine disease severity and facilitate obesity staging (**Grade D; BEL 4**).

- **R41.** Lifestyle modifications including behavioral changes, reduced calorie diets, and appropriately prescribed physical activity should be implemented as the cornerstone of obesity management (**Grade A; BEL 1**). Pharmacotherapy for weight loss may be considered when lifestyle modification fails to achieve the targeted goal (**Grade A; BEL 1**). Pharmacotherapy may be initiated at the same time as lifestyle modification in patients with BMIs of 27 to 29.9 kg/m$^2$ and $\geq$1 obesity-related complication such as T2D (**Grade D; BEL 4**). Pharmacotherapy and lifestyle modification may be initiated together in patients with BMI $\geq$30 kg/m$^2$ regardless of the presence of complications (**Grade D; BEL 4**). Bariatric surgery should be

considered in patients with severe obesity-related complications including T2D if the BMI is $\geq$35 kg/m$^2$ (**Grade B; BEL 2**). Patients with T2D who undergo malabsorptive procedures, such as Roux-en-Y gastric bypass or biliopancreatic diversion with duodenal switch, must have careful postoperative follow-up because of risks of micronutrient deficiencies and hypoglycemia (**Grade D; BEL 4**).

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

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

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

- **R43.** Insulin can rapidly control hyperglycemia and therefore should be used for the majority of hospitalized patients with hyperglycemia (**Grade A; BEL 1**). Intravenous insulin infusion should be used to treat persistent hyperglycemia among critically ill patients in the intensive care unit (ICU) (**Grade A; BEL 1**). Scheduled subcutaneous insulin therapy with basal, nutritional, and correctional components should be used for glycemic management in noncritically ill patients (**Grade A; BEL 1**). Insulin dosing should be synchronized with provision of meals or enteral or parenteral nutrition (**Grade A; BEL 1**). Exclusive use of "sliding scale" insulin should be discouraged (**Grade A; BEL 1**). Preference should be given to regular insulin for intravenous administration and insulin analogs for subcutaneous administration (**Grade D; BEL 4**).

- **R44.** All patients, independent of a prior diagnosis of DM, should have laboratory blood glucose testing upon hospital admission (**Grade C; BEL 3**). Patients with known history of DM should have their A1C measured in the hospital if this

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

- **R45.** A plan for preventing and treating hypoglycemia should be established for each patient, and hypoglycemic episodes should be documented in the medical record (**Grade C; BEL 3**).

- **R46.** Appropriate plans for follow-up and care should be documented at hospital discharge for inpatients with a prior history of DM as well as nondiabetic patients with hyperglycemia or increased A1C levels (**Grade D; BEL 4**). DM discharge planning should start soon after hospitalization, and clear DM management instructions should be provided at discharge (**Grade D; BEL 4**).

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

- **R47.** The pharmacologic treatment of any form of DM in children should not, at this stage of our knowledge, differ in substance from treatment for adults (**Grade D; BEL 4**), except in children younger than about 4 years, when bolus premeal insulin may be administered after rather than before a meal due to variable and inconsistent calorie/carbohydrate intake. In children or adolescents with T1D, MDI or CSII insulin regimens are preferred (**Grade C; BEL 3**). Injection frequencies may become problematic in some school settings. Higher insulin-to-carbohydrate ratios and basal insulin dosages may be needed during puberty (**Grade C; BEL 3**). Insulin requirements may be increased 20 to 50% during menstrual periods in pubescent girls (**Grade C; BEL 3**). In children or adolescents with T2D, diet and lifestyle modification should be implemented first (**Grade A; BEL 1**). Addition of metformin and/or insulin should be considered when glycemic targets are not achievable with lifestyle measures (**Grade B; BEL 2**). An extensive review of guidelines for the care of children with DM from the International Society of Pediatric and Adolescent

Diabetes was published in 2009 and is available on their website (13).

- **R48.** T1D in adolescents should be managed in close consultation with the patient and their family members. The ADA; Juvenile Diabetes Research Foundation (JDRF); and National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) offer resources to help with transition planning (14-16).

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

- **R49.** For females with GDM, glucose should be managed with the following treatment goals: preprandial glucose concentration ≤95 mg/dL and either a 1-hour postmeal glucose ≤140 mg/dL or a 2-hour postmeal glucose ≤120 mg/dL (**Grade C; BEL 3**).

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

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

- **R51.** A1C should be measured at least twice yearly in all patients with DM and at least 4 times yearly in patients not at target (**Grade D; BEL 4**).

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

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

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

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

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

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

- **R55.** An organized multidisciplinary team may best deliver care for patients with DM (**Grade D; BEL 4**). Members of such a team can include a primary care physician, endocrinologist, physician assistant, nurse practitioner, registered nurse, dietitian, exercise specialist, and mental health professional. The educational, social, and logistical elements of therapy and variations in successful care delivery associated with age and maturation increase the complexity of caring for children with DM.
- **R56.** Persons with DM should receive comprehensive diabetes self-management education (DSME) at the time of DM diagnosis and subsequently as appropriate (**Grade D; BEL 4**). DSME improves clinical outcomes and quality of life in individuals with DM by providing the knowledge and skills necessary for DM self-care. Therapeutic lifestyle management must be discussed with all patients with DM or prediabetes at the time of diagnosis and throughout their lifetime (**Grade D; BEL 4**). This includes MNT (with reduction and modification of caloric and fat intake to achieve weight loss in those who are overweight or obese), appropriately prescribed physical activity, avoidance of tobacco products, and adequate

sleep quantity and quality. Additional topics commonly taught in DSME programs outline principles of glycemia treatment options; blood glucose monitoring; insulin dosage adjustments; acute complications of DM; and prevention, recognition, and treatment of hypoglycemia.

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

- **R57.** AACE supports the recommendations of the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) that all patients with DM be vaccinated for influenza and pneumococcal infection. An annual influenza vaccine should be provided to those with DM who are ≥6 months old (**Grade C; BEL 3**). Furthermore, a pneumococcal polysaccharide vaccine should be administered to patients with DM age ≥2 years (**Grade C; BEL 3**). A single administration of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) should be administered to adults with DM age 19 to 64 years (**Grade C; BEL 3**). The 13-valent pneumococcal conjugate vaccine should be administered in series with the PPSV23 to all adults aged ≥65 years (**Grade C; BEL 3**). Revaccination is also indicated for those with nephrotic syndrome, chronic renal disease, and other immunocompromised states, such as posttransplantation.
- **R58.** Hepatitis B vaccinations should be administered to adults 20 to 59 years of age as soon after DM diagnosis as possible (**Grade C; BEL 3**). Vaccination of adults ≥60 years should be considered based on assessment of risk and likelihood of an adequate immune response (**Grade C; BEL 3**).
- **R59.** All children and adolescents with DM should receive routine childhood vaccinations according to the normal schedule (**Grade C; BEL 3**).
- **R60.** Tetanus-diphtheria-pertussis (Tdap) vaccine is typically included with routine childhood vaccinations. However, all adults with DM should receive a tetanus-diphtheria (Td) booster every 10 years (**Grade D; BEL 4**).
- **R61.** Patients with DM may need other vaccines to protect themselves against other illnesses. Healthcare professionals may consider vaccines for the following diseases based on individual needs of the patient: measles/mumps/rubella, varicella (chicken pox), and polio. In addition, patients traveling to other countries may require vaccines for endemic diseases (**Grade D; BEL 4**).

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

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

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

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

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

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

**4. APPENDIX: EVIDENCE BASE**

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

**4.Q1. How is Diabetes Screened and Diagnosed?**

*4.Q1.1. Diagnosis of DM*

DM refers to a group of metabolic disorders that result in hyperglycemia, regardless of the underlying etiology. DM is diagnosed by using any of 3 established criteria for elevated blood glucose concentrations (Table 6) (17 [EL 4; consensus NE]).

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

*4.Q1.2. Classification of DM*

DM is classified into T1D, T2D, GDM, monogenic DM, and other less common conditions such as chronic pancreatitis, pancreatic resection, or rare insulin resistance and mitochondrial syndromes. T1D accounts for <10% of all DM cases and occurs more commonly in children and young adults but can occur at any age. It is also more common in persons of European ancestry and is caused

by absolute insulin deficiency that usually results from an immune-mediated destruction of the pancreatic β cells. In a minority of patients with T1D, evidence for autoimmunity is lacking, and the etiology of islet destruction is unclear. Severe insulinopenia in T1D predisposes patients to diabetic ketoacidosis (DKA). However, DKA can also occur in patients with T2D (25 [El 4; NE]; 26 [EL 3; SS]).

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

### 4.Q2.  How is Prediabetes Managed?

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

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

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

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

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

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

#### 4.Q.3.1.  Outpatient Glucose Targets for Nonpregnant Adults

There is no dispute that elevated glucose levels are associated with micro- and macrovascular complications of DM. Similarly, it has been accepted that strategies aimed at lowering glucose concentrations can lead to lower rates of microvascular and perhaps macroangiopathic complications (47 [EL 1; RCT]; 48 [EL 3; SS]; 49 [EL 1; RCT,

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

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

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

No RCTs have yet established optimal glycemic targets. Professional organizations have relied on results from existing intervention trials achieving improved A1C levels and epidemiologic analyses of various studies to arrive at consensus statements or expert opinions regarding targets. Thus, some (4 [EL 4; NE]) have recommended a general target A1C level ≤6.5%, while others have recommended a general target of <7% (65 [EL 4; NE]; 66 [EL 4; CPG NE]). In all cases, the potential risks of intensive glycemic control may outweigh its benefits, especially in patients with frequent severe hypoglycemia, hypoglycemia unawareness, or a very long duration of DM, particularly in the presence of established and advanced atherosclerosis, advanced age, and terminal illness.

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

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

#### 4.Q4.1.  *Therapeutic Lifestyle Changes*
The components of therapeutic lifestyle changes include healthful eating, regular physical activity, sufficient sleep, avoidance of tobacco products, limited alcohol consumption, and stress reduction.

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

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

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

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

A review and position paper on MNT for both T1D and T2D was recently published (94 [EL 4; NE]). Key recommendations address the need for consistency in day-to-day carbohydrate intake, adjusting insulin doses to match carbohydrate intake (e.g., use of carbohydrate counting), limitation of sucrose-containing or high-glycemic index foods, adequate protein intake, "heart-healthy" diets, weight management, regular physical activity, and increased glucose monitoring. Data from the Look AHEAD (Action for Health in Diabetes) and DPP studies provide additional evidence that lowering caloric intake is the main driver for weight loss. The Look AHEAD trial

is the longest RCT to evaluate intensive lifestyle change on weight loss in patients with T2D (95 [EL 1; RCT, not blinded]). The maximal weight loss in patients with T2D in Look AHEAD was greater than among patients with prediabetes in the DPP. The magnitude of weight loss after 1 year in Look AHEAD was related to the frequency of using meal replacements, amount of physical activity performed, and attendance at behavioral sessions (96 [EL 1; RCT]). For a discussion of the Look AHEAD results, see section 4.Q13.4.

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

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

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

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

### 4.Q4.2. Antihyperglycemic Pharmacotherapy

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

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

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

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

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

to TZD-associated weight gain and peripheral edema. Because of this, TZDs are contraindicated in patients with New York Heart Association class 3 and 4 congestive heart failure. TZDs can also reduce bone mineralization and are associated with nonosteoporotic bone fractures (123 [EL 1; RCT, posthoc analysis]; 124 [EL 2; PCS]). The TZD rosiglitazone has been withdrawn from use in Europe and was severely restricted in the United States because of concerns over a possible increase in CVD risk (125 [EL 4; review NE]). The FDA recently lifted this restriction (126 [EL 4; NE]). According to the FDA, pioglitazone, but not rosiglitazone, may be associated with increased rates of bladder cancer, although there is not enough evidence to support a clear association (127 [EL 4; NE]). A recent cumulative exposure analysis involving data from 1.01 million persons from multiple countries over 5.9 million person-years found no association between exposure to pioglitazone and bladder cancer (128 [EL 3; SS]).

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

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

| Table 10 Pharmacologic Agents for T2D Treatment[a] | | |
|---|---|---|
| **Monotherapy** | **Dual therapy** | **Triple therapy** |
| | Metformin (or other first-line agent) plus | First- and second-line agent plus |
| **Metformin** | **GLP1RA** | **GLP1RA** |
| **GLP1RA** | **SGLT2I** | **SGLT2I** |
| **SGLT2I** | **DPP4I** | TZD[b] |
| **DPP4I** | TZD[b] | Basal insulin[b] |
| **AGI** | Basal insulin[b] | **DPP4I** |
| TZD[b] | **Colesevelam** | **Colesevelam** |
| SU/glinide[b] | **BCR-QR** | **BCR-QR** |
| | **AGI** | **AGI** |
| | SU/glinide[b] | SU/glinide[b] |

Abbreviations: A1C = hemoglobin A1C; AGI = α-glucosidase inhibitors; BCR-QR = bromocriptine quick release; DPP4I = dipeptidyl peptidase 4 inhibitors; GLP1RA = glucagon-like peptide 1 receptor agonists; SGLT2I = sodium-glucose cotransporter 2 inhibitors; SU = sulfonylureas; TZD = thiazolidinediones.
[a] Intensify therapy whenever A1C exceeds individualized target. Boldface denotes little or no risk of hypoglycemia or weight gain, few adverse events, and/or the possibility of benefits beyond glucose lowering.
[b] Use with caution.

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

DPP-4 inhibitors do not cause weight gain; they can be administered in patients with CKD at full dosage when not cleared by the kidneys (linagliptin) or with appropriate dose adjustment for agents that are renally cleared (sitagliptin, saxagliptin, alogliptin); they lack significant GI adverse effects (143 [EL 4; opinion NE]); and they have been associated with reduction in cardiovascular events in analyses of registration trials (144 [EL 1; MRCT]), although neither benefit nor harm was seen in cardiovascular outcome studies conducted in subjects with advanced CVD in placebo-controlled, randomized studies with alogliptin or saxagliptin (145 [EL 1; RCT]; 146 [EL 1; RCT]). The trial comparing saxagliptin with placebo showed an increased likelihood of hospitalization for congestive heart failure and an increase in hypoglycemia (146 [EL 1; RCT]); this should lead to caution in the use of this agent in persons with a history of heart failure who also have existing CVD. With regard to hypoglycemia, it should be noted that approximately  40% of the patients receiving saxagliptin in the trial also received a sulfonylurea, a combination that increases the likelihood of hypoglycemia. The main adverse effects noted with DPP-4 inhibitors are a small increase in upper respiratory tract viral infections (rates of nasopharyngitis were 6.4% with a DPP-4 inhibitor versus 6.1% with comparators; risk ratio, 1.2; 95% confidence interval [CI] 1.0 to 1.4) and a rare hypersensitivity reaction (141 [EL 1; MNCT]).

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

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

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

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

Because many patients do not achieve adequate glycemic control with monotherapy, combining antihyperglycemic agents is often appropriate (4 [EL 4; NE]). Metformin is quite effective when administered in combination with the other agents, as long as one avoids its use in patients with CKD (creatinine ≥1.4 mg/dL in females or ≥1.5 mg/dL in males) (4 [EL 4; NE]) or GI intolerance. Sulfonylureas, in contrast, are problematic when used in combinations because they can cause hypoglycemia and may reduce, eliminate, or minimize the weight-loss benefit of drugs such as metformin, GLP-1 receptor agonists, and SGLT2 inhibitors (122 [EL 2; MNRCT]).

### 4.Q4.2.1.  Insulin Use in T2D

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

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

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

| Glucose Value | Total Daily Dose | Notes/Caveats |
|---|---|---|
| **Step 1. Start basal (long-acting insulin)** | | Consider discontinuing SU therapy Basal analogs preferred over NPH |
| A1C <8% | 0.1-0.2 units/kg | |
| A1C >8% | 0.2-0.3 units/kg | |
| **Step 2. Titrate insulin every 2-3 days to reach glycemic goals[a]** | | |
| Fixed regimen | Increase by 2 units/day | |
| Adjustable regimen | | |
|     FBG >180 mg/dL | Add 4 units | |
|     FBG 140-180 mg/dL | Add 2 units | |
|     FBG 110-139 mg/dL | Add 1 unit | |
| **Step 3. Monitor for hypoglycemia** | | |
| BG <70 mg/dL | Reduce by 10 to 20% | |
| BG <40 mg/dL | Reduce by 20 to 40% | |

Abbreviations: A1C = hemoglobin A1C; BG = blood glucose; FBG = fasting blood glucose; NPH = neutral protamine Hagedorn; SU = sulfonylureas.
[a] For most patients with T2D taking insulin, glucose goals are A1C <7% and fasting and premeal blood glucose <110 mg/dL in the absence of hypoglycemia. A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk.

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

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

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

When mealtime glucose control is needed or when glycemic goals are not met on a basal insulin regimen plus oral agents or a GLP-1 receptor agonist, insulin therapy intensification to a basal-bolus regimen (using a rapid-acting insulin analog or inhaled insulin) should be considered (Table 12).

Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with T2D (157 [EL 1; RCT, small sample size]; 158 [EL 1; RCT, not blinded]). The incretins (GLP-1 receptor agonists and DDP-4 inhibitors) have properties similar to those of pramlintide and also increase endogenous insulin

secretion. The combination of basal insulin and incretin therapy decreases basal glucose and PPG and may minimize weight gain and the risk of hypoglycemia compared with basal-bolus insulin regimens. Pharmacokinetic and pharmacodynamic studies of combination GLP-1 receptor agonists and basal insulin analogs have shown an additive effect on blood glucose decreases (138 [EL 1; RCT]; 159 [EL 1; RCT]; 160 [EL 4; NE]; 161 [EL 1; RCT]; 162 [EL 1; RCT, not blinded, not placebo controlled]). The combined use of DPP-4 inhibitors or SGLT2 inhibitors with insulin is also effective in improving glycemic control with a relatively low risk of hypoglycemia (163 [EL 1; RCT]; 164 [EL 1; RCT]).

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

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

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

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

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

Insulin therapy is necessary for life in all patients with T1D (EL 1; "all-or-nothing"). Physiologic insulin regimens, using both basal and prandial insulin, provided by either MDI or CSII, have not been formally tested in RCTs against nonphysiologic insulin regimens (once or twice daily insulin). Rather, physiologic insulin regimens have been formally studied as 1 component of a comprehensive treatment strategy for patients with T1D.

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

| Table 12<br>Recommended Steps for the Intensification of Insulin Therapy When<br>Prandial Control is Needed (4 [EL 4; NE]) | | |
|---|---|---|
| **Therapeutic option** | **Insulin dose** | **Notes/caveats** |
| **Step 1.  Add prandial therapy** | | |
| GLP-1 receptor agonist, SGLT2 inhibitor, or DPP-4 inhibitor | — | If glucose goals remain unmet, add prandial insulin |
| Prandial insulin | TDD 0.3-0.5 units/kg (50% basal; 50% prandial) | Basal + prandial insulin analogs preferred over NPH + regular insulin or premixed insulin |
| **Step 2. Titrate insulin every 2-3 days to reach glycemic goals[a]** | | |
| Fixed regimen | Increase TDD by 2 units/day | |
| Adjustable regimen | | |
|     FBG >180 mg/dL | Increase TDD by 4 units | |
|     FBG 140-180 mg/dL | Increase TDD by 2 units | |
|     FBG 110-139 mg/dL | Increase TDD by 1 unit | |
|     2-h PPG or next premeal glucose >180 mg/dL | Increase prandial dose for the next meal by 10% | |
| Premixed insulin | | |
|     FBG/premeal BG >180 mg/dL | Increase TDD by 10% | |
| **Step 3. Monitor for hypoglycemia** | | |
| Fasting hypoglycemia | Reduce basal insulin dose | |
| Nighttime hypoglycemia | Reduce basal insulin or reduce short/rapid-acting insulin taken before supper or evening snack | |
| Between meal hypoglycemia | Reduce previous premeal short/rapid-acting insulin | |
| Abbreviations: BG = blood glucose; DPP-4 = dipeptidyl peptidase 4 inhibitors; FBG = fasting blood glucose; GLP-1 = glucagon-like peptide 1 receptor agonists; NPH = neutral protamine Hagedorn; PPG = postprandial glucose; SGLT2 = sodium glucose cotransporter 2; TDD = total daily dose.<br>[a] For most patients with T2D taking insulin, glucose goals are A1C <7% and fasting and premeal blood glucose <110 mg/dL in the absence of hypoglycemia. A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk. | | |

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

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

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

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

The dose of prandial insulin is usually determined by estimating the carbohydrate content of the meal. Insulin-to-carbohydrate (I:C) ratios usually range from 1:20 for the very insulin sensitive to 1:5 for the insulin-resistant patient. Similarly, correction dose insulin for premeal or between-meal hyperglycemia is based on the insulin sensitivity factor (ISF), which is based on the overall insulin sensitivity of the patient, loosely estimated by the individual's total daily insulin dose. Although various formulas have been used to estimate the appropriate ISF, this parameter should only be viewed as an estimation due to numerous factors that can alter blood glucose. The most commonly used formula is:

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

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

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

### 4.Q5.2. Adjunctive Medications for T1D

The amylin analog pramlintide, the only other medication approved for the treatment of T1D, is administered with prandial insulin. A1C reductions are consistently modest, and mild weight loss is common. Nausea is a common adverse effect. There is a potential risk of severe hypoglycemia if patients do not appropriately reduce the prandial insulin dosage (173 [EL 1; RCT]; 174 [EL 1; RCT]; 175 [EL 1; RCT]; 176 [EL 1; MRCT]). Tachyphylaxis is often seen after several years of therapy.

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

### 4.Q6. How is Hypoglycemia Managed?

### 4.Q6.1. Definition

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

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

### 4.Q6.2. Symptoms

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

### 4.Q6.3. Etiology

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

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

### 4.Q6.4.  Risks

The primary cause of hypoglycemia is intensification of therapy to achieve a lower A1C target, as demonstrated by intensive therapy trials. Over 3.5 years in the ACCORD study, severe hypoglycemia occurred at an annualized rate of 3.1% of patients in the intensive therapy group (mean endpoint A1C 6.4%; target <6.0%) versus 1.0% per year in the standard therapy group (mean endpoint A1C 7.5%) (62 [EL 1; RCT]). During the ADVANCE study, in which the goal A1C of 6.5% was met in the intensive group, 0.7% of intensively treated patients experienced severe hypoglycemia on an annual basis compared with 0.4% of patients per year in the standard care group (57 [EL 1; RCT]). Finally, in the UKPDS (United Kingdom Prospective Diabetes Study), wherein intensive treatment led to a mean endpoint A1C of 7.0%, hypoglycemia occurred in 1.8% of insulin-treated patients per year in the intensive group versus 0.7% of conventionally treated patients per year (69 [EL 1; RCT]). The risk of hypoglycemia is greater in older patients and those with longer DM duration, kidney failure, or lesser insulin reserve. Dementia is another important risk factor for hypoglycemia, and recurrent hypoglycemia appears to increase the risk of dementia (181 [EL 3; SS]; 182 [EL 2; RCCS]; 183 [EL 2; PCS]). The failure to recognize symptoms of hypoglycemia can increase the risk of subsequent hypoglycemia by causing autonomic failure, leading to a cycle of recurrent hypoglycemia and hypoglycemia unawareness (180 [EL 4; NE]).

### 4.Q6.5.  Sequelae

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

hypoglycemia at baseline (185 [EL 2; PCS]). The proposed mechanism for these effects posits that hypoglycemia reduces baroreceptor sensitivity and increases symphatho-adrenal system activity, which can trigger a fatal ventricular arrhythmia in the setting of reduced baroreflex sensitivity (186 [EL 4; NE]).

Other short- and long-term consequences of severe hypoglycemia include neurologic conditions ranging from temporary cognitive impairment to dementia as well as major vascular events such as stroke, myocardial infarction, acute cardiac failure, ventricular arrhythmias, and sudden death (166 [EL 4; NE]; 180 [EL 4; NE]; 187 [EL 4; NE]). The complications of hypoglycemia are also associated with short-term disability and higher healthcare costs (188 [EL 4; NE]).

### 4.Q6.6.  Management

Hypoglycemia is the primary limiting factor in the treatment of both T1D and T2D. It remains a significant barrier in terms of treatment adherence and achievement of glycemic goals (166 [EL 4; NE]).

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

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

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

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

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

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

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

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

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

Accurate measurement of blood pressure remains fundamental to the diagnosis and effective management of hypertension (8 [EL 4; NE]). The equipment, which can be aneroid, mercury, or electronic, should be inspected and validated on a regular maintenance schedule. Initial training and regularly scheduled retraining in the standardized technique provides consistency in measurements. The patient must be properly prepared and positioned; blood pressure should be measured after being seated quietly for at least 5 minutes in a chair (rather than on an exam table), with feet on the floor and arm supported at heart level. Caffeine, exercise, and smoking should be avoided for at least 30 minutes prior to measurement. Measurement of blood pressure in the standing position is indicated periodically, especially in those at risk for postural hypotension. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. At least 2, and preferably 3, measurements should be made and the average recorded.

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

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

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

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

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

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

### 4.Q8.1.  *Lipid Targets*

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

### 4.Q8.2.  *Managing Dyslipidemia*

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

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

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

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

### 4.Q8.4. Dyslipidemia Therapeutic Recommendations

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

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

**Table 13**
**Suggested Priority of Initiating Blood Pressure-Lowering Agents**

| Therapy | Reference (evidence level and study design) |
|---|---|
| Evidence based | |
| RAAS blockers (ACE inhibitor or ARB) | (198 [EL 1; RCT]; 199 [EL 1; RCT]) |
| Thiazide diuretic | (194 [EL 4; review NE]) |
| β-Adrenergic blocker | (199 [EL 1; RCT]) |
| Individualized therapy | |
| Calcium channel blockers | (214 [EL 1; RCT, posthoc analysis]) |
| Aldosterone receptor blockers | (202 [EL 4; CPG NE]) |
| Direct renin inhibitor | |
| Selective $\alpha_1$-adrenergic blockers | |
| Central $\alpha_2$ agonists | |
| Direct vasodilators | |
| Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; RAAS = renin-angiotensin-aldosterone system. | |

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

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

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

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

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

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

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

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

### 4.Q8.5.  *Lipid Management in Prediabetes*

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

Moderate-potency or high-potency statins, possibly combined with cholesterol absorption inhibitors or bile acid sequestrants, are effective for achieving LDL-C, non-HDL-C, and ApoB or LDL-P goals in prediabetes (7 [EL 4; CPG NE]). Low HDL-C is also common in prediabetes. Low HDL-C and high triglycerides are both associated with increased levels of LDL-P. Niacin is effective in raising HDL-C, but it also increases insulin resistance and may accelerate the appearance of overt DM. Fibrates may be considered, but the use of gemfibrozil is discouraged owing to its interaction with statin clearance and the risk for severe rhabdomyolysis.

Meta-analyses of statin RCTs indicate that statin use is associated with significant increases in the risk of progression to T2D among patients with prediabetes: a 9% increase with moderate statin dosing and 12% increase with intensive statin dosing (258 [EL 1; MRCT]; 259 [EL 1; MRCT]). Patients with prediabetes should be warned of the potential added risk of conversion to DM with statin use. The net comparison of benefit versus risk is >4 ASCVD events prevented for 1 conversion from prediabetes to DM (260 [EL 4; NE]). A thorough risk-benefit analysis, taking into account the patient's individual risk of converting to DM versus prevention of ASCVD, should be discussed with the patient.

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

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

The KDIGO guidelines recommend phasing out the term *microalbuminuria* and replacing it with the term *albuminuria*. Testing for the presence of albuminuria can be done using a spot urine sample or a timed collection. AER levels >30 mg/g creatinine or 30 mg/day indicate kidney damage and are also a marker of cardiovascular risk (263 [EL 4; NE]; 264 [EL 4; NE]). Urinary albumin may be seen in the setting of urinary tract or systemic infection, after exercise, or in the presence of hematuria, so confirmation is necessary to establish the diagnosis of diabetic nephropathy. An AER of >300 mg/g creatinine or >300 mg/day indicates greater damage and greater risk for progression of renal insufficiency, anemia, CVD, and infections. Sudden onset or rapidly increasing AER should prompt additional

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

GFR should be estimated from a creatinine-based calculation such as the Modification in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology (CKD-EPI) equations. The CKD-EPI equation is more accurate for calculation of eGFR above 60 mL/min/1.73 m$^2$, and this equation is currently preferred (263 [EL 4; NE]). However, most laboratories report a calculated eGFR using the MDRD when eGFR is <60 mL/min/1.73 m$^2$. Figure 2 depicts the new classification system for CKD in patients with DM that incorporates both eGFR and albuminuria in the risk assessment. Note that in Figure 2, stage 3 CKD has been divided into 2 categories, G3a for eGFR 45 to 60 mL/min/1.73 m$^2$ and G3b for eGFR 30 to 45 mL/min/1.73 m$^2$. The terminology used to describe CKD provides a composite picture by integrating the cause, eGFR, and AER. For example, a patient with DM, an eGFR of 40 mL/min/1.73 m$^2$, and an AER of 250 mg/g creatinine would be categorized as "diabetes/G3b/A2." The "heat grid" shown in Figure 2 indicates the new terminology, the level of risk for cardiovascular events and progression of kidney disease by color intensity, and the recommended frequency for monitoring renal parameters (263 [EL 4; NE]; 265 [EL 2; MNRST]; 266 [EL 4; NE]). Progression of CKD is classified as rapid if the decline in eGFR is ≥5 mL/min per 1.73 m$^2$ per year or if the patient has a dramatic increase in AER.

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

| Table 14 Relationship Among Categories For Albuminuria and Proteinuria (263 [EL 4; NE])[a,b] | | | |
|---|---|---|---|
| | **Categories** | | |
| **Measure** | **Normal to mildly increased (A1)** | **Moderately increased (A2)** | **Severely increased (A3)** |
| AER (mg/24 hours) | <30 | 30-300 | >300 |
| PER (mg/24 hours) | <150 | 150-500 | >500 |
| ACR (mg/mmol) | <3 | 3-30 | >30 |
| (mg/g) | <30 | 30-300 | >300 |
| PCR (mg/mmol) | <15 | 15-50 | >50 |
| (mg/g) | <150 | 150-500 | >500 |
| Protein reagent strip | Negative to trace | Trace to + | + or greater |

Abbreviations: ACR = albumin-to-creatinine ratio; AER = albumin excretion rate; PCR = protein-to-creatinine ratio; PER = protein excretion rate.
[a] Reprinted with permission from Macmillan Publishers Ltd: *Kidney International Supplement.* 2013;3(1):1-150, copyright 2013..
[b] Albuminuria and proteinuria can be measured using excretion rates in timed urine collections, ratio of concentrations to creatinine concentration in spot urine samples, and using reagent strips in spot urine samples. Relationships among measurement methods within a category are not exact. For example, the relationships between AER and ACR and between PER and PCR are based on the assumption that average creatinine excretion rate is approximately 1.0 g/d or 10 mmol/day. The conversions are rounded for pragmatic reasons. (For an exact conversion from mg/g of creatinine to mg/mmol of creatinine, multiply by 0.113.) Creatinine excretion varies with age, sex, race and diet; therefore the relationship among these categories is approximate only. ACR <10 mg/g (<1 mg/mmol) is considered normal; ACR 10-30 mg/g (1-3 mg/mmol) is considered "high normal." ACR >2,200 mg/g (>220 mg/mmol) is considered "nephrotic range." The relationship between urine reagent strip results and other measures depends on urine concentration.

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

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

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

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

If the GFR continues to decline despite excellent glycemic and blood pressure control, protein restriction may be of some benefit. KDIGO recommends limiting protein intake to 0.8 g/kg per day (approximately 10% of daily calories) in patients with progressive diabetic nephropathy or eGFR <30 mL/min/1.73 m². Additional dietary restrictions may be required to control potassium and phosphorus levels. Salt intake should be limited to 2 g per day in all patients with DM who require antihypertensive medications. Obesity is a risk factor for hypertension and incident CKD, so weight loss along with exercise is recommended for patients with DM without evidence of kidney disease as well as patients with category G2 to G4 CKD. Unintended weight loss is associated with poorer outcomes in dialysis patients.

Patients with CKD are at risk for drug toxicity and acute kidney injury. Antihyperglycemic therapies should be modified to reduce excessive drug exposure and hypoglycemia (276 [EL 3; CSS]). Many other drugs should be avoided or used with caution in patients with CKD. Patients should be informed of their CKD diagnosis and should avoid dehydration and imaging that requires gadolinium, high phosphate-containing bowel preparations, or high doses of iodinated contrast dyes.

Patients with diabetic nephropathy should undergo annual or more frequent assessment of electrolytes to assess potassium and acid-base status; blood counts to assess anemia status; and calcium, phosphorus, vitamin D, and parathyroid hormone (PTH) measurements to assess mineral metabolism (263 [EL 4; NE]). Hyperkalemia is managed by dietary restriction and adjustment of antihypertensive medications. For those with a bicarbonate level <22 mEq/L, the addition of oral sodium bicarbonate is recommended to correct the acidosis. Anemia, defined as hemoglobin (Hb) <13 g/dL in males and <12 g/dL in females, should be further investigated with iron, transferring saturation (TSAT), ferritin, vitamin $B_{12}$, and folate levels (277 [EL 4; NE]). Deficiencies should be replaced, and a TSAT target of ≥30% achieved, regardless of ferritin level (277 [EL 4; NE]). Iron given intravenously may produce better results than oral replacement. AACE recommends adequate calcium intake and achievement of 25(OH)$D_3$ levels of >30 ng/dL in all patients. Supplementing vitamin $D_2$ or $D_3$ may reduce PTH without causing harm (277 [EL 4; NE]; 278 [EL 3; SS]). Active vitamin D preparations may be necessary to keep the PTH level from increasing as kidney function declines. Hyperphosphatemia should be corrected into the normal range with dietary modification and judicious use of phosphate binders.

Referral to a nephrologist is appropriate when the presentation is atypical, progression of albuminuria or decline in eGFR is rapid, or when secondary manifestations of CKD require expert advice. Referral of patients with stage 4 CKD to a nephrologist allows time for sufficient planning to accommodate individual patient needs (279 [EL 4; opinion NE]). Renal transplantation is the preferred replacement therapy for patients with DM and ESRD because long-term outcomes are superior to those achieved with dialysis. For patients with T1D, the possibility of combined kidney-pancreas transplantation allows for considerably better outcomes (280 [EL 2; PCS]).

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

Diabetic retinopathy is the leading cause of blindness in adults. The lesions of diabetic retinopathy include background or nonproliferative retinopathy, macular edema, preproliferative retinopathy, and proliferative retinopathy. Approximately 50% of patients with T1D develop background retinopathy after 7 years, and most have some form of retinopathy after 20 years (281 [EL 4; review NE]). Diabetic retinopathy is present in 25 to 45% of patients with T2D, and between 2 and 8% of patients with T2D have proliferative retinopathy and/or macular edema (282 [EL 3; SS]). Diabetic retinopathy is present in approximately 20, 40, and 70% of patients with T2D after <10, 10 to 20, and >20 years of the disease, respectively, with prevalence rates of proliferative retinopathy and/or macular edema around 2, 10, and 25% at the respective durations (283 [EL 2; MNRCT]). Higher levels of glucose and blood pressure, as well as the presence of nerve and renal diabetic complications, are associated with greater likelihood of developing retinopathy (284 [EL 3; SS]).

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

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

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

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

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

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

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

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

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

1. Possible DSPN. The presence of symptoms or signs of DSPN, which may include the following:
   - Symptoms: decreased sensation, positive neuropathic sensory symptoms (e.g., "asleep numbness," prickling or stabbing, burning, or aching pain) predominantly in the toes, feet, or legs
   - Signs: symmetric decrease of distal sensation or unequivocally decreased or absent ankle reflexes
2. Probable DSPN. The presence of a combination of symptoms and signs of neuropathy including any 2 or more of the following: neuropathic symptoms, decreased distal sensation, or unequivocally decreased or absent ankle reflexes
3. Confirmed DSPN. The presence of an abnormality of nerve conduction plus a symptom or symptoms, or a sign or signs, of neuropathy. If nerve conduction is normal, a validated measure of SFN (with class 1 evidence) may be used. To assess for

the severity of DSPN, several approaches have been recommended (329 [EL 4; NE]).

4. Subclinical DSPN. Abnormal nerve conduction or a validated measure of SFN (with class 1 evidence) without signs or symptoms of neuropathy. Definitions 1, 2, or 3 can be used for clinical practice, and definitions 3 or 4 can be used for research studies.
5. SFN should be graded as follows (330 [EL 4; NE]):
   a. Possible: the presence of length-dependent symptoms and/or clinical signs of small-fiber damage
   b. Probable: the presence of length-dependent symptoms, clinical signs of small-fiber damage, and normal sural nerve conduction
   c. Definite: the presence of length-dependent symptoms, clinical signs of small-fiber damage, normal sural nerve conduction, and altered intraepidermal nerve-fiber density at the ankle and/or abnormal thermal thresholds at the foot

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

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

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

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

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

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

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

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

Physicians must be able to differentiate painful diabetic neuropathy from other unrelated or coexisting conditions. The most common of these are claudication, Morton's neuroma, Charcot neuroarthropathy, fasciitis, osteoarthritis, and radiculopathy. The algorithm provided (Fig. 3) distinguishes between the different conditions that can produce pain and provides recommendations for their management (314 [EL 4; review NE]; 357 [EL 4; NE]). The FDA has approved only the serotonin and norepinephrine reuptake inhibitor duloxetine, the anticonvulsant pregabalin, and the opioid tapentadol for neuropathic pain, but level 1 evidence also exists to support the use of tricyclic antidepressants (e.g., amitriptyline) and the anticonvulsant gabapentin (358 [EL 1; MRCT]; 359 [EL 1; MRCT]). Recent studies have shown improvement of pain with an α2δ1 calcium antagonist (360 [EL 1; RCT, posthoc analysis]) and tapentadol, a weak opioid agonist with norepinephrine
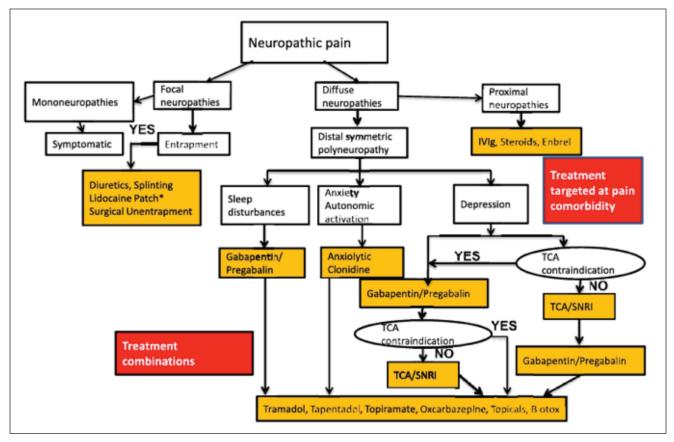
**Fig. 3.** Treatment algorithm for neuropathic pain after exclusion of nondiabetic etiology and stabilization of glycemic control (314 [EL 4; review NE]; 357 [EL 4; NE]). Reprinted from the *Journal of Clinical Endocrinology and Metabolism*, Vol. 95, A. Vinik, "The approach to the management of the patient with neuropathic pain," pp. 4802-4816. Copyright 2010, with permission from Elsevier.

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

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

Cardiovascular autonomic neuropathy is significantly associated with overall mortality (367 [EL 4; review NE]; 368 [EL 2; MNRCT]) and in some studies, but not all, with morbidity including silent myocardial ischemia, coronary artery disease, stroke, diabetic neuropathy progression, and perioperative morbidity. Some pathogenetic mechanisms may link cardiovascular autonomic neuropathy to cardiovascular dysfunction and diabetic complications (367 [EL 4; review NE]). Cardiovascular autonomic neuropathy assessment may be used for cardiovascular risk stratification in patients with and without established CVD, as a marker for patients requiring more intensive monitoring during the perioperative period and other physiological

stresses, and as an indicator for more or less intensive pharmacotherapeutic and lifestyle management of comorbid conditions. Cardiovascular autonomic neuropathy may be useful for prediction of cardiovascular risk, and a combination of cardiovascular autonomic neuropathy (369 [EL 3; SS]) and symptoms of peripheral neuropathy increase the odds ratio to 4.55 for CVD and mortality (314 [EL 4; review NE]). Indeed, this is the strongest predictor of CVD risk, far greater than blood pressure, lipoprotein profile, and even adenosine scans (370 [EL 4; NE]). The reported prevalence of diabetic autonomic neuropathy varies widely (7.7 to 90%) depending on the cohort studied and the methods used for diagnosis (371 [EL 4; review NE]; 372 [EL 4; review NE]). All the manifestations of autonomic nerve dysfunction, along with suggested testing, the symptom complex, and possible therapies, are listed in Table 15 (310 [EL 3; CSS]). A more complete discussion can be found in recent reviews (369 [EL 3; SS]; 373 [EL 4; NE]).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### 4.Q12.1.  Glycemic Control

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

The beneficial effects of intensive glycemic control in reducing vascular complications appear to be inversely related to the extent of vascular disease at the time it is initiated. The ACCORD (62 [EL 1; RCT]), ADVANCE (57 [EL 1; RCT]), and VADT (Veterans Affairs Diabetes Trial) (61 [EL 1; RCT]) trials investigated the effect of intensive glycemic control versus standard glycemic control on the development of new cardiovascular events in patients with mean durations of diagnosed T2D of 8.5 to 11 years either

with baseline previous cardiovascular events (35 to 45% of patients) or high cardiovascular risk. The duration of the trials was 3.5 to 7.0 years. All 3 trials failed to show a significant benefit of intensive glycemic control in reducing new cardiovascular events.

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

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

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

### 4.Q12.2.  Antiplatelet Therapy

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

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

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

### 4.Q12.3.  *Asymptomatic Coronary Artery Disease*

Although screening for asymptomatic coronary artery disease in patients with T2D does not improve cardiac outcomes, the measurement of coronary artery calcification may be useful in assessing whether some patients with long-standing DM are reasonable candidates for intensification of glycemic control and or lipid lowering.

The impression in the past was that diagnosing asymptomatic CVD in patients with DM would result in improved care and better long-term clinical outcomes; however, findings from well-conducted clinical trials have not supported this idea (405 [EL 1; RCT]).

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

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

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

is considered overweight in southeast Asians) (420 [EL 4; NE]).

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

### 4.Q13.1.  *Lifestyle Modification for Weight Loss*

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

Increased physical activity is important for maintaining weight loss. For cardiometabolic conditioning, a recommendation consistent with guidelines proposed by the ADA, AHA, and American College of Sports Medicine (ACSM) would include 30 minutes of moderate intensity exercise 5 days per week for a total of 150 minutes/week, or 20 to 25 minutes of intense exercise 3 days per week for a total of 60 to 75 minutes/week combined with resistance training involving each major muscle group 2 to 3 days per week (104 [EL 4; consensus NE]; 424 [EL 4; NE]).

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

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

### 4.Q13.2. Obesity Pharmacotherapy

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

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

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

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

### 4.Q13.3. Bariatric Surgery

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

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

1990s has significantly reduced perioperative morbidity and mortality.

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

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

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

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

Until 2012, the only obesity medication approved for chronic use in the U.S. was orlistat, which has been shown to be effective in T2D (456 [EL 1; RCT]; 460 [EL 1; RCT];

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

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

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

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

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

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

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

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

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

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

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

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

The management of hyperglycemia in the hospital setting presents multiple challenges including variable nutritional status and altered levels of consciousness, as well as resource limitations for monitoring glycemia during these changes. Given the paramount importance of patient safety, reasonable glucose targets in the hospital setting should be set at modestly higher levels than targets for outpatients with DM. For most critically ill patients in the ICU, a glucose concentration range of 140 to 180 mg/dL is recommended, provided these targets can be safely achieved. For patients in non-ICU settings, a premeal glucose target of <140 mg/dL and a random blood glucose of <180 mg/dL is recommended; however, glycemic targets should be modified according to clinical status. For patients who are able to achieve and maintain glycemic control without hypoglycemia, a lower target range may be reasonable. For patients with terminal illness and/or with limited life expectancy or at high risk for hypoglycemia, a higher target range (<180 mg/dL) may be reasonable.

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

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

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

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

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

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

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

MNT is an essential component of inpatient glycemic management in patients with DM and hyperglycemia. The goals of inpatient MNT for patients with DM are to help optimize glycemic control, provide adequate calories to meet metabolic demands, address individual needs based on personal food preferences, and provide a discharge plan for follow-up care. Most hospitalized patients require 25 to 35 calories/kg/day; critically ill patients require between 15 and 25 calories/kg/day (514 [EL 4; NE]; 515 [EL 4; NE]). This translates to a diet containing approximately 1,800 to 2,000 calories/day or ~200 g carbohydrate per day divided between meals. Care must be taken not to overfeed hospitalized patients because this can exacerbate hyperglycemia. No single meal planning system is ideal for hospitalized patients; however, hospitals should provide a consistent carbohydrate DM meal-planning system (514 [EL 4; NE]). The carbohydrate components of breakfast, lunch, dinner, and snacks may vary, but the day-to-day carbohydrate content of specific meals and snacks should be kept constant. Patients requiring clear or full liquid diets should receive ~200 g carbohydrate per day in equally divided amounts at meal and snack times. Patients on liquid diets, in particular during the perioperative period, do not meet these nutritional needs. Increasing evidence indicates that food intake should be initiated as quickly as possible with progression from clear liquids to full liquids to solid foods as rapidly as tolerated in surgical patients (516 [EL 4; NE]). Early enteral feeding is safe and well tolerated and is associated with reduced wound morbidity, improved wound healing, fewer septic complications, diminished weight loss, and improved protein kinetics (516 [EL 4; NE]).

**4.Q15.4.  *Hypoglycemia and Hospital Outcomes***

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

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

**4.Q15.5.  *Recommendations After Hospital Discharge***

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Abnormal glucose tolerance develops at higher rates and at younger ages among offspring of females with DM. Maternal DM is one of the strongest risk factors for the development of T2D among Pima Indian children (546 [EL 2; PCS]; 547 [EL 3; CCS]; 548 [EL 3; SS]). By the time these offspring reach childbearing age, they are very likely to be obese and have DM, thereby perpetuating a vicious cycle (548 [EL 3; SS]). That this is not simply a genetic predisposition is inferred from the finding of lower rates of DM in offspring of females who were born before

their mothers developed DM (549 [EL 3; SS]); this is true among sibling pairs whose birth dates straddle the onset of their mother's DM (546 [EL 2; PCS]). Thus, all females with DM in the childbearing years should have preconception care and guidance to target an A1C level of <6.5% (212 [EL 4; NE]; 550 [EL 2; PCS]). Frequent POC A1C monitoring allows the clinician to assess the most recent average glucose by comparing the current A1C POC test with the previous week's POC A1C. The rate of change and direction of the change reflects the trend of recent glucose levels. Although the steady state is not achieved until 6 to 8 weeks later, a rising A1C reflects recent hyperglycemia and allows the clinician an opportunity to discuss the observation and work with the patient for solutions.

The HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) study confirmed findings in the Pima Indians (546 [EL 2; PCS]) that, even among offspring of females without GDM as it is currently defined (551 [EL 2; PCS]; 552 [EL 4; consensus NE]; 553 [EL 4; review NE]; 554 [EL 3; PCS]; 555 [EL 3; SS]), there is a linear association between maternal glucose concentration during pregnancy and newborn weight, rates of large-for-gestational-age, and cesarean delivery. DM during pregnancy and even maternal obesity itself (552 [EL 4; consensus NE]) set the stage for a vicious cycle with offspring of mothers with DM during pregnancy being more likely to become obese and to develop DM at younger ages (554 [EL 3; PCS]). Maternal DM and obesity, although major risk factors for the metabolic health of the offspring, are not the only factors at play in the early stages of childhood that can have lasting adverse effects on offspring. Both low and high birth weight are associated with higher rates of DM (555 [EL 3; SS]). Abnormal birth weight directly affects the offspring and leads to higher rates of GDM eventually in the offspring, thereby compounding the vicious cycle. Early diagnosis and treatment of DM, careful preconception care and guidance for females with DM or at risk for GDM, and meticulous control of glucose abnormalities throughout pregnancy are currently our best hope to break this cycle (556 [EL 4; review NE]). Thus, subjects with DM risk factors (Table 5) should be screened at the first prenatal visit for undiagnosed T2D using standard criteria (Table 6), and all pregnant subjects without a prior diagnosis of DM should be screened for GDM with a 2-hour OGTT using a 75-g glucose load at 24 to 28 weeks' gestation. Glucose criteria diagnostic for GDM are an FPG >92 mg/dL, 1-hour post-glucose challenge value ≥180 mg/dL, or 2-hour value ≥153 mg/ dL (557 [EL 4; CPG]).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

contact with members of their healthcare team, in particu-lar their pump-supervising physician and CDE.

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

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

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

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

### 4.Q20.1.  *Certified Diabetes Educators*
A CDE is generally a nurse or registered dietitian but could be another healthcare professional. CDEs teach in a variety of inpatient and outpatient settings. They cover all topics related to DM management from insulin administra-tion to foot care. They often have more time than physi-cians to devote to each patient, which allows them to focus on specific needs. Often patients report they receive more practical knowledge from their CDE than they do from their physician. Having a CDE credential indicates the passing of the certification examination and special ability in this area.

### 4.Q20.2.  *Registered Dietitians*
A healthful diet is necessary for everyone to maintain good health. However, persons with DM especially need to follow their prescribed meal plan and physical activ-ity program as an integral part of their therapy. Registered

## Table 16
### Meta-Analyses of Studies of CSII in T1D Published Since 2003

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

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

**Table 17**
**RCTs Comparing CSII and MDI for Patients With T2D**

| Reference | Number randomized | Design | Follow-up | Baseline | A1C (%) (SD)[a] | | P value |
|---|---|---|---|---|---|---|---|
| | | | | | CSII | MDI | |
| (595 [EL 3; CCSI]) | 15 | Observational | 30 weeks | 7.9 (1.9) | 5.0 (0.9) | NA | <.001 |
| (594 [EL 3; CCSI]) | 10 | Observational | 3 successive nights | FPG: 209 (52.3) mg/dL | FPG: 99.1 (28.8) mg/dL | NA | <.0001 |
| (593 [EL 1; RCT, small sample size, not blinded]) | 17 | Crossover | 2 periods of 12 weeks | 9 (1.6) | 7.7 (0.8) | 8.6 (1.6) | <.03 |
| (592 [EL 1; RCT, not blinded]) | 107 | Parallel | 1 year | CSII: 8.4 (1.1) MDI: 8.1 (1.2) | 6.6 (0.8) | 6.4 (0.8) | .19 |
| (591 [EL 1; RCT, not blinded, small sample size]) | 40 | Crossover | 2 periods of 18 weeks | CSII-MDI: 10.1 (1.6) MDI-CSII 10.2 (1.4) | −0.8 (1.5)[b] | +0.4 (1.3)[b] | .007 |
| (590 [EL 1; RCT, not blinded]) | 132 | Parallel | 24 weeks | CSII: 8.2 (1.4) MDI: 8.0 (1.1) | 7.6 (1.2) | 7.5 (1.2) | NS |
| (597 [EL 1; RCT, small sample size, not blinded]) | 20 | RCT | 4 months | CSII: 13.2[c] MDI: 12.8 | 9.2 (HbA$_1$) | 10.6 (HbA$_1$) | <.05 |
| (596 [EL 1; RCT, not blinded]) | 331 | RCT | 6 months | 9 | 1.1 (1.2) | 0.4 (1.1) | <.0001 |

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

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

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

[c] Reported in study as median mmol hydroxymethylfurfural (HMF) per mol hemoglobin (Hb) and converted to median percentage HbA$_1$ based on the following formula, which was determined via comparison with a column chromatography method over the range of 4 to 13%: HbA$_1$ (%) = 0.21 (A1C in mmol HMF/mol Hb) - 0.35 (597 [EL 1; RCT, small sample size, not blinded]).

**Table 18**

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

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

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

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

### 4.Q20.3. Nurses and Medical Assistants

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

### 4.Q20.4. Nurse Practitioners and Physician Assistants

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

### 4.Q20.5. Primary Care Physicians

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

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

Bacterial and viral infections cause significant morbidity and mortality in patients with DM (606 [EL 4; NE]). A recent Canadian cohort study of adults with DM <65 years of age showed that DM increased the risk of influenza-associated hospitalizations by 6% (risk ratio 1.06, 95% CI 1.02 to 1.10; absolute risk difference 6 per 1,000 adults per year) even though the rates of influenza and pneumonia were similar between diabetic and nondiabetic populations ($P = .11$) (607 [EL 3; SS]). Both community-acquired and nosocomial infections with pneumococcal bacteria may also be higher among patients with DM, who may also be at greater risk of death from these diseases (608 [EL 3; CSS];

609 [EL 2; PCS]; 610 [EL 2; PCS]). However, vaccines can safely and effectively reduce serious complications from influenza. A case-control study demonstrated that vaccines reduced DM-related hospital admissions by as much as 79% during flu epidemics (611 [EL 2; RCCS]). In addition, no evidence suggests that people with DM have inadequate serologic or clinical responses to these vaccinations. The CDC ACIP recommends a yearly influenza vaccine for all individuals with DM, although live attenuated influenza vaccine should be used with caution because its safety in patients with DM has not been established. Inactivated influenza vaccine may be considered for patients with DM (612 [EL 4; NE]). The CDC ACIP also recommends single administration of the 23-valent pneumococcal vaccine (PPSV23) for adults with diabetes aged 19 to 64 years (613 [EL 4; NE]). Furthermore, the 13-valent pneumococcal conjugate vaccine (PCV13) should be administered in series with the PPSV23 to all adults ≥65 years (614 [EL 4; NE]).

### 4.Q21.1. Hepatitis B Vaccine

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

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

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

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

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

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

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

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

Increased BMI (>25 kg/m$^2$) is associated with an increased risk of a wide variety of cancers. The strongest associations appear to be for endometrial, gall bladder, esophageal (adenocarcinoma), renal, thyroid, ovarian, breast, and colorectal cancer, with weaker but still statistically significant associations for leukemia, malignant and multiple melanoma, pancreatic cancer, and non-Hodgkin lymphoma (627 [EL 2; MNRCT]; 628 [EL 2; MNRCT]; 629 [EL 2; MNRCT]; 630 [EL 2; MNRCT]; 631 [EL 2; MNRCT]). Increased BMI may, however, be protective for lung, esophageal (squamous) (628 [EL 2; MNRCT]), and prostate cancer (632 [EL 3; SS]) in males, although more aggressive prostate cancers seem to be more common in males who are overweight or obese (633 [EL 4; NE]). In females, increased BMI may be protective for premenopausal breast and lung cancer (628 [EL 2; MNRCT]). As noted in the 2013 AACE/ACE Consensus Statement on

Diabetes and Cancer, a higher BMI is also closely associated with increased levels of endogenous insulin, insulin-like growth factors, inflammatory cytokines, and other factors that can have downstream procancer growth effects (626 [EL 4; NE]). These and other potential mechanisms have been recently reviewed (634 [EL 4; NE]).

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

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

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

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

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

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

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

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

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

#### 4.Q24.1. *Risk of Accidents*

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

piloting ability. The U.S. Federal Motor Carrier Safety Administration and Federal Aviation Administration both require medical certification for operating commercial motor vehicles (used in interstate commerce) and airplanes; these are based on a medical examination including vision, audiometric, and cardiac assessments, as well as standard history and physical examination. Both organizations cite the use of insulin for glycemic control as a criterion for disqualification. Although an insulin-waiver program exists for drivers, this is a complex undertaking, leading many to refuse the treatment even if medically needed. It should be noted that individual states might have separate regulations governing commercial drivers' licenses (661 [EL 4; NE]). For commercial pilots, insulin treatment is an absolute disqualification (662 [EL 4; NE]).

#### 4.Q24.2. *Hypoglycemia and Antihyperglycemic Treatments*

Hypoglycemia may impair judgment and motor ability, which could increase the likelihood of an accident during operation of a motor vehicle or airplane. The Federal Motor Carrier Safety Administration Evidence Report on Diabetes and Commercial Motor Vehicle Driver Safety addressed a set of key questions relevant to this topic (663 [EL 4; NE]):

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

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

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

The applicability of these studies to the current population of persons with DM in the U.S. is limited because recommended treatment goals and approaches have changed dramatically since the follow-up periods of most of the cited studies. First, the studies of insulin users involved mostly patients with T1D, but the use of a basal insulin analog as the sole administered insulin for T2D is associated with considerably lower hypoglycemia rates than older insulin preparations or the use of basal-bolus treatment (667 [EL 1; RCT, not blinded]). Second, sulfonylurea treatment is associated with a greater likelihood of hypoglycemia than all other noninsulin antihyperglycemic agents (metformin, TZDs, α-glucosidase inhibitors, DPP-4 inhibitors, and GLP-1 receptor agonists) and carries a nearly a twofold greater likelihood of hypoglycemia than basal insulin (668 [EL 1; MRCT]). Unfortunately, reliable large population studies of motor vehicle accidents involving patients with T2D treated with current approaches are not available (studies of oral antihyperglycemic agents included in the meta-analysis examined data from the late 1980s to early 1990s). Finally, and perhaps most importantly, the role of SMBG in preventing episodes of hypoglycemia was not well addressed in the available studies.

### 4.Q24.3. *Commercial Drivers and Lifestyle*

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

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

### DISCLOSURE

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## REFERENCES

*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.*

1. **Handelsman Y, Mechanick JI, Blonde L, et al.** American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. *Endocr Pract.* 2011;17 Suppl 2:1-53. [EL 4; NE]
2. **Mechanick JI, Camacho PM, Cobin RH, et al.** American Association of Clinical Endocrinologists Protocol for Standardized Production of Clinical Practice Guidelines--2010 update. *Endocr Pract.* 2010;16:270-83. [EL 4; CPG NE; see Fig. 1; Tables 1-4]
3. **Mechanick JI, Camacho PM, Garber AJ, et al.** American Association of Clinical Endocrinologists and American College of Endocrinology Protocol for Standardized Production of Clinical Practice Guidelines, Algorithms, and Checklists - 2014 Update and the AACe G4G Program. *Endocr Pract.* 2014;20:692-702. [EL 4; CPG NE; see Tables 1-4]
4. **Garber AJ, Abrahamson MJ, Barzilay JI, et al.** American association of clinical endocrinologists/ American college of endocrinology' comprehensive diabetes management algorithm 2015. *Endocr Pract.* 2015; 21:000-000. [EL 4; NE]
5. **Moghissi ES, Korytkowski MT, DiNardo M, et al.** American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Endocr Pract.* 2009;15:353-369. [EL 4; consensus NE]
6. **Boulton AJ, Armstrong DG, Albert SF, et al.** Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. *Diabetes Care.* 2008;31:1679-1685. [EL 4; NE]
7. **Grundy SM, Cleeman JI, Merz CN, et al.** Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004;110:227-239. [EL 4; CPG NE]
8. **James PA, Oparil S, Carter BL, et al.** 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA.* 2014;311:507-520. [EL 4; NE]
9. **Younis N, Williams S, Ammori B, Soran H.** Role of aspirin in the primary prevention of cardiovascular disease in diabetes mellitus: a meta-analysis. *Expert Opin Pharmacother.* 2010;11:1459-1466. [EL 1; MRCT but small sample sizes and event rates]
10. **Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, et al.** Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet.* 2009;373:1849-1860. [EL 1; MRCT]
11. **Zhang C, Sun A, Zhang P, et al.** Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis. *Diabetes Res Clin Pract.* 2010;87:211-218. [EL 1; MRCT]
12. **Ong G, Davis TM, Davis WA.** Aspirin is associated with reduced cardiovascular and all-cause mortality in type 2 diabetes in a primary prevention setting: the Fremantle Diabetes study. *Diabetes Care.* 2010;33:317-321. [EL 2; PCS]
13. **Hanas R, Donaghue KC, Klingensmith G, Swift PG.** ISPAD clinical practice consensus guidelines 2009 compendium. Introduction. *Pediatr Diabetes.* 2009;10 Suppl 12:1-2. [EL 4; CPG NE]
14. National Diabetes Education Program. *Transitions From Pediatric to Adult Health Care.* Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases. Available at: http://ndep.nih.gov/transitions/. [EL 4; NE]
15. **Peters A, Laffel L; American Diabetes Association Transitions Working Group.** Diabetes care for emerging adults: recommendations for transition from pediatric to adult diabetes care systems: a position statement of the American Diabetes Association, with representation by the American College of Osteopathic Family Physicians, the American Academy of Pediatrics, the American Association of Clinical Endocrinologists, the American Osteopathic Association, the Centers for Disease Control and Prevention, Children with Diabetes, The Endocrine Society, the International Society for Pediatric and Adolescent Diabetes, Juvenile Diabetes Research Foundation International, the National Diabetes Education Program, and the Pediatric Endocrine Society (formerly Lawson Wilkins Pediatric Endocrine Society). *Diabetes Care.* 2011;34:2477-85. [EL 4; NE]
16. **Juvenile Diabetes Research Foundation.** Life Stages. New York, NY: JDRF. Available at: http://jdrf.org/life-with-t1d/#life-stages. [EL 4; NE]
17. **American Association of Clinical Endocrinologists/ American College of Endocrinology.** American Association of Clinical Endocrinologists/American College of Endocrinology statement on the use of hemoglobin A1c for the diagnosis of diabetes. *Endocr Pract.* 2010;16:155-156. [EL 4; consensus NE]
18. **International Expert Committee.** International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care.* 2009;32:1327-1334. [EL 4; consensus NE]
19. **Cowie CC, Rust KF, Byrd-Holt DD, et al.** Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988-2006. *Diabetes Care.* 2010;33:562-568. [EL 3; SS]
20. **Christensen DL, Witte DR, Kaduka L, et al.** Moving to an A1C-based diagnosis of diabetes has a different impact on prevalence in different ethnic groups. *Diabetes Care.* 2010;33:580-582. [EL 3; SS]
21. **Dagogo-Jack S.** Pitfalls in the use of HbA(1)(c) as a diagnostic test: the ethnic conundrum. *Nat Rev Endocrinol.* 2010;6:589-593. [EL 4; review NE]
22. **Guo F, Moellering DR, Garvey WT.** Use of HbA1c for diagnoses of diabetes and prediabetes: comparison with diagnoses based on fasting and 2-hr glucose values and effects of gender, race, and age. *Metab Syndr Relat Disord.* 2014;12:258-268. [EL 3; SS]

23. **Sacks DB.** A1C versus glucose testing: a comparison. *Diabetes Care*. 2011;34:518-523. [EL 4; review NE]

24. **Versantvoort AR, van Roosmalen J, Radder JK.** Course of HbA1c in non-diabetic pregnancy related to birth weight. *Neth J Med*. 2013;71:22-25. [EL 3; CCS]

25. **Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN.** Hyperglycemic crises in adult patients with diabetes. *Diabetes Care*. 2009;32:1335-1343. [El 4; NE]

26. **Banerji MA, Chaiken RL, Huey H, et al.** GAD antibody negative NIDDM in adult black subjects with diabetic ketoacidosis and increased frequency of human leukocyte antigen DR3 and DR4. Flatbush diabetes. *Diabetes*. 1994;43:741-745. [EL 3; SS]

27. **United Kingdom Prospective Diabetes Study Group.** UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. *Diabetologia*. 1991;34:877-890. [EL 1; RCT]

28. **Unger RH, Cherrington AD.** Glucagonocentric restructuring of diabetes: a pathophysiologic and therapeutic makeover. *J Clin Invest*. 2012;122:4-12. [EL 4; NE]

29. **Weyer C, Bogardus C, Mott DM, Pratley RE.** The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest*. 1999;104:787-794. [EL 2; PCS]

30. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014. Available at: http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf [EL 3; SS]

31. **Garber AJ, Handelsman Y, Einhorn D, et al.** Diagnosis and management of prediabetes in the continuum of hyperglycemia: when do the risks of diabetes begin? A consensus statement from the American College of Endocrinology and the American Association of Clinical Endocrinologists. *Endocr Pract*. 2008;14:933-946. [EL 4; consensus NE]

32. **Torgerson JS, Hauptman J, Boldrin MN, Sjöström L.** XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomised study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients [Erratum in *Diabetes Care*. 2004;27:856]. *Diabetes Care*. 2004;27:155-161. [EL 1; RCT]

33. **Garvey WT, Ryan DH, Henry R, et al.** Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. *Diabetes Care*. 2014;37:912-921. [EL 1; RCT]

34. **Sjöström L, Lindroos AK, Peltonen M, et al.** Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med*. 2004;351:2683-2693. [EL 2; PCS]

35. **Knowler WC, Barrett-Connor E, Fowler SE, et al.** Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403. [EL 1; RCT]

36. **Chiasson JL, Josse RG, Gomis R, et al.** Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*. 2002;359:2072-2077. [EL 1; RCT]

37. **Chiasson JL, Josse RG, Gomis R, et al.** Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA*. 2003;290:486-494. [EL 1; RCT]

38. **Chiasson JL, Josse RG, Gomis R, et al.** Acarbose for the prevention of type 2 diabetes, hypertension and cardiovascular disease in subjects with impaired glucose tolerance: facts and interpretations concerning the critical analysis of the STOP-NIDDM Trial data. *Diabetologia*. 2004;47:969-975; discussion 976-977. [EL 4; opinion NE]

39. **DeFronzo RA, Banerji M, Bray GA, et al.** Actos Now for the prevention of diabetes (ACT NOW) study. *BMC Endocr Disord*. 2009;9:17. [EL 1; RCT]

40. **DREAM (Diabetes REduction Assessment with rampipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, et al.** Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial [Erratum in: Lancet. 2006;368:1770]. *Lancet*. 2006;368:1096-1105. [EL 1; RCT]

41. **Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, et al.** 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study [Erratum in *Lancet*. 2009;374:2054]. *Lancet*. 2009;374:1677-1686. [EL 1; RCT, follow-up study]

42. **Richelsen B, Tonstad S, Rossner S, et al.** Effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet in abdominally obese patients: a 3-year randomized, placebo-controlled study. *Diabetes Care*. 2007;30:27-32. [EL 1; RCT]

43. **Gillies CL, Abrams KR, Lambert PC, et al.** Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. *BMJ*. 2007;334:299. [EL 1; MRCT]

44. **Norris SL, Zhang X, Avenell A, et al.** Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med*. 2004;164:1395-1404. [EL 2; MNRCT]

45. **Astrup A, Carraro R, Finer N, et al.** Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes (Lond)*. 2012;36:843-854. [EL 1; RCT]

46. **Astrup A, Rössner S, Van Gaal L, et al.** Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet*. 2009;374:1606-1616. [EL 1; RCT]

47. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). United Kingdom Prospective Diabetes Study Group. *Lancet*. 1998;352:854-865. [EL 1; RCT]

48. **Adler AI, Stevens RJ, Manley SE, et al.** Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int*. 2003;63:225-232. [EL 3; SS]

49. **Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA.** 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577-1589. [EL 1; RCT, posttrial monitoring]

50. **Stratton IM, Adler AI, Neil HA, et al.** Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321:405-412. [EL 3; SS]

51. **Ohkubo Y, Kishikawa H, Araki E, et al.** Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract*. 1995;28:103-117. [EL 1; RCT]

52. **Ismail-Beigi F, Craven T, Banerji MA, et al.** Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet*. 2010;376:419-430. [EL 1; RCT, posthoc analysis]

53. **Tirosh A, Shai I, Tekes-Manova D, et al.** Normal fasting plasma glucose levels and type 2 diabetes in young men [Erratum in *N Engl J Med*. 2006;354:2401]. *N Engl J Med*. 2005;353:1454-1462. [EL 3; SS]

54. **Hayashino Y, Fukuhara S, Suzukamo Y, Okamura T, Tanaka T, Ueshima H.** Normal fasting plasma glucose levels and type 2 diabetes: the high-risk and population strategy for occupational health promotion (HIPOP-OHP) [corrected] study [Erratum in *Acta Diabetol*. 2007;44:241]. *Acta Diabetol*. 2007;44:164-166. [EL 3; SS]

55. **Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N.** Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med*. 2004;141:413-420. [EL 2; PCS]

56. **ACCORD Study Group, ACCORD Eye Study Group, Chew EY, et al.** Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med*. 2010;363:233-244. [EL 1; RCT]

57. **ADVANCE Collaborative Group, Patel A, MacMahon S, et al.** Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560-2572. [EL 1; RCT]

58. **Riddle MC, Ambrosius WT, Brillon DJ, et al.** Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care*. 2010;33:983-990. [EL 1; RCT]

59. **Schoenaker DA, Simon D, Chaturvedi N, Fuller JH, Soedamah-Muthu SS.** Glycemic control and all-cause mortality risk in type 1 diabetes patients: The EURODIAB Prospective Complications Study. *J Clin Endocrinol Metab*. 2014;99:800-807. [EL 2; PCS]

60. **Currie CJ, Peters JR, Tynan A, et al.** Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. *Lancet*. 2010;375:481-489. [EL 2; RCCS]

61. **Duckworth W, Abraira C, Moritz T, et al.** Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360:129-139. [EL 1; RCT]

62. **Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al.** Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545-2559. [EL 1; RCT]

63. **ACCORD Study Group, Gerstein HC, Miller ME, et al.** Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med*. 2011;364:818-828. [EL 1; RCT]

64. **Bonds DE, Miller ME, Bergenstal RM, et al.** The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ*. 2010;340:b4909. [EL 3; SS]

65. National Institute for Health and Care Excellence. Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults. 2004 (updated December 2014). Available at: http://www.nice.org.uk/guidance/cg15/resources/guidance-type-1-diabetes-pdf [EL 4; NE]

66. The National Collaborating Centre for Chronic Conditions (UK). Type 2 Diabetes: National clinical guideline for management in primary and secondary care (Update). London: Royal College of Physicians (UK); 2008. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0010129/ [EL 4; CPG NE]

67. The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. *Diabetes*. 1996;45:1289-1298. [EL 1; RCT]

68. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med*. 1993;329:977-986. [EL 1; RCT]

69. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-853. [EL 1; RCT]

70. Glucose tolerance and mortality: comparison of WHO and American Diabetic Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. *Lancet*. 1999;354:617-621. [EL 2; PCS]

71. **Lewis JE, Arheart KL, LeBlanc WG, et al.** Food label use and awareness of nutritional information and recommendations among persons with chronic disease. *Am J Clin Nutr*. 2009;90:1351-1357. [EL 3; SS]

72. **Craig WJ, Mangels AR; American Dietetic Association.** Position of the American Dietetic Association: vegetarian diets. *J Am Diet Assoc*. 2009;109:1266-1282. [EL 4; position NE]

73. Dietary Guidelines for Americans, 2010. Washington, DC: US Government Printing Office; 2010. Available at: http://www.health.gov/dietaryguidelines/2010.asp [EL 4; position NE]

74. **Jones JM, Anderson JW.** Grain foods and health: a primer for clinicians. *Phys Sportsmed*. 2008;36:18-33. [EL 4; review NE]

75. **Pawlak R, Colby S.** Benefits, barriers, self-efficacy and knowledge regarding healthy foods; perception of African Americans living in eastern North Carolina. *Nutr Res Pract*. 2009;3:56-63. [EL 3; SS]

76. **Birlouez-Aragon I, Saavedra G, Tessier FJ, et al.** A diet based on high-heat-treated foods promotes risk factors for diabetes mellitus and cardiovascular diseases. *Am J Clin Nutr*. 2010;91:1220-1226. [EL 1; RCT]

77. **Vuksan V, Rogovik AL, Jovanovski E, Jenkins AL.** Fiber facts: benefits and recommendations for individuals with type 2 diabetes. *Curr Diab Rep*. 2009;9:405-411. [EL 4; review NE]

78. **Wheeler ML, Pi-Sunyer FX.** Carbohydrate issues: type and amount. *J Am Diet Assoc*. 2008;108:S34-S39. [EL 4; review NE]

79. **Trinidad TP, Mallillin AC, Loyola AS, Sagum RS, Encabo RR.** The potential health benefits of legumes as a good source of dietary fibre. *Br J Nutr*. 2010;103:569-574. [EL 4; review NE]

80. **Hare-Bruun H, Nielsen BM, Grau K, Oxlund AL, Heitmann BL.** Should glycemic index and glycemic load be considered in dietary recommendations? *Nutr Rev*. 2008;66:569-590. [EL 4; NE review]

81. **Palou A, Bonet ML, Pico C.** On the role and fate of sugars in human nutrition and health. Introduction. *Obes Rev*. 2009;10 Suppl 1:1-8. [EL 4; review NE]

82. **Minihane AM, Harland JI.** Impact of oil used by the frying industry on population fat intake. *Crit Rev Food Sci Nutr*. 2007;47:287-297. [EL 4; review NE]

83. **Micha R, Wallace SK, Mozaffarian D.** Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. *Circulation*. 2010;121:2271-2283. [EL 2; MNRCT]

84. **Mechanick JI, Brett EM, Chausmer AB, Dickey RA, Wallach S; American Association of Clinical Endocrinologists.** American Association of Clinical Endocrinologists medical guidelines for the clinical use of dietary supplements and nutraceuticals [Erratum in *Endocr Pract*. 2008;14:802-803]. *Endocr Pract*. 2003;9:417-470. [EL 4; CPG NE]

85. **Vang A, Singh PN, Lee JW, Haddad EH, Brinegar CH.** Meats, processed meats, obesity, weight gain and occurrence of diabetes among adults: findings from Adventist Health Studies [Erratum in *Ann Nutr Metab*. 2010;56:232]. *Ann Nutr Metab*. 2008;52:96-104. [EL 2; PCS, data may not be generalizable to patients with diabetes already]

86. **Corsino L, Svetkey LP, Ayotte BJ, Bosworth HB.** Patient characteristics associated with receipt of lifestyle behavior advice. *N C Med J*. 2009;70:391-398. [EL 3; SS]

87. **Micha R, Mozaffarian D.** Saturated fat and cardiometabolic risk factors, coronary heart disease, stroke, and diabetes: a fresh look at the evidence. *Lipids*. 2010;45:893-905. [EL 4; review NE]

88. **Booker CS, Mann JI.** Trans fatty acids and cardiovascular health: translation of the evidence base. *Nutr Metab Cardiovasc Dis*. 2008;18:448-456. [EL 4; NE review]

89. **Willcox DC, Willcox BJ, Todoriki H, Suzuki M.** The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load. *J Am Coll Nutr*. 2009;28 Suppl:500S-516S. [EL 4; review NE]

90. **Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ.** Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA*. 2005;293:43-53. [EL 1; RCT, single blinded]

91. **Gardner CD, Kiazand A, Alhassan S, et al.** Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. *JAMA*. 2007;297:969-977. [EL 1; RCT, not blinded, adherence not controlled for]

92. **Foster GD, Wyatt HR, Hill JO, et al.** Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. *Ann Intern Med*. 2010;153:147-157. [EL 1; RCT, not blinded]

93. **Sacks FM, Bray GA, Carey VJ, et al.** Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med*. 2009;360:859-873. [EL 1; RCT]

94. **Evert AB, Boucher JL, Cypress M, et al.** Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2013;36:3821-3842. [EL 4; NE]

95. **Look AHEAD Research Group.** Eight-year weight losses with an intensive lifestyle intervention: the Look AHEAD study. *Obesity (Silver Spring)*. 2014;22:5-13. [EL 1; RCT, not blinded]

96. **Wadden TA, West DS, Neiberg RH, et al.** One-year weight losses in the Look AHEAD study: factors associated with success. *Obesity (Silver Spring)*. 2009;17:713-722. [EL 1; RCT]

97. **Manders RJ, Van Dijk JW, van Loon LJ.** Low-intensity exercise reduces the prevalence of hyperglycemia in type 2 diabetes. *Med Sci Sports Exerc*. 2010;42:219-225. [EL 1; RCT, small sample size]

98. **Hansen D, Dendale P, Jonkers RA, et al.** Continuous low- to moderate-intensity exercise training is as effective as moderate- to high-intensity exercise training at lowering blood HbA(1c) in obese type 2 diabetes patients. *Diabetologia*. 2009;52:1789-1797. [EL 2; NRCT]

99. **Praet SF, Manders RJ, Lieverse AG, et al.** Influence of acute exercise on hyperglycemia in insulin-treated type 2 diabetes. *Med Sci Sports Exerc*. 2006;38:2037-2044. [EL 2; NRCT]

100. **De Feyter HM, Praet SF, van den Broek NM, et al.** Exercise training improves glycemic control in long-standing insulin-treated type 2 diabetic patients. *Diabetes Care*. 2007;30:2511-2513. [EL 2; NRCT]

101. **Church TS, Blair SN, Cocreham S, et al.** Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial [Erratum in *JAMA*. 2011;305:892]. *JAMA*. 2010;304:2253-2262. [EL 1; RCT]

102. **Balducci S, Alessi E, Cardelli P, Cavallo S, Fallucca F, Pugliese G.** Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis: response to Snowling and Hopkins. *Diabetes Care*. 2007;30:e25; author reply e6. [EL 4; commentary NE]

103. **Balducci S, Zanuso S, Nicolucci A, et al.** Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 diabetes mellitus: a randomized controlled trial: the Italian Diabetes and Exercise Study (IDES). *Arch Intern Med*. 2010;170:1794-1803. [EL 1; RCT]

104. **Colberg SR, Sigal RJ, Fernhall B, et al.** Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary. *Diabetes Care*. 2010;33:2692-2696. [EL 4; consensus NE]

105. **Steppel JH, Horton ES.** Exercise in the management of type 1 diabetes mellitus. *Rev Endocr Metab Disord*. 2003;4:355-360. [EL 4; NE]

106. **Ross R, Lam M, Blair SN, et al.** Trial of prevention and reduction of obesity through active living in clinical settings: a randomized controlled trial. *Arch Intern Med*. 2012;172:414-424. [EL 1; RCT, not blinded]

107. **Phung OJ, Scholle JM, Talwar M, Coleman CI.** Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA*. 2010;303:1410-1418. [EL 1; MRCT]

108. **Parchman ML, Pugh JA, Wang CP, Romero RL.** Glucose control, self-care behaviors, and the presence of the chronic care model in primary care clinics. *Diabetes Care*. 2007;30:2849-2854. [EL 3; CSS]

109. **Inzucchi SE, Bergenstal RM, Buse JB, et al.** Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [Erratum in *Diabetes Care*. 2013;36:490]. *Diabetes Care*. 2012;35:1364-1379. [EL 4; NE]

110. **Kahn SE, Haffner SM, Heise MA, et al.** Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006;355:2427-2443. [EL 1; RCT]

111. **Bailey CJ, Turner RC.** Metformin. *N Engl J Med*. 1996; 334:574-579. [EL 4; NE]

112. **Roumie CL, Hung AM, Greevy RA, et al.** Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. *Ann Intern Med*. 2012;157:601-610. [EL 2; RCCS]

113. **Boussageon R, Supper I, Bejan-Angoulvant T, et al.** Reappraisal of metformin efficacy in the treatment of type 2 diabetes: a meta-analysis of randomised controlled trials. *PLoS Med*. 2012;9:e1001204. [EL 1; MRCT]

114. **de Jager J, Kooy A, Lehert P, et al.** Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ*. 2010;340:c2181. [EL 1; RCT]

115. **Wright A, Burden AC, Paisey RB, Cull CA, Holman RR; U.K. Prospective Diabetes Sutdy Group.** Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). *Diabetes Care*. 2002;25:330-336. [EL 1; RCT]

116. **Thulé PM, Umpierrez G.** Sulfonylureas: a new look at old therapy. *Curr Diabetes Rep*. 2014;14:473. [EL 4; NE]

117. **Gerstein HC, Ratner RE, Cannon CP, et al.** Effect of rosiglitazone on progression of coronary atherosclerosis in patients with type 2 diabetes mellitus and coronary artery disease: the assessment on the prevention of progression by rosiglitazone on atherosclerosis in diabetes patients with cardiovascular history trial. *Circulation*. 2010;121:1176-1187. [EL 1; RCT]

118. **Riche DM, Valderrama R, Henyan NN.** Thiazolidinediones and risk of repeat target vessel revascularization following percutaneous coronary intervention: a meta-analysis. *Diabetes Care*. 2007;30:384-388. [EL 1; MRCT]

119. **Abbatecola AM, Lattanzio F, Spazzafumo L, et al.** Adiposity predicts cognitive decline in older persons with diabetes: a 2-year follow-up. *PLoS One*. 2010;5:e10333. [EL 2; PCS]

120. **Lincoff AM, Wolski K, Nicholls SJ, Nissen SE.** Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA*. 2007;298:1180-1188. [EL 1; MRCT]

121. **Stein LL, Dong MH, Loomba R.** Insulin sensitizers in nonalcoholic fatty liver disease and steatohepatitis: Current status. *Adv Ther*. 2009;26:893-907. [EL 4; review NE]

122. **Bolen S, Feldman L, Vassy J, et al.** Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus [Erratum in *Ann Intern Med*. 2007;147:887]. *Ann Intern Med*. 2007;147:386-399. [EL 2; MNRCT]

123. **Kahn SE, Zinman B, Lachin JM, et al.** Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care*. 2008;31:845-851. [EL 1; RCT, posthoc analysis]

124. **Schwartz AV, Sellmeyer DE, Vittinghoff E, et al.** Thiazolidinedione use and bone loss in older diabetic adults. *J Clin Endocrinol Metab*. 2006;91:3349-3354. [EL 2; PCS]

125. **Woodcock J, Sharfstein JM, Hamburg M.** Regulatory action on rosiglitazone by the U.S. Food and Drug Administration. *N Engl J Med*. 2010;363:1489-1491. [EL 4; review NE]

126. **Hiatt WR, Kaul S, Smith RJ.** The cardiovascular safety of diabetes drugs--insights from the rosiglitazone experience. *N Engl J Med*. 2013;369:1285-1287. [EL 4; NE]

127. **Wang T, Ning G, Bloomgarden Z.** Diabetes and cancer relationships. *J Diabetes*. 2013;5:378-390. [EL 4; NE]

128. **Levin D, Bell S, Sund R, et al.** Pioglitazone and bladder cancer risk: a multipopulation pooled, cumulative exposure analysis. *Diabetologia*. 2014;58:493-504. [EL 3; SS]

129. **Arnolds S, Dellweg S, Clair J, et al.** Further improvement in postprandial glucose control with addition of exenatide or sitagliptin to combination therapy with insulin glargine and metformin: a proof-of-concept study. *Diabetes Care*. 2010;33:1509-1515. [EL 1; RCT]

130. **Riddle MC, Henry RR, Poon TH, et al.** Exenatide elicits sustained glycaemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulphonylureas with or without metformin. *Diabetes Metab Res Rev*. 2006;22:483-491. [EL 1; RCT follow-up study]

131. **DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD.** Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care*. 2005;28:1092-1100. [EL 1; RCT]

132. **Kendall DM, Riddle MC, Rosenstock J, et al.** Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care*. 2005;28:1083-1091. [EL 1; RCT]

133. **Zinman B, Hoogwerf BJ, Durán García S, et al.** The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial [Erratum in *Ann Intern Med*. 2007;146:896]. *Ann Intern Med*. 2007;146:477-485. [EL 1; RCT]

134. **Larsen PJ, Wulff EM, Gotfredsen CF, et al.** Combination of the insulin sensitizer, pioglitazone, and the long-acting GLP-1 human analog, liraglutide, exerts potent synergistic glucose-lowering efficacy in severely diabetic ZDF rats. *Diabetes Obes Metab*. 2008;10:301-311. [EL 4; animal study NE]

135. **Zinman B, Gerich J, Buse JB, et al.** Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care*. 2009;32:1224-1230. [EL 1; RCT]

136. **Nauck M, Marre M.** Adding liraglutide to oral anti-diabetic drug monotherapy: efficacy and weight benefits. *Postgrad Med*. 2009;121:5-15. [EL 1; RCT]

137. **Marre M, Shaw J, Brändle M, et al.** Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabet Med*. 2009;26:268-278. [EL 1; RCT]

138. **Russell-Jones D, Vaag A, Schmitz O, et al.** Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia*. 2009;52:2046-2055. [EL 1; RCT]

139. **Bergenstal R, Lewin A, Bailey T, et al.** Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea. *Curr Med Res Opin*. 2009;25:65-75. [EL 1; RCT]

140. **Blevins T, Han J, Nicewarner D, Chen S, Oliveira JH, Aronoff S.** Exenatide is non-inferior to insulin in reducing HbA1c: an integrated analysis of 1423 patients with type 2 diabetes. *Postgrad Med*. 2010;122:118-128. [EL 1; MRCT]

141.  **Amori RE, Lau J, Pittas AG.** Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA.* 2007;298:194-206. [EL 1; MNCT]

142.  **Parks M, Rosebraugh C.** Weighing risks and benefits of liraglutide--the FDA's review of a new antidiabetic therapy. *N Engl J Med.* 2010;362:774-777. [EL 4; NE]

143.  **Bloomgarden Z, Drexler A.** What role will 'gliptins' play in glycemic control? *Cleve Clin J Med.* 2008;75:305-310. [EL 4; opinion NE]

144.  **Williams-Herman D, Engel SS, Round E, et al.** Safety and tolerability of sitagliptin in clinical studies: a pooled analysis of data from 10,246 patients with type 2 diabetes. *BMC Endocr Disord.* 2010;10:7. [EL 1; MRCT]

145.  **White WB, Cannon CP, Heller SR, et al.** Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med.* 2013;369:1327-1335. [EL 1; RCT]

146.  **Scirica BM, Bhatt DL, Braunwald E, et al.** Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med.* 2013;369:1317-1326. [EL 1; RCT]

147.  **Bloomgarden Z.** Sodium glucose transporter 2 inhibition: a new approach to diabetes treatment. *J Diabetes.* 2013;5:225-227. [EL 4; NE]

148.  **Fonseca VA, Handelsman Y, Staels B.** Colesevelam lowers glucose and lipid levels in type 2 diabetes: the clinical evidence. *Diabetes Obes Metab.* 2010;12:384-392. [EL 4; NE]

149.  **Gaziano JM, Cincotta AH, O'Connor CM, et al.** Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care.* 2010;33:1503-1508. [EL 1; RCT]

150.  **Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P.** A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care.* 2006;29:1269-1274. [EL 1; RCT]

151.  **Home PD, Fritsche A, Schinzel S, Massi-Benedetti M.** Meta-analysis of individual patient data to assess the risk of hypoglycaemia in people with type 2 diabetes using NPH insulin or insulin glargine. *Diabetes Obes Metab.* 2010;12:772-779. [EL 1; MRCT]

152.  **Monami M, Marchionni N, Mannucci E.** Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract.* 2008;81:184-189. [EL 1; MRCT]

153.  **Riddle MC, Rosenstock J, Gerich J, Insulin Glargine Study 4002 Study Investigators.** The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care.* 2003;26:3080-3086. [EL 1; RCT]

154.  **Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Järvinen H.** Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. *Diabetes Care.* 2005;28:254-259. [EL 1; RCT]

155.  **Tunis SL, Sauriol L, Minshall ME.** Cost effectiveness of insulin glargine plus oral antidiabetes drugs compared with premixed insulin alone in patients with type 2 diabetes mellitus in Canada. *Appl Health Econ Health Policy.* 2010;8:267-280. [EL 3; SS]

156.  **Yki-Järvinen H, Kauppila M, Kujansuu E, et al.** Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med.* 1992;327:1426-1433. [EL 1; RCT]

157.  **Peyrot M, Rubin RR, Polonsky WH, Best JH.** Patient reported outcomes in adults with type 2 diabetes on basal insulin randomized to addition of mealtime pramlintide or rapid-acting insulin analogs. *Curr Med Res Opin.* 2010;26:1047-1054. [EL 1; RCT, small sample size]

158.  **Riddle M, Pencek R, Charenkavanich S, Lutz K, Wilhelm K, Porter L.** Randomized comparison of pramlintide or mealtime insulin added to basal insulin treatment for patients with type 2 diabetes. *Diabetes Care.* 2009;32:1577-1582. [EL 1; RCT, not blinded]

159.  **Bell DS, Dharmalingam M, Kumar S, Sawakhande RB.** Triple oral fixed-dose diabetes polypill versus insulin plus metformin efficacy demonstration study in the treatment of advanced type 2 diabetes (TrIED study-II). *Diabetes Obes Metab.* 2011;13:800-805. [EL 1; RCT]

160.  **Garber AJ.** Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. *Diabetes Care.* 2011;34 Suppl 2:S279-S284. [EL 4; NE]

161.  **Buse JB, Bergenstal RM, Glass LC, et al.** Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med.* 2011;154:103-112. [EL 1; RCT]

162.  **Devries JH, Bain SC, Rodbard HW, et al.** Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1C targets. *Diabetes Care.* 2012;35:1446-1454. [EL 1; RCT, not blinded, not placebo controlled]

163.  **Vilsbøll T, Rosenstock J, Yki-Järvinen H, et al.** Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. *Diabetes Obes Metab.* 2010;12:167-177. [EL 1; RCT]

164.  **Barnett AH, Charbonnel B, Donovan M, Fleming D, Chen R.** Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. *Curr Med Res Opin.* 2012;28:513-523. [EL 1; RCT]

165.  **DeWitt DE, Hirsch IB.** Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA.* 2003;289:2254-2264. [EL 4; NE]

166.  **Moghissi E, Ismail-Beigi F, Devine RC.** Hypoglycemia: minimizing its impact in type 2 diabetes. *Endocr Pract.* 2013;19:526-535. [EL 4; NE]

167.  **United Kingdom Hypoglycaemia Study Group.** Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia.* 2007;50:1140-1147. [EL 1; RCT, not blinded]

168.  **Zoungas S, Patel A, Chalmers J, et al.** Severe hypoglycemia and risks of vascular events and death. *N Engl J Med.* 2010;363:1410-1418. [EL 1; RCT]

169.  **Chantelau E, Kohner EM.** Why some cases of retinopathy worsen when diabetic control improves. *BMJ.* 1997;315:1105-1106. [EL 4; NE]

170.  **Hirsch IB.** Insulin analogues. *N Engl J Med.* 2005;352:174-183. [EL 4; review NE]

171.  **Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J.** Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. *Cochrane Database Syst Rev.* 2010:CD005103. [EL 1; MRCT]

172.  **Monami M, Lamanna C, Marchionni N, Mannucci E.** Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 2 diabetes: a meta-analysis. *Exp Clin Endocrinol Diabetes.* 2009;117:220-222. [EL 1; MRCT]

173. **Edelman S, Garg S, Frias J, et al.** A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes. *Diabetes Care.* 2006;29:2189-2195. [EL 1; RCT]

174. **Ratner RE, Dickey R, Fineman M, et al.** Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial. *Diabet Med.* 2004;21:1204-1212. [EL 1; RCT]

175. **Whitehouse F, Kruger DF, Fineman M, et al.** A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. *Diabetes Care.* 2002;25:724-730. [EL 1; RCT]

176. **Lee NJ, Norris SL, Thakurta S.** Efficacy and harms of the hypoglycemic agent pramlintide in diabetes mellitus. *Ann Fam Med.* 2010;8:542-549. [EL 1; MRCT]

177. **Vella S, Buetow L, Royle P, Livingstone S, Colhoun HM, Petrie JR.** The use of metformin in type 1 diabetes: a systematic review of efficacy. *Diabetologia.* 2010;53:809-820. [EL 1; MRCT]

178. **Whipple AO.** The surgical therapy of hyperinsulinism. *J Int Chir.* 1938;3:237-276. [EL 4; review NE]

179. **Seaquist ER, Anderson J, Childs B, et al.** Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care.* 2013;36:1384-95. [EL 4; NE]

180. **Cryer PE.** Mechanisms of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med.* 2013;369:362-372. [EL 4; NE]

181. **Kostev K, Dippel FW, Rathmann W.** Predictors of hypoglycaemia in insulin-treated type 2 diabetes patients in primary care: A retrospective database analysis. *Prim Care Diabetes.* 2014;8:127-131. [EL 3; SS]

182. **Bruderer SG, Bodmer M, Jick SS, Bader G, Schlienger RG, Meier CR.** Incidence of and risk factors for severe hypoglycaemia in treated type 2 diabetes mellitus patients in the UK - a nested case-control analysis. *Diabetes Obes Metab.* 2014;16:801-811. [EL 2; RCCS]

183. **Feinkohl I, Aung PP, Keller M, et al.** Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the edinburgh type 2 diabetes study. *Diabetes Care.* 2014;37:507-515. [EL 2; PCS]

184. **Goto A, Arah OA, Goto M, Terauchi Y, Noda M.** Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. *BMJ.* 2013;347:f4533. [EL 2; MNRCT]

185. **McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA.** Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care.* 2012;35:1897-1901. [EL 2; PCS]

186. **Cryer PE.** Death during intensive glycemic therapy of diabetes: mechanisms and implications. *Am J Med.* 2011;124:993-996. [EL 4; NE]

187. **Cryer PE, Davis SN, Shamoon H.** Hypoglycemia in diabetes. *Diabetes Care.* 2003;26:1902-1912. [EL 4; NE]

188. **Liu S, Zhao Y, Hempe JM, Fonseca V, Shi L.** Economic burden of hypoglycemia in patients with Type 2 diabetes. *Expert Rev Pharmacoecon Outcomes Res.* 2012;12:47-51. [EL 4; NE]

189. **Gangji AS, Cukierman T, Gerstein HC, Goldsmith CH, Clase CM.** A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. *Diabetes Care.* 2007;30:389-394. [EL 1; MRCT]

190. **Fritsche A, Stefan N, Häring H, Gerich J, Stumvoll M.** Avoidance of hypoglycemia restores hypoglycemia awareness by increasing beta-adrenergic sensitivity in type 1 diabetes. *Ann Intern Med.* 2001;134:729-736. [EL 2; NRCT]

191. **Fritsche A, Stumvoll M, Häring HU, Gerich JE.** Reversal of hypoglycemia unawareness in a long-term type 1 diabetic patient by improvement of beta-adrenergic sensitivity after prevention of hypoglycemia. *J Clin Endocrinol Metab.* 2000;85:523-525. [EL 3; SCR]

192. **Suh DC, Kim CM, Choi IS, Plauschinat CA, Barone JA.** Trends in blood pressure control and treatment among type 2 diabetes with comorbid hypertension in the United States: 1988-2004. *J Hypertens.* 2009;27:1908-1916. [EL 3; SS]

193. **Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL.** Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med.* 2000;342:905-912. [EL 2; PCS]

194. **Sowers JR, Williams M, Epstein M, Bakris G.** Hypertension in patients with diabetes. Strategies for drug therapy to reduce complications. *Postgrad Med.* 2000;107:47-54, 60. [EL 4; review NE]

195. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. United Kingdom Prospective Diabetes Study Group. *BMJ.* 1998;317:703-713. [EL 1; RCT]

196. **Adler AI, Stratton IM, Neil HA, et al.** Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ.* 2000;321:412-419. [EL 2; PCS]

197. **Hansson L, Zanchetti A, Carruthers SG, et al.** Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet.* 1998;351:1755-1762. [EL 1; RCT]

198. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. [Erratum in *Lancet.* 2000;356:860]. *Lancet.* 2000;355:253-259. [EL 1; RCT]

199. **Dahlöf B, Devereux RB, Kjeldsen SE, et al.** Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet.* 2002;359:995-1003. [EL 1; RCT]

200. **Whelton PK, Barzilay J, Cushman WC, et al.** Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med.* 2005;165:1401-1409. [EL 1; RCT]

201. **Lenfant C, Chobanian AV, Jones DW, et al.** Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. *Hypertension.* 2003;41:1178-1179. [EL 4; NE]

202. **Chobanian AV, Bakris GL, Black HR, et al.** The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA.* 2003;289:2560-2572. [EL 4; CPG NE]

203. **Torre JJ, Bloomgarden ZT, Dickey RA, et al.** American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of hypertension. *Endocr Pract.* 2006;12:193-222. [EL 4; NE]

204. **American Diabetes Association.** Standards of medical care in diabetes--2012. *Diabetes Care.* 2012;35 Suppl 1: S11-S63. [EL 4; NE]

205. **Writing Team for the Diabetes C, Complications Trial/Epidemiology of Diabetes Inventions and Complications Research Group.** Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA.* 2002;287:2563-2569. [EL 4; review NE]

206. **Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR.** Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med.* 2008;359:1565-1576. [EL 1; RCT, questionnaires and other variables may have confounded]

207. **ACCORD Study Group, Cushman WC, Evans GW, et al.** Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med.* 2010;362:1575-1585. [EL 1; RCT]

208. **Pearson TA, Palaniappan LP, Artinian NT, et al.** American Heart Association Guide for Improving Cardiovascular Health at the Community Level, 2013 update: a scientific statement for public health practitioners, healthcare providers, and health policy makers. *Circulation.* 2013;127:1730-1753. [EL 4; NE]

209. **Mancia G, Fagard R, Narkiewicz K, et al.** 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J.* 2013;34:2159-2219. [EL 4; NE]

210. **Go AS, Bauman MA, Coleman King SM, et al.** An effective approach to high blood pressure control: a science advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. *Hypertension.* 2014;63:878-885. [EL 4; NE]

211. **Weber MA, Schiffrin EL, White WB, et al.** Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens.* 2014;16:14-26. [EL 4; NE]

212. **American Diabetes Association.** Standards of medical care in diabetes--2014. *Diabetes Care.* 2014;37 Suppl 1: S14-S80. [EL 4; NE]

213. **Verdecchia P.** Prognostic value of ambulatory blood pressure : current evidence and clinical implications. *Hypertension.* 2000;35:844-851. [EL 4; review NE]

214. **Rahman M, Pressel S, Davis BR, et al.** Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med.* 2005;165:936-946. [EL 1; RCT, posthoc analysis]

215. **Parving HH, Brenner BM, McMurray JJ, et al.** Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med.* 2012;367:2204-2213. [EL 1; RCT]

216. **Fried LF, Emanuele N, Zhang JH, et al.** Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med.* 2013;369:1892-1903. [EL 4; NE]

217. **Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, Grundy SM.** Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. *Am J Cardiol.* 2006;98:1363-1368. [EL 3; SS]

218. **Jellinger PS, Smith DA, Mehta AE, et al.** American Association of Clinical Endocrinologists' guidelines for management of dyslipidemia and prevention of atherosclerosis. *Endocr Pract.* 2012;18 Suppl 1:1-78. [EL 4; NE]

219. **Taskinen MR.** Diabetic dyslipidaemia: from basic research to clinical practice. *Diabetologia.* 2003;46:733-749. [EL 4; review NE]

220. **Ganda OP.** *Dyslipidemia: Pathogenesis and Management.* 2nd ed. New York, NY: Springer; 2009. [EL 4; review NE]

221. **Bakris GL, Molitch M.** Microalbuminuria as a risk predictor in diabetes: the continuing saga. *Diabetes Care.* 2014;37:867-875. [EL 4; NE]

222. **Purnell JQ, Zinman B, Brunzell JD.** The effect of excess weight gain with intensive diabetes mellitus treatment on cardiovascular disease risk factors and atherosclerosis in type 1 diabetes mellitus: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) study. *Circulation.* 2013;127:180-187. [EL 1; RCT]

223. **Ridker PM, Danielson E, Fonseca FA, et al.** Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359:2195-2207. [EL 1; RCT]

224. **Colhoun HM, Betteridge DJ, Durrington PN, et al.** Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet.* 2004;364:685-696. [EL 1; RCT]

225. **Shepherd J, Barter P, Carmena R, et al.** Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. *Diabetes Care.* 2006;29:1220-1226. [EL 1; RCT]

226. **Athyros VG, Papageorgiou AA, Symeonidis AN, et al.** Early benefit from structured care with atorvastatin in patients with coronary heart disease and diabetes mellitus. *Angiology.* 2003;54:679-690. [EL 1; RCT]

227. **Ahmed S, Cannon CP, Murphy SA, Braunwald E.** Acute coronary syndromes and diabetes: Is intensive lipid lowering beneficial? Results of the PROVE IT-TIMI 22 trial. *Eur Heart J.* 2006;27:2323-2329. [EL 1; RCT, retrospective study]

228. **Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, et al.** Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet.* 2008;371:117-125. [EL 1; MRCT]

229. **Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al.** Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet.* 2010;376:1670-1681. [EL 1; MRCT]

230. **Collins R, Armitage J, Parish S, Sleigh P, Peto R, Heart Protection Study Collaborative Group.** MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet.* 2003;361:2005-2016. [EL 1; RCT]

231. **Stone NJ, Robinson JG, Lichtenstein AH, et al.** 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;129:S1-S45. [EL 4; NE]

232. **Ridker PM, Cook NR.** Statins: new American guidelines for prevention of cardiovascular disease. *Lancet*. 2013;382:1762-1765. [EL 4; NE]

233. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA*. 1984;251:365-374. [EL 1; RCT]

234. **Brown BG, Zhao XQ, Chait A, et al.** Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345:1583-1592. [EL 1; RCT]

235. **Brunzell JD.** Clinical practice. Hypertriglyceridemia. *N Engl J Med*. 2007;357:1009-1017. [EL 4; review NE]

236. Clofibrate and niacin in coronary heart disease. *JAMA*. 1975;231:360-381. [EL 1; RCT]

237. **Foody JM, Brown WV, Zieve F, Adewale AJ, Flaim D, Lowe RS, et al.** Safety and efficacy of ezetimibe/simvastatin combination versus atorvastatin alone in adults ≥65 years of age with hypercholesterolemia and with or at moderately high/high risk for coronary heart disease (the VYTELD study). *Am J Cardiol*. 2010;106:1255-1263. [EL 1; RCT]

238. **Zieve F, Wenger NK, Ben-Yehuda O, et al.** Safety and efficacy of ezetimibe added to atorvastatin versus up titration of atorvastatin to 40 mg in Patients > or = 65 years of age (from the ZETia in the ELDerly [ZETELD] study). *Am J Cardiol*. 2010;105:656-663. [EL 1; RCT]

239. **Tonelli M, Wanner C; Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members.** Lipid management in chronic kidney disease: synopsis of the Kidney Disease: Improving Global Outcomes 2013 clinical practice guideline. *Ann Intern Med*. 2014;160:182. [EL 4; NE]

240. **Ganda OM.** Effects of post-transplant drugs on lipids and treatment options. Jacksonville, FL: The National Lipid Association; 2014. Available at: https://www.lipid.org/communications/lipidspin/2014POTPOURRI/15. [EL 4; NE]

241. **Lu W, Resnick HE, Jablonski KA, et al.** Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. *Diabetes Care*. 2003;26:16-23. [EL 2; PCS]

242. **Brunzell JD, Davidson M, Furberg CD, et al.** Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care*. 2008;31:811-822. [EL 4; consensus]

243. **Ganda OP.** Refining lipoprotein assessment in diabetes: apolipoprotein B makes sense. *Endocr Pract*. 2009;15:370-376. [EL 4; review NE]

244. **Scott R, O'Brien R, Fulcher G, et al.** Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetes Care*. 2009;32:493-498. [EL 3; SS]

245. **ACCORD Study Group, Ginsberg HN, Elam MB, et al.** Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1563-1574. [EL 1; RCT]

246. **Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, et al.** Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302:1993-2000. [EL 3; SS]

247. **Bays HE, Tighe AP, Sadovsky R, Davidson MH.** Prescription omega-3 fatty acids and their lipid effects: physiologic mechanisms of action and clinical implications. *Expert Rev Cardiovasc Ther*. 2008;6:391-409. [EL 4; review NE]

248. **Hegele RA, Ginsberg HN, Chapman MJ, et al.** The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. *Lancet Diabetes Endocrinol*. 2014;2:655-666. [EL 4; NE]

249. **Christian JB, Arondekar B, Buysman EK, Jacobson TA, Snipes RG, Horwitz RI.** Determining triglyceride reductions needed for clinical impact in severe hypertriglyceridemia. *Am J Med*. 2014;127:36-44.e1. [EL 3; SS]

250. **Berglund L, Brunzell JD, Goldberg AC, et al.** Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97:2969-2989. [EL 4; NE]

251. **Keech A, Simes RJ, Barter P, et al.** Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005;366:1849-1861. [EL 1; RCT]

252. **Rosenblit PD.** Do persons with diabetes benefit from combination statin and fibrate therapy? *Curr Cardiol Rep*. 2012;14:112-124. [EL 4; NE]

253. **Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B.** Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. *Atherosclerosis*. 2011;217:492-498. [EL 1; MRCT]

254. **Bruckert E, Labreuche J, Deplanque D, Touboul PJ, Amarenco P.** Fibrates effect on cardiovascular risk is greater in patients with high triglyceride levels or atherogenic dyslipidemia profile: a systematic review and meta-analysis. *J Cardiovasc Pharmacol*. 2011;57:267-272. [EL 1; MRCT]

255. **Sacks FM, Carey VJ, Fruchart JC.** Combination lipid therapy in type 2 diabetes. *N Engl J Med*. 2010;363:692-694; author reply 4-5. [EL 4; NE]

256. **AIM-HIGH Investigators, Boden WE, Probstfield JL, et al.** Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365:2255-2267. [EL 1; RCT]

257. **HPS2-THRIVE Collaborative Group.** HPS2-THRIVE randomized placebo-controlled trial in 25,673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J*. 2013;34:1279-1291. [EL 1; RCT]

258. **Preiss D, Seshasai SR, Welsh P, et al.** Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011;305:2556-2564. [EL 1; MRCT]

259. **Sattar N, Preiss D, Murray HM, et al.** Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375:735-742. [EL 1; MRCT]

260. **Maki KC, Ridker PM, Brown WV, Grundy SM, Sattar N, The Diabetes Subpanel of the Lipid Association Expert Panel.** An assessment by the Statin Diabetes Safety Task Force: 2014 update. *J Clin Lipidol*. 2014;8:S17-S29. [EL 4; NE]

261.  **de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J.** Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA.* 2011;305:2532-2539. [EL 3; SS]

262.  **Fioretto P, Mauer M.** Histopathology of diabetic nephropathy. *Semin Nephrol.* 2007;27:195-207. [EL 4; NE]

263.  **Kidney Disease: Improving Global Outcomes CKD Work Group.** KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013;3:1-150. [EL 4; NE]

264.  **National Kidney Foundation.** KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. *Am J Kidney Dis.* 2012;60:850-886. [EL 4; NE]

265.  **Newman DJ, Mattock MB, Dawnay AB, et al.** Systematic review on urine albumin testing for early detection of diabetic complications. *Health Technol Assess.* 2005;9:iii-vi, xiii-163. [EL 2; MNRST]

266.  **Levey AS, de Jong PE, Coresh J, et al.** The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int.* 2011;80:17-28. [EL 4; NE]

267.  **Kidney Disease: Improving Global Outcomes Blood Pressure Work Group.** KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney int Suppl.* 2012;2:337-414. [EL 4; NE]

268.  **Wanner C, Krane V, Marz W, et al.** Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med.* 2005;353:238-248. [EL 1; RCT]

269.  **Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF.** Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med.* 2012;157:263-275. [EL 1; MRCT]

270.  **Baigent C, Landray MJ, Reith C, et al.** The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet.* 2011;377:2181-2192. [EL 1; RCT]

271.  **Slinin Y, Ishani A, Rector T, et al.** Management of hyperglycemia, dyslipidemia, and albuminuria in patients with diabetes and CKD: a systematic review for a KDOQI clinical practice guideline. *Am J Kidney Dis.* 2012;60:747-769. [EL 1; MRCT]

272.  **Lewis EJ, Hunsicker LG, Bain RP, Rohde RD.** The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med.* 1993;329:1456-1462. [EL 1; RCT]

273.  **Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK; AVOID Study Investigators.** Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med.* 2008;358:2433-2446. [EL 1; RCT]

274.  **ONTARGET Investigators, Yusuf S, Teo KK, et al.** Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med.* 2008;358:1547-1559. [EL 1; RCT]

275.  **Halimi JM, Asmar R, Ribstein J.** Optimal nephroprotection: use, misuse and misconceptions about blockade of the renin-angiotensin system. Lessons from the ONTARGET and other recent trials. *Diabetes Metab.* 2009;35:425-430. [EL 4; review NE]

276.  **Koro CE, Lee BH, Bowlin SJ.** Antidiabetic medication use and prevalence of chronic kidney disease among patients with type 2 diabetes mellitus in the United States. *Clin Ther.* 2009;31:2608-2617. [EL 3; CSS]

277.  **Kidney Disease: Improving Global Outcomes Anemia Work Group.** KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl.* 2012;2:279-335. [EL 4; NE]

278.  **Al-Aly Z, Qazi RA, González EA, Zeringue A, Martin KJ.** Changes in serum 25-hydroxyvitamin D and plasma intact PTH levels following treatment with ergocalciferol in patients with CKD. *Am J Kidney Dis.* 2007;50:59-68. [EL 3; SS]

279.  **Levinsky NG.** Specialist evaluation in chronic kidney disease: too little, too late. *Ann Intern Med.* 2002;137:542-543. [EL 4; opinion NE]

280.  **Becker BN, Brazy PC, Becker YT, et al.** Simultaneous pancreas-kidney transplantation reduces excess mortality in type 1 diabetic patients with end-stage renal disease. *Kidney Int.* 2000;57:2129-2135. [EL 2; PCS]

281.  **Nathan DM.** Long-term complications of diabetes mellitus. *N Engl J Med.* 1993;328:1676-1685. [EL 4; review NE]

282.  **Ruta LM, Magliano DJ, Lemesurier R, Taylor HR, Zimmet PZ, Shaw JE.** Prevalence of diabetic retinopathy in type 2 diabetes in developing and developed countries. *Diabet Med.* 2013;30:387-398. [EL 3; SS]

283.  **Yau JW, Rogers SL, Kawasaki R, et al.** Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care.* 2012;35:556-564. [EL 2; MNRCT]

284.  **Harris Nwanyanwu K, Talwar N, Gardner TW, Wrobel JS, Herman WH, Stein JD.** Predicting development of proliferative diabetic retinopathy. *Diabetes Care.* 2013;36:1562-1568. [EL 3; SS]

285.  **Williams R, Airey M, Baxter H, Forrester J, Kennedy-Martin T, Girach A.** Epidemiology of diabetic retinopathy and macular oedema: a systematic review. *Eye (Lond).* 2004;18:963-983. [EL 2; MNRCT]

286.  **Hansen AB, Hartvig NV, Jensen MS, Borch-Johnsen K, Lund-Andersen H, Larsen M.** Diabetic retinopathy screening using digital non-mydriatic fundus photography and automated image analysis. *Acta Ophthalmol Scand.* 2004;82:666-672. [EL 3; SS]

287.  **Ahmed J, Ward TP, Bursell SE, Aiello LM, Cavallerano JD, Vigersky RA.** The sensitivity and specificity of non-mydriatic digital stereoscopic retinal imaging in detecting diabetic retinopathy. *Diabetes Care.* 2006;29:2205-2209. [EL 3; SS]

288.  **Harris MI, Klein R, Welborn TA, Knuiman MW.** Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care.* 1992;15:815-819. [EL 3; CSS]

289.  **Chalk D, Pitt M, Vaidya B, Stein K.** Can the retinal screening interval be safely increased to 2 years for type 2 diabetic patients without retinopathy? *Diabetes Care.* 2012;35:1663-1668. [EL 4; NE]

290.  **Looker HC, Nyangoma SO, Cromie DT, et al.** Predicted impact of extending the screening interval for diabetic retinopathy: the Scottish Diabetic Retinopathy Screening programme. *Diabetologia.* 2013;56:1716-1725. [EL 2; RCCS]

291.  **Klein R, Klein BE, Moss SE, Davis MD, DeMets DL.** The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol.* 1984;102:520-526. [EL 3; SS]

292.  **Diabetes Control and Complications Trial Research Group.** Effect of pregnancy on microvascular complications in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. *Diabetes Care.* 2000;23:1084-1091. [EL 2; PCS, longitudinal follow-up study]

293. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med.* 2000;342:381-389. [EL 2; PCS]

294. **Mauer M, Zinman B, Gardiner R, et al.** Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med.* 2009;361:40-51. [EL 1; RCT]

295. **Sjølie AK, Klein R, Porta M, et al.** Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial. *Lancet.* 2008;372:1385-1393. [EL 1; RCT]

296. **Keech AC, Mitchell P, Summanen PA, et al.** Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet.* 2007;370:1687-1697. [EL 1; RCT, substudy]

297. **Morgan CL, Owens DR, Aubonnet P, et al.** Primary prevention of diabetic retinopathy with fibrates: a retrospective, matched cohort study. *BMJ Open.* 2013;3:e004025. [EL 2; RCCS]

298. **Scott IU, Jackson GR, Quillen DA, et al.** Effect of doxycycline vs placebo on retinal function and diabetic retinopathy progression in patients with severe nonproliferative or non-high-risk proliferative diabetic retinopathy: a randomized clinical trial. *JAMA Ophthalmol.* 2014;132:535-543. [EL 1; RCT, small sample size]

299. **Ferris FL 3rd, Davis MD, Aiello LM.** Treatment of diabetic retinopathy. *N Engl J Med.* 1999;341:667-678. [EL 4; review NE]

300. **Virgili G, Parravano M, Menchini F, Brunetti M.** Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for diabetic macular oedema. *Cochrane Database Syst Rev.* 2012;12:CD007419. [EL 1; MRCT]

301. **Vinik AI, Michell BD, Leichter SB, Wagner AL, O'Brien JT, Georges LP.** Epidemiology of the complications of diabetes. In: Leslie RDG, Robbins DC, eds. *Diabetes: Clinical Science in Practice.* Cambridge, U.K.: Cambridge University Press; 1995: 221-287. [EL 4; NE]

302. **Holzer SE, Camerota A, Martens L, Cuerdon T, Crystal-Peters J, Zagari M.** Costs and duration of care for lower extremity ulcers in patients with diabetes. *Clin Ther.* 1998;20:169-181. [EL 3; SS]

303. **Caputo GM, Cavanagh PR, Ulbrecht JS, Gibbons GW, Karchmer AW.** Assessment and management of foot disease in patients with diabetes. *N Engl J Med.* 1994;331:854-860. [EL 4; NE]

304. **Vinik AI, Nevoret ML, Casellini C, Parson H.** Diabetic neuropathy. *Endocrinol Metab Clin North Am.* 2013;42:747-787. [EL 4; NE]

305. **Herman WH, Kennedy L.** Underdiagnosis of peripheral neuropathy in type 2 diabetes. *Diabetes Care.* 2005;28:1480-1481. [EL 1; RCT]

306. **Thomas PK.** Classification, differential diagnosis, and staging of diabetic peripheral neuropathy. *Diabetes.* 1997; 46 Suppl 2:S54-S57. [EL 4; NE]

307. **Boulton AJ, Vinik AI, Arezzo JC, et al.** Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care.* 2005;28:956-962. [EL 4; review NE]

308. **Treede RD, Jensen TS, Campbell JN, et al.** Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology.* 2008;70:1630-1635. [EL 4; position NE]

309. **England JD, Gronseth GS, Franklin G, et al.** Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology.* 2005;64:199-207. [EL 4; NE]

310. **Dyck PJ, Davies JL, Clark VM, et al.** Modeling chronic glycemic exposure variables as correlates and predictors of microvascular complications of diabetes. *Diabetes Care.* 2006;29:2282-2288. [EL 3; CSS]

311. **Dyck PJ, Davies JL, Wilson DM, Service FJ, Melton LJ 3rd, O'Brien PC.** Risk factors for severity of diabetic polyneuropathy: intensive longitudinal assessment of the Rochester Diabetic Neuropathy Study cohort. *Diabetes Care.* 1999;22:1479-1486. [EL 2; PCS]

312. **Tesfaye S, Chaturvedi N, Eaton SE, al.** Vascular risk factors and diabetic neuropathy. *N Engl J Med.* 2005;352:341-350. [EL 2; PCS]

313. **Gibbons CH, Freeman R.** Treatment-induced diabetic neuropathy: a reversible painful autonomic neuropathy. *Ann Neurol.* 2010;67:534-541. [EL 2; PCS]

314. **Vinik A.** The approach to the management of the patient with neuropathic pain. *J Clin Endocrinol Metab.* 2010;95:4802-4811. [EL 4; review NE]

315. **Archer AG, Watkins PJ, Thomas PK, Sharma AK, Payan J.** The natural history of acute painful neuropathy in diabetes mellitus. *J Neurol Neurosurg Psychiatry.* 1983;46:491-499. [EL 2; CSS]

316. **Pittenger GL, Mehrabyan A, Simmons K, et al.** Small fiber neuropathy is associated with the metabolic syndrome. *Metab Syndr Relat Disord.* 2005;3:113-121. [EL 3; CSS]

317. **Singleton JR, Smith AG, Bromberg MB.** Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. *Diabetes Care.* 2001;24:1448-1453. [EL 2; PCS]

318. **Singleton JR, Smith AG, Bromberg MB.** Painful sensory polyneuropathy associated with impaired glucose tolerance. *Muscle Nerve.* 2001;24:1225-1228. [EL 3; retrospective chart review SS]

319. **Vinik A.** Diabetic neuropathy in older adults. In: Pathy MSJ, Sinclair AJ, Morley JE, eds. *Principles and Practice of Geriatric Medicine.* Hoboken, NJ: Wiley; 2010. [EL 4; review NE]

320. **Vinik A, Strotmeyer E.** Diabetic neuropathy. In: Sinclair AJ, Morley JE, Vellas B, eds. *Principles and Practice of Geriatric Medicine.* 5th ed. Chichester, U.K.: John Wiley & Sons, Ltd.; 2012: 751-766. [EL 4; NE]

321. **Cheer K, Shearman C, Jude EB.** Managing complications of the diabetic foot. *BMJ.* 2009;339:b4905. [EL 4; NE]

322. **Boulton AJ, Kirsner RS, Vileikyte L.** Clinical practice. Neuropathic diabetic foot ulcers. *N Engl J Med.* 2004;351:48-55. [EL 4; NE]

323. **Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL.** Diabetic neuropathy: clinical manifestations and current treatments. *Lancet Neurol.* 2012;11:521-534. [EL 4; NE]

324. **Tesfaye S, Boulton AJ, Dickenson AH.** Mechanisms and management of diabetic painful distal symmetrical polyneuropathy. *Diabetes Care.* 2013;36:2456-2465. [EL 4; NE]

325. **Wong MC, Chung JW, Wong TK.** Effects of treatments for symptoms of painful diabetic neuropathy: systematic review. *BMJ.* 2007;335:87. [EL 1; MRCT]

326. **Peltier A, Goutman SA, Callaghan BC.** Painful diabetic neuropathy. *BMJ.* 2014;348:g1799. [EL 4; NE]

327. **Knuiman MW, Welborn TA, McCann VJ, Stanton KG, Constable IJ.** Prevalence of diabetic complications in relation to risk factors. *Diabetes*. 1986;35:1332-1339. [EL 3; CSS]

328. **Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH.** A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia*. 1993;36:150-154. [EL 3; CSS]

329. **Tesfaye S, Vileikyte L, Rayman G, et al.** Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. *Diabetes Metab Res Rev*. 2011;27:629-638. [EL 4; NE]

330. **Tesfaye S, Boulton AJ, Dyck PJ, et al.** Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care*. 2010;33:2285-2293. [EL 4; NE]

331. **Vinik AI, Erbas T.** Recognizing and treating diabetic autonomic neuropathy. *Cleve Clin J Med*. 2001;68:928-930, 932, 934-944. [EL 4; review NE]

332. **Vinik AI, Mehrabyan A.** Diagnosis and management of diabetic autonomic neuropathy. *Compr Ther*. 2003;29:130-45. [EL 4; review NE]

333. **Bril V, England J, Franklin GM, et al.** Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011;76:1758-1765. [EL 4; NE CPG]

334. **Attal N, Cruccu G, Baron R, et al.** EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010;17:1113-e88. [EL 1; NE CPG]

335. **Callaghan BC, Little AA, Feldman EL, Hughes RA.** Enhanced glucose control for preventing and treating diabetic neuropathy. *Cochrane Database Syst Rev*. 2012;6:CD007543. [EL 4; NE]

336. **Yu RK, Ariga T, Kohriyama T, Kusunoki S, Maeda Y, Miyatani N.** Autoimmune mechanisms in peripheral neuropathies. *Ann Neurol*. 1990;27 Suppl:S30-S5. [EL 4; review NE]

337. **Morrison S, Colberg SR, Mariano M, Parson HK, Vinik AI.** Balance training reduces falls risk in older individuals with type 2 diabetes. *Diabetes Care*. 2010;33:748-750. [EL 2; PCS]

338. **Nelson ME, Fiatarone MA, Morganti CM, Trice I, Greenberg RA, Evans WJ.** Effects of high-intensity strength training on multiple risk factors for osteoporotic fractures. A randomized controlled trial. *JAMA*. 1994;272:1909-1914. [EL 1; RCT]

339. **Liu-Ambrose T, Khan KM, Eng JJ, Janssen PA, Lord SR, McKay HA.** Resistance and agility training reduce fall risk in women aged 75 to 85 with low bone mass: a 6-month randomized, controlled trial. *J Am Geriatr Soc*. 2004;52:657-665. [EL 1; RCT]

340. **Cavanagh PR, Derr JA, Ulbrecht JS, Maser RE, Orchard TJ.** Problems with gait and posture in neuropathic patients with insulin-dependent diabetes mellitus. *Diabet Med*. 1992;9:469-474. [EL 2; RCCS]

341. **Morrison S, Colberg SR, Parson HK, Vinik AI.** Exercise improves gait, reaction time and postural stability in older adults with type 2 diabetes and neuropathy. *J Diabetes Complications*. 2014;28:715-722. [EL 2; PCS, small sample size]

342. **Morrison S, Colberg SR, Parson HK, Vinik AI.** Relation between risk of falling and postural sway complexity in diabetes. *Gait Posture*. 2012;35:662-668. [EL 2; PCS, small sample size]

343. **Vinik AI, Suwanwalaikorn S, Stansberry KB, Holland MT, McNitt PM, Colen LE.** Quantitative measurement of cutaneous perception in diabetic neuropathy. *Muscle Nerve*. 1995;18:574-584. [EL 3; SS]

344. **Lauria G, Hsieh ST, Johansson O, et al.** European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Eur J Neurol*. 2010;17:903-912, e44-e49. [EL 4; consensus NE]

345. **Shun CT, Chang YC, Wu HP, et al.** Skin denervation in type 2 diabetes: correlations with diabetic duration and functional impairments. *Brain*. 2004;127:1593-1605. [EL 3; CSS]

346. **Loseth S, Stalberg E, Jorde R, Mellgren SI.** Early diabetic neuropathy: thermal thresholds and intraepidermal nerve fibre density in patients with normal nerve conduction studies. *J Neurol*. 2008;255:1197-1202. [EL 3; CSS]

347. **Quattrini C, Tavakoli M, Jeziorska M, et al.** Surrogate markers of small fiber damage in human diabetic neuropathy. *Diabetes*. 2007;56:2148-2154. [EL 3; CSS]

348. **Sorensen L, Molyneaux L, Yue DK.** The relationship among pain, sensory loss, and small nerve fibers in diabetes. *Diabetes Care*. 2006;29:883-887. [EL 3; SS]

349. **Smith AG, Russell J, Feldman EL, et al.** Lifestyle intervention for pre-diabetic neuropathy. *Diabetes Care*. 2006;29:1294-1299. [EL 2; PCS]

350. **Parson HK, Nguyen VT, Orciga MA, Boyd AL, Casellini CM, Vinik AI.** Contact heat-evoked potential stimulation for the evaluation of small nerve fiber function. *Diabetes Technol Ther*. 2013;15:150-157. [EL 2; NRCT]

351. **Casellini CM, Parson HK, Richardson MS, Nevoret ML, Vinik AI.** Sudoscan, a noninvasive tool for detecting diabetic small fiber neuropathy and autonomic dysfunction. *Diabetes Technol Ther*. 2013;15:948-953. [EL 2; PCS]

352. **Murray HJ, Veves A, Young MJ, Richie DH, Boulton AJ.** Role of experimental socks in the care of the high-risk diabetic foot. A multicenter patient evaluation study. American Group for the Study of Experimental Hosiery in the Diabetic Foot. *Diabetes Care*. 1993;16:1190-1192. [EL 2; PCS]

353. **Boulton AJ, Malik RA, Arezzo JC, Sosenko JM.** Diabetic somatic neuropathies. *Diabetes Care*. 2004;27:1458-1486. [EL 4; review NE]

354. **Apfel SC, Asbury AK, Bril V, et al.** Positive neuropathic sensory symptoms as endpoints in diabetic neuropathy trials. *J Neurol Sci*. 2001;189:3-5. [EL 4; review]

355. **Cruccu G, Truini A.** Tools for assessing neuropathic pain. *PLoS Med*. 2009;6:e1000045. [EL 4; review NE]

356. **Vinik EJ, Hayes RP, Oglesby A, et al.** The development and validation of the Norfolk QOL-DN, a new measure of patients' perception of the effects of diabetes and diabetic neuropathy. *Diabetes Technol Ther*. 2005;7:497-508. [EL 3; SS]

357. **Vinik A.** Management of the patient with neuropathic pain. In: Wartofsky L, ed. *A Clinical Approach to Endocrine and Metabolic Diseases*. 2nd ed. Washington, D.C.: The Endocrine Society; 2012: 177-194. [EL 4; NE]

358. **McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA.** A systematic review of antidepressants in neuropathic pain. *Pain*. 1996;68:217-227. [EL 1; MRCT]

359. **Lunn MP, Hughes RA, Wiffen PJ.** Duloxetine for treating painful neuropathy or chronic pain. *Cochrane Database Syst Rev*. 2009:CD007115. [EL 1; MRCT]

360. **Vinik A, Emir B, Parsons B, Cheung R.** Prediction of pregabalin-mediated pain response by severity of sleep disturbance in patients with painful diabetic neuropathy and post-herpetic neuralgia. *Pain Med*. 2014;15:661-670. [EL 1; RCT, posthoc analysis]

361. **Vinik A, Shapiro DY, Rauschkolb C, et al.** A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. *Diabetes Care*. 2014;37:2302-2309. [EL 1; RCT]

362. **Baron R, Mayoral V, Leijon G, Binder A, Steigerwald I, Serpell M.** 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study. *Curr Med Res Opin*. 2009;25:1663-1676. [EL 1; RCT]

363. **Fonseca VA, Lavery LA, Thethi TK, et al.** Metanx in type 2 diabetes with peripheral neuropathy: a randomized trial. *Am J Med*. 2013;126:141-149. [EL 1; RCT]

364. **Vinik AI.** A medicinal food provides food for thought in managing diabetic neuropathy. *Am J Med*. 2013;126:95-96. [EL 4; NE]

365. **Leishear K, Boudreau RM, Studenski SA, et al.** Relationship between vitamin B12 and sensory and motor peripheral nerve function in older adults. *J Am Geriatr Soc*. 2012;60:1057-1063. [EL 3; CSS]

366. **Okada K, Tanaka H, Temporin K, et al.** Methylcobalamin increases Erk1/2 and Akt activities through the methylation cycle and promotes nerve regeneration in a rat sciatic nerve injury model. *Exp Neurol*. 2010;222:191-203. [EL 4; NE]

367. **Vinik AI, Ziegler D.** Diabetic cardiovascular autonomic neuropathy. *Circulation*. 2007;115:387-397. [EL 4; review NE]

368. **Maser RE, Mitchell BD, Vinik AI, Freeman R.** The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. *Diabetes Care*. 2003;26:1895-1901. [EL 2; MNRCT]

369. **Pop-Busui R, Evans GW, Gerstein HC, et al.** Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care*. 2010;33:1578-1584. [EL 3; SS]

370. **Vinik AI, Maser RE, Ziegler D.** Neuropathy: the crystal ball for cardiovascular disease? *Diabetes Care*. 2010;33:1688-1690. [EL 4; NE]

371. **Vinik AI, Maser RE, Mitchell BD, Freeman R.** Diabetic autonomic neuropathy. *Diabetes Care*. 2003;26:1553-1579. [EL 4; review NE]

372. **Ziegler D, Gries FA, Spüler M, Lessmann F.** The epidemiology of diabetic neuropathy. Diabetic Cardiovascular Autonomic Neuropathy Multicenter Study Group. *J Diabetes Complications*. 1992;6:49-57. [EL 4; review NE]

373. **Vinik AI, Erbas T, Casellini CM.** Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. *J Diabetes Investig*. 2013;4:4-18. [EL 4; NE]

374. Assessment: Clinical autonomic testing report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 1996;46:873-880. [EL 4; position NE]

375. **England JD, Gronseth GS, Franklin G, et al.** Practice Parameter: evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2009;72:177-184. [EL 4; NE]

376. **Lieb DC, Parson HK, Mamikunian G, Vinik AI.** Cardiac autonomic imbalance in newly diagnosed and established diabetes is associated with markers of adipose tissue inflammation. *Exp Diabetes Res*. 2012;2012:878760. [EL 2; PCS]

377. **Vinik AI, Nevoret M, Casellini C, Parson H.** Neurovascular function and sudorimetry in health and disease. *Curr Diab Rep*. 2013;13:517-532. [EL 4; NE]

378. **Pirart J.** Why don't we teach and treat diabetic patients better? *Diabetes Care*. 1978;1:139-140. [EL 4; review NE]

379. **Ziegler D, Hanefeld M, Ruhnau KJ, et al.** Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. *Diabetes Care*. 1999;22:1296-1301. [EL 1; RCT]

380. **Ruhnau KJ, Meissner HP, Finn JR, et al.** Effects of 3-week oral treatment with the antioxidant thioctic acid (alpha-lipoic acid) in symptomatic diabetic polyneuropathy. *Diabet Med*. 1999;16:1040-1043. [EL 1; RCT]

381. **Valensi P, Le Devehat C, Richard JL, et al.** A multicenter, double-blind, safety study of QR-333 for the treatment of symptomatic diabetic peripheral neuropathy. A preliminary report. *J Diabetes Complications*. 2005;19:247-253. [EL 1; RCT]

382. **Ziegler D, Schatz H, Conrad F, Gries FA, Ulrich H, Reichel G.** Effects of treatment with the antioxidant alpha-lipoic acid on cardiac autonomic neuropathy in NIDDM patients. A 4-month randomized controlled multicenter trial (DEKAN Study). Deutsche Kardiale Autonome Neuropathie. *Diabetes Care*. 1997;20:369-373. [EL 1; RCT]

383. **Vallianou N, Evangelopoulos A, Koutalas P.** Alpha-lipoic acid and diabetic neuropathy. *Rev Diabet Stud*. 2009;6:230-236. [EL 4; NE]

384. **Ziegler D, Ametov A, Barinov A, , et al.** Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. *Diabetes Care*. 2006;29:2365-2370. [EL 1; RCT]

385. **Ziegler D, Low PA, Litchy WJ, et al.** Efficacy and safety of antioxidant treatment with α-lipoic acid over 4 years in diabetic polyneuropathy: The NATHAN 1 Trial. *Diabetes Care*. 2011;34:2054-2060. [EL 1; RCT]

386. **Viberti G.** Thiazolidinediones-benefits on microvascular complications of type 2 diabetes. *J Diabetes Complications*. 2005;19:168-177. [EL 4; review NE]

387. **Vinik AI, Ullal J, Parson HK, Barlow PM, Casellini CM.** Pioglitazone treatment improves nitrosative stress in type 2 diabetes. *Diabetes Care*. 2006;29:869-76. [EL 1; RCT]

388. **Vinik AI, Zhang Q.** Adding insulin glargine versus rosiglitazone: health-related quality-of-life impact in type 2 diabetes [Erratum in *Diabetes Care*. 2007;30:1684]. *Diabetes Care*. 2007;30:795-800. [EL 3; SS]

389. **Davis TM, Yeap BB, Davis WA, Bruce DG.** Lipid-lowering therapy and peripheral sensory neuropathy in type 2 diabetes: the Fremantle Diabetes Study. *Diabetologia*. 2008;51:562-566. [EL 2; PCS]

390. **Parson HK, Bundy MA, Dublin CB, Boyd AL, Paulson JF, Vinik AI.** Pleiotropic effects of rosuvastatin on microvascular function in type 2 diabetes. *Diabetes Metab Syndr Obes*. 2010;3:19-26. [EL 2; PCS]

391. **Jacobson TA.** Overcoming 'ageism' bias in the treatment of hypercholesterolaemia : a review of safety issues with statins in the elderly. *Drug Saf*. 2006;29:421-448. [EL 4; review NE]

392. **Tierney EF, Thurman DJ, Beckles GL, Cadwell BL.** Association of statin use with peripheral neuropathy in the U.S. population 40 years of age or older. *J Diabetes*. 2013;5:207-215. [EL 3; SS]

393. **Pagkalos M, Koutlianos N, Kouidi E, Pagkalos E, Mandroukas K, Deligiannis A.** Heart rate variability modifications following exercise training in type 2 diabetic patients with definite cardiac autonomic neuropathy. *Br J Sports Med*. 2008;42:47-54. [EL 2; PCS]

394. **Bulat T, Hart-Hughes S, Ahmed S, et al.** Effect of a group-based exercise program on balance in elderly. *Clin Interv Aging*. 2007;2:655-660. [EL 3; SS]

395. **Richardson JK, Sandman D, Vela S.** A focused exercise regimen improves clinical measures of balance in patients with peripheral neuropathy. *Arch Phys Med Rehabil*. 2001;82:205-209. [EL 2; NRCT single-blinded]

396. **Ning F, Tuomilehto J, Pyörälä K, et al.** Cardiovascular disease mortality in Europeans in relation to fasting and 2-h plasma glucose levels within a normoglycemic range. *Diabetes Care*. 2010;33:2211-2216. [EL 2; RCCS]

397. **Doerr R, Hoffmann U, Otter W, et al.** Oral glucose tolerance test and HbA(1)c for diagnosis of diabetes in patients undergoing coronary angiography: [corrected] the Silent Diabetes Study. *Diabetologia*. 2011;54:2923-2930. [EL 3; SS]

398. **Selvin E, Steffes MW, Zhu H, et al.** Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med*. 2010;362:800-811. [EL 2; PCS]

399. **Huxley R, Barzi F, Woodward M.** Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ*. 2006;332:73-78. [EL 2; MNRCT]

400. **Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M.** Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229-234. [EL 3; SS]

401. **Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M.** Type 2 diabetes as a "coronary heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. *Diabetes Care*. 2005;28:2901-2907. [EL 3; SS]

402. **Schramm TK, Gislason GH, Kober L, et al.** Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. *Circulation*. 2008;117:1945-1954. [EL 3; SS]

403. **Kannel WB, Wilson PW, Zhang TJ.** The epidemiology of impaired glucose tolerance and hypertension. *Am Heart J*. 1991;121:1268-1273. [EL 4; review NE]

404. **Stamler J, Vaccaro O, Neaton JD, Wentworth D.** Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;16:434-444. [EL 2; PCS]

405. **Young LH, Wackers FJ, Chyun DA, et al.** Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA*. 2009;301:1547-1555. [EL 1; RCT]

406. **Gregg EW, Li Y, Wang J, et al.** Changes in diabetes-related complications in the United States, 1990-2010. *N Engl J Med*. 2014;370:1514-1523. [EL 3; SS]

407. **Goff DC Jr, Lloyd-Jones DM, Bennett G, al.** 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;129:S49-S73. [EL 4; NE]

408. **Bartnik M, Rydén L, Ferrari R, et al.** The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart. *Eur Heart J*. 2004;25:1880-1890. [EL 3; SS]

409. **Bartnik M, Malmberg K, Norhammar A, Tenerz A, Ohrvik J, Rydén L.** Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction. *Eur Heart J*. 2004;25:1990-1997. [EL 2; PCS]

410. **Anselmino M, Ohrvik J, Malmberg K, Standl E, Rydén L, Euro Heart Survey Investigators.** Glucose lowering treatment in patients with coronary artery disease is prognostically important not only in established but also in newly detected diabetes mellitus: a report from the Euro Heart Survey on Diabetes and the Heart. *Eur Heart J*. 2008;29:177-184. [EL 3; SS]

411. **Nathan DM, Cleary PA, Backlund JY, et al.** Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643-2653. [EL 1; RCT]

412. **Duckworth WC, Abraira C, Moritz TE, et al.** The duration of diabetes affects the response to intensive glucose control in type 2 subjects: the VA Diabetes Trial. *J Diabetes Complications*. 2011;25:355-361. [EL 2; PCS]

413. **Reaven PD, Moritz TE, Schwenke DC, et al.** Intensive glucose-lowering therapy reduces cardiovascular disease events in Veterans Affairs Diabetes Trial participants with lower calcified coronary atherosclerosis. *Diabetes*. 2009;58:2642-2648. [EL 1; RCT, posthoc analysis with other methodological limitations]

414. **Ogawa H, Nakayama M, Morimoto T, et al.** Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA*. 2008;300:2134-2141. [EL 1; RCT]

415. **Calvin AD, Aggarwal NR, Murad MH, et al.** Aspirin for the primary prevention of cardiovascular events: a systematic review and meta-analysis comparing patients with and without diabetes. *Diabetes Care*. 2009;32:2300-2306. [EL 1; MRCT]

416. **Leung WY, So WY, Stewart D, et al.** Lack of benefits for prevention of cardiovascular disease with aspirin therapy in type 2 diabetic patients--a longitudinal observational study. *Cardiovasc Diabetol*. 2009;8:57. [EL 2; PCS]

417. **Pulcinelli FM, Biasucci LM, Riondino S, et al.** COX-1 sensitivity and thromboxane A2 production in type 1 and type 2 diabetic patients under chronic aspirin treatment. *Eur Heart J*. 2009;30:1279-1286. [EL 2; PCS]

418. **Dillinger JG, Drissa A, Sideris G, et al.** Biological efficacy of twice daily aspirin in type 2 diabetic patients with coronary artery disease. *Am Heart J*. 2012;164:600-606.e1. [EL 1; RCT]

419. National Heart Lung and Blood Institute Obesity Education Initiative. The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Bethesda, MD: National Institutes of Health; 2000. Available at: http://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf. [EL 4; NE]

420. **WHO Expert Consultation.** Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet.* 2004;363:157-163. [EL 4; NE]

421. **Garvey WT, Garber AJ, Mechanick JI, et al.** American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the 2014 advanced framework for a new diagnosis of obesity as a chronic disease. *Endocr Pract.* 2014;20:977-989. [EL 4; NE]

422. **Johnston BC, Kanters S, Bandayrel K, et al.** Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA.* 2014;312:923-933. [EL 1; MRCT]

423. **Gonzalez-Campoy JM, St Jeor ST, Castorino K, et al.** Clinical practice guidelines for healthy eating for the prevention and treatment of metabolic and endocrine diseases in adults: cosponsored by the American Association of Clinical Endocrinologists/the American College of Endocrinology and the Obesity Society. *Endocr Pract.* 2013;19 Suppl 3:1-82. [EL 4; NE]

424. **Haskell WL, Lee IM, Pate RR, et al.** Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation.* 2007;116:1081-1093. [EL 4; NE]

425. **Bray GA.** *A Guide to Obesity and the Metabolic Syndrome.* Boca Raton, FL: CRC Press, Taylor & Francis Group; 2011. [EL 4; NE]

426. **Bray GA, Ryan DH.** Medical therapy for the patient with obesity. *Circulation.* 2012;125:1695-1703. [EL 4; NE]

427. **Leslie WS, Hankey CR, Lean ME.** Weight gain as an adverse effect of some commonly prescribed drugs: a systematic review. *QJM.* 2007;100:395-404. [EL 1; RCT]

428. **Ryan DH, Bray GA.** Pharmacologic treatment options for obesity: what is old is new again. *Curr Hypertens Rep.* 2013;15:182-189. [EL 4; NE]

429. **Hutton B, Fergusson D.** Changes in body weight and serum lipid profile in obese patients treated with orlistat in addition to a hypocaloric diet: a systematic review of randomized clinical trials. *Am J Clin Nutr.* 2004;80:1461-1468. [EL 1; MRCT]

430. **Smith SR, Weissman NJ, Anderson CM, et al.** Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med.* 2010;363:245-256. [EL 1; RCT]

431. **O'Neil PM, Smith SR, Weissman NJ, et al.** Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring).* 2012;20:1426-1436. [EL 1; RCT]

432. **Fidler MC, Sanchez M, Raether B, et al.** A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J Clin Endocrinol Metab.* 2011;96:3067-3077. [EL 1; RCT]

433. **Garvey WT, Ryan DH, Look M, et al.** Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr.* 2012;95:297-308. [EL 1; RCT]

434. **Allison DB, Gadde KM, Garvey WT, et al.** Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity (Silver Spring).* 2012;20:330-342. [EL 1; RCT]

435. **Gadde KM, Allison DB, Ryan DH, et al.** Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet.* 2011;377:1341-1352. [EL 1; RCT]

436. **Garvey WT, Ryan DH, Bohannon NJ, et al.** Weight-loss therapy in type 2 diabetes: effects of phentermine and topiramate extended-release. *Diabetes Care.* 2014;37:3309-3316. [EL 1; RCT]

437. **Apovian CM, Aronne L, Rubino D, et al.** A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring).* 2013;21:935-943. [EL 1; RCT]

438. **Hollander P, Gupta AK, Plodkowski R, et al.** Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care.* 2013;36:4022-4029. [EL 1; RCT]

439. **Wadden TA, Foreyt JP, Foster GD, et al.** Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring).* 2011;19:110-120. [EL 1; RCT]

440. **Greenway FL, Fujioka K, Plodkowski RA, et al.** Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2010;376:595-605. [EL 1; RCT]

441. **Wadden TA, Hollander P, Klein S, et al.** Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond).* 2013;37:1443-1451. [EL 1; RCT]

442. Office of Diversion Control. List of controlled substances. Springfield, VA: U.S. Department of Justice Drug Enforcement Administration; 2014. Available at: http://www.deadiversion.usdoj.gov/schedules/. [EL 4; NE]

443. **Rissanen A, Lean M, Rössner S, Segal KR, Sjöström L.** Predictive value of early weight loss in obesity management with orlistat: an evidence-based assessment of prescribing guidelines. *Int J Obes Relat Metab Disord.* 2003;27:103-109. [EL 1; MRCT]

444. **Finer N, Ryan DH, Renz CL, Hewkin AC.** Prediction of response to sibutramine therapy in obese non-diabetic and diabetic patients. *Diabetes Obes Metab.* 2006;8:206-213. [EL 1; MRCT]

445. **Buchwald H, Avidor Y, Braunwald E, et al.** Bariatric surgery: a systematic review and meta-analysis. *JAMA.* 2004;292:1724-1737. [EL 2; MNRCT]

446. **Schauer PR, Kashyap SR, Wolski K, al.** Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med.* 2012;366:1567-1576. [EL 1; RCT, not blinded]

447. **Schauer PR, Bhatt DL, Kirwan JP, et al.** Bariatric surgery versus intensive medical therapy for diabetes: 3-year outcomes. *N Engl J Med.* 2014;370:2002-2013. [EL 1; RCT, not blinded]

448. NIH conference. Gastrointestinal surgery for severe obesity. Consensus Development Conference Panel. *Ann Intern Med.* 1991;115:956-961. [EL 4; NE]

449.  **Dixon JB, Zimmet P, Alberti KG, Rubino F.** Bariatric surgery: an IDF statement for obese type 2 diabetes. *Diabet Med*. 2011;28:628-642. [EL 4; NE]

450.  **Mechanick JI, Youdim A, Jones DB, et al.** Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Endocr Pract*. 2013;19:337-372. [EL 4; NE]

451.  **Henry RR, Chilton R, Garvey WT.** New options for the treatment of obesity and type 2 diabetes mellitus (narrative review). *J Diabetes Complications*. 2013;27:508-518. [EL 4; NE]

452.  **Look AHEAD Research Group, Wing RR.** Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med*. 2010;170:1566-75. [EL 1; RCT]

453.  UK Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients, UKPDS Group. *Metabolism*. 1990;39:905-912. [EL 2; PCS]

454.  **Norris SL, Zhang X, Avenell A, et al.** Long-term non-pharmacologic weight loss interventions for adults with type 2 diabetes. *Cochrane Database Syst Rev*. 2005:CD004095. [EL 1; MRCT]

455.  **Belalcazar LM, Haffner SM, Lang W, et al.** Lifestyle intervention and/or statins for the reduction of C-reactive protein in type 2 diabetes: from the look AHEAD study. *Obesity (Silver Spring)*. 2013;21:944-950. [EL 1; RCT]

456.  **Miles JM, Leiter L, Hollander P, et al.** Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. *Diabetes Care*. 2002;25:1123-1128. [EL 1; RCT]

457.  **Sjostrom L, Peltonen M, Jacobson P, et al.** Bariatric surgery and long-term cardiovascular events. *JAMA*. 2012;307:56-65. [EL 2; PCS]

458.  **Look AHEAD Research Group, Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, et al.** Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care*. 2007;30:1374-83. [EL 1; RCT]

459.  **Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, et al.** Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369:145-54. [EL 1; RCT]

460.  **Hanefeld M, Sachse G.** The effects of orlistat on body weight and glycaemic control in overweight patients with type 2 diabetes: a randomized, placebo-controlled trial. *Diabetes Obes Metab*. 2002;4:415-23. [EL 1; RCT]

461.  **Hollander PA, Elbein SC, Hirsch IB, Kelley D, McGill J, Taylor T, et al.** Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. *Diabetes Care*. 1998;21:1288-94. [EL 1; RCT]

462.  **Sjöström L, Peltonen M, Jacobson P, et al.** Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA*. 2014;311:2297-2304. [EL 2; PCS]

463.  **Lindberg E, Carter N, Gislason T, Janson C.** Role of snoring and daytime sleepiness in occupational accidents. *Am J Respir Crit Care Med*. 2001;164:2031-2035. [EL 3; SS]

464.  **Kemlink D, Polo O, Frauscher B, et al.** Replication of restless legs syndrome loci in three European populations. *J Med Genet*. 2009;46:315-318. [EL 3; CSS]

465.  **Collop NA, Anderson WM, Boehlecke B, et al.** Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2007;3:737-747. [EL 4; NE]

466.  **Rosen CL, Auckley D, Benca R, et al.** A multisite randomized trial of portable sleep studies and positive airway pressure autotitration versus laboratory-based polysomnography for the diagnosis and treatment of obstructive sleep apnea: the HomePAP study. *Sleep*. 2012;35:757-767. [EL 1; RCT, not blinded]

467.  **Tasali E, Mokhlesi B, Van Cauter E.** Obstructive sleep apnea and type 2 diabetes: interacting epidemics. *Chest*. 2008;133:496-506. [EL 4; review NE]

468.  **Winkelman JW, Redline S, Baldwin CM, Resnick HE, Newman AB, Gottlieb DJ.** Polysomnographic and health-related quality of life correlates of restless legs syndrome in the Sleep Heart Health Study. *Sleep*. 2009;32:772-8. [EL 3; CSS]

469.  **Valencia-Flores M, Orea A, Castano VA, et al.** Prevalence of sleep apnea and electrocardiographic disturbances in morbidly obese patients. *Obes Res*. 2000;8:262-269. [EL 3; CSS]

470.  **Babu AR, Herdegen J, Fogelfeld L, Shott S, Mazzone T.** Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. *Arch Intern Med*. 2005;165:447-452. [EL 3; CSS]

471.  **Hassaballa HA, Tulaimat A, Herdegen JJ, Mokhlesi B.** The effect of continuous positive airway pressure on glucose control in diabetic patients with severe obstructive sleep apnea. *Sleep Breath*. 2005;9:176-180. [EL 3; SS]

472.  **Kasai T, Narui K, Dohi T, et al.** Prognosis of patients with heart failure and obstructive sleep apnea treated with continuous positive airway pressure. *Chest*. 2008;133:690-696. [EL 2; PCS]

473.  **Becker HF, Jerrentrup A, Ploch T, et al.** Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation*. 2003;107:68-73. [EL 1; RCT, single-blind]

474.  **Kaneko Y, Floras JS, Usui K, et al.** Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med*. 2003;348:1233-1241. [EL 1; RCT, single-blind]

475.  **West SD, Nicoll DJ, Wallace TM, Matthews DR, Stradling JR.** Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. *Thorax*. 2007;62:969-974. [EL 1; RCT, small sample size]

476.  **Weinstock TG, Wang X, Rueschman M, et al.** A controlled trial of CPAP therapy on metabolic control in individuals with impaired glucose tolerance and sleep apnea. *Sleep*. 2012;35:617-625B. [EL 1; RCT, small sample size]

477.  **Myhill PC, Davis WA, Peters KE, Chubb SA, Hillman D, Davis TM.** Effect of continuous positive airway pressure therapy on cardiovascular risk factors in patients with type 2 diabetes and obstructive sleep apnea. *J Clin Endocrinol Metab*. 2012;97:4212-4218. [EL 2; PCS]

478.  **Lindberg E, Berne C, Elmasry A, Hedner J, Janson C.** CPAP treatment of a population-based sample--what are the benefits and the treatment compliance? *Sleep Med*. 2006;7:553-560. [EL 2; CPS]

479. **Heron M, Hoyert DL, Murphy SL, Xu J, Kochanek KD, Tejada-Vera B.** Deaths: final data for 2006. *Natl Vital Stat Rep*. 2009;57:1-134. [EL 3; SS]

480. **Kozak LJ, Lees KA, DeFrances CJ.** National Hospital Discharge Survey: 2003 annual summary with detailed diagnosis and procedure data. *Vital Health Stat 13*. 2006:1-206. [EL 3; SS]

481. **Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML.** Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med*. 2009;37:3001-3009. [EL 3: SS]

482. **Frisch A, Chandra P, Smiley D, et al.** Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. *Diabetes Care*. 2010;33:1783-1788. [EL 2; PCS]

483. **Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE.** Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab*. 2002;87:978-982. [EL 2; RCCS]

484. **Kwon S, Thompson R, Dellinger P, Yanez D, Farrohki E, Flum D.** Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program. *Ann Surg*. 2013;257:8-14. [EL 2; PCS]

485. **Umpierrez GE, Smiley D, Jacobs S, et al.** Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). *Diabetes Care*. 2011;34:256-261. [EL 1; RCT]

486. **Murad MH, Coburn JA, Coto-Yglesias F, et al.** Glycemic control in non-critically ill hospitalized patients: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2012;97:49-58. [EL 2; MNRCT]

487. **Finfer S, Chittock DR, Su SY, et al.** Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283-1297. [EL 1; RCT]

488. **Preiser JC, Devos P, Ruiz-Santana S, et al.** A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med*. 2009;35:1738-1748. [EL 1; RCT, protocol violations]

489. **Brunkhorst FM, Engel C, Bloos F, et al.** Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008;358:125-139. [EL 1 RCT, not blinded]

490. **Griesdale DE, de Souza RJ, van Dam RM, et al.** Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ*. 2009;180:821-827. [EL 1, MRCT]

491. **Wiener RS, Wiener DC, Larson RJ.** Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA*. 2008;300:933-944. [EL 1, MRCT]

492. **Lipska KJ, Venkitachalam L, Gosch K, et al.** Glucose variability and mortality in patients hospitalized with acute myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2012;5:550-557. [EL 2; PCS]

493. **Farrokhi F, Chandra P, Smiley D, et al.** Glucose variability is an independent predictor of mortality in hospitalized patients treated with total parenteral nutrition. *Endocr Pract*. 2014;20:41-45. [EL 3: SS]

494. **Krinsley JS.** Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med*. 2008;36:3008-3013. [EL 2; RCCS]

495. **Mendez CE, Mok KT, Ata A, Tanenberg RJ, Calles-Escandon J, Umpierrez GE.** Increased glycemic variability is independently associated with length of stay and mortality in noncritically ill hospitalized patients. *Diabetes Care*. 2013;36:4091-4097. [EL 2; RCCS]

496. **Jiang HJ, Stryer D, Friedman B, Andrews R.** Multiple hospitalizations for patients with diabetes. *Diabetes Care*. 2003;26:1421-1426. [EL 3; SS]

497. **Donnan PT, Leese GP, Morris AD; Diabetes Audit and Research in Tayside, Scotland/Medicine Monitoring Unit Collaboration.** Hospitalizations for people with type 1 and type 2 diabetes compared with the nondiabetic population of Tayside, Scotland: a retrospective cohort study of resource use. *Diabetes Care*. 2000;23:1774-1779. [EL 3; SS]

498. **Kosiborod M, Rathore SS, Inzucchi SE, et al.** Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. *Circulation*. 2005;111:3078-3086. [EL 2; PCS]

499. **van den Berghe G, Wouters P, Weekers F, et al.** Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359-1367. [EL 1, RCT]

500. **Furnary AP, Gao G, Grunkemeier GL, et al.** Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2003;125:1007-1021. [EL 2; PCS]

501. **Umpierrez GE, Hellman R, Korytkowski MT, et al.** Management of hyperglycemia in hospitalized patients in non-critical care setting: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97:16-38. [EL 4; NE]

502. **Goldberg PA, Siegel MD, Sherwin RS, \ et al.** Implementation of a safe and effective insulin infusion protocol in a medical intensive care unit. *Diabetes Care*. 2004;27:461-467. [EL 3; SS]

503. **Brown G, Dodek P.** Intravenous insulin nomogram improves blood glucose control in the critically ill. *Crit Care Med*. 2001;29:1714-1719. [EL 3; SS]

504. **Juneja R, Roudebush C, Kumar N, et al.** Utilization of a computerized intravenous insulin infusion program to control blood glucose in the intensive care unit. *Diabetes Technol Ther*. 2007;9:232-240. [EL 3; SS]

505. **Davidson PC, Steed RD, Bode BW.** Glucommander: a computer-directed intravenous insulin system shown to be safe, simple, and effective in 120,618 h of operation. *Diabetes Care*. 2005;28:2418-2423. [EL 3; SS]

506. **Kavanagh BP, McCowen KC.** Clinical practice. Glycemic control in the ICU. *N Engl J Med*. 2010;363:2540-2546. [EL 4; NE]

507. **Umpierrez GE, Smiley D, Hermayer K, et al.** Randomized study comparing a basal-bolus with a basal plus correction insulin regimen for the hospital management of medical and surgical patients with type 2 diabetes: basal plus trial. *Diabetes Care*. 2013;36:2169-2174. [EL 1; RCT]

508. **Umpierrez GE, Smiley D, Zisman A, et al.** Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). *Diabetes Care*. 2007;30:2181-2186. [EL 1; RCT]

509. **Inzucchi SE.** Clinical practice. Management of hyperglycemia in the hospital setting. *N Engl J Med*. 2006;355:1903-1911. [EL 4; NE]

510. **Baldwin D, Zander J, Munoz C, et al.** A randomized trial of two weight-based doses of insulin glargine and glulisine in hospitalized subjects with type 2 diabetes and renal insufficiency. *Diabetes Care*. 2012;35:1970-1974. [EL 1; RCT, not blinded, small sample size]

511. **Rubin DJ, Rybin D, Doros G, McDonnell ME.** Weight-based, insulin dose-related hypoglycemia in hospitalized patients with diabetes. *Diabetes Care*. 2011;34:1723-1728. [EL 2; RCCS]

512. **Farrokhi F, Klindukhova O, Chandra P, et al.** Risk factors for inpatient hypoglycemia during subcutaneous insulin therapy in non-critically ill patients with type 2 diabetes. *J Diabetes Sci Technol*. 2012;6:1022-1029. [EL 3; SS]

513. **Umpierrez GE, Gianchandani R, Smiley D, et al.** Safety and efficacy of sitagliptin therapy for the inpatient management of general medicine and surgery patients with type 2 diabetes: a pilot, randomized, controlled study. *Diabetes Care*. 2013;36:3430-3435. [EL 1; RCT, not blinded]

514. **Bantle JP, Wylie-Rosett J, Albright AL, et al.** Nutrition recommendations and interventions for diabetes--2006: a position statement of the American Diabetes Association. *Diabetes Care*. 2006;29:2140-2157. [EL 4; NE]

515. **McClave SA, Martindale RG, Vanek VW, et al.** Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2009;33:277-316. [EL 4; NE]

516. **Warren J, Bhalla V, Cresci G.** Postoperative diet advancement: surgical dogma vs evidence-based medicine. *Nutr Clin Pract*. 2011;26:115-125. [EL 4; NE]

517. **Marik PE, Preiser JC.** Toward understanding tight glycemic control in the ICU: a systematic review and meta-analysis. *Chest*. 2010;137:544-551. [EL 1; MRCT]

518. **Kosiborod M, Inzucchi SE, Krumholz HM, et al.** Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. *Circulation*. 2008;117:1018-1027. [EL 3; CSS]

519. **Egi M, Bellomo R, Stachowski E, et al.** Hypoglycemia and outcome in critically ill patients. *Mayo Clin Proc*. 2010;85:217-224. [EL 3; SS]

520. **Stagnaro-Green A, Barton MK, Linekin PL, Corkery E, deBeer K, Roman SH.** Mortality in hospitalized patients with hypoglycemia and severe hyperglycemia. *Mt Sinai J Med*. 1995;62:422-426. [EL 2; PCS]

521. **Desouza C, Salazar H, Cheong B, Murgo J, Fonseca V.** Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. *Diabetes Care*. 2003;26:1485-1489. [EL 2; PCS]

522. **Boucai L, Southern WN, Zonszein J.** Hypoglycemia-associated mortality is not drug-associated but linked to comorbidities. *Am J Med*. 2011;124:1028-1035. [EL 3; SS]

523. **Kosiborod M, Inzucchi SE, Goyal A, et al.** Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. *JAMA*. 2009;301:1556-14564. [EL 2; RCCS]

524. **Gamble JM, Eurich DT, Marrie TJ, Majumdar SR.** Admission hypoglycemia and increased mortality in patients hospitalized with pneumonia. *Am J Med*;123:556 e11-e16. [EL 2; PCS]

525. **Greci LS, Kailasam M, Malkani S, et al.** Utility of HbA(1c) levels for diabetes case finding in hospitalized patients with hyperglycemia. *Diabetes Care*. 2003;26:1064-1068. [EL 2; PCS]

526. **Umpierrez GE, Reyes D, Smiley D, et al.** Hospital discharge algorithm based on admission HbA1c for the management of patients with type 2 diabetes. *Diabetes Care*. 2014;37:2934-2939. [EL 2; PCS]

527. **Gloyn AL, Pearson ER, Antcliff JF, et al.** Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N Engl J Med*. 2004;350:1838-1849. [EL 3; SS]

528. **Babenko AP, Polak M, Cave H, et al.** Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. *N Engl J Med*. 2006;355:456-466. [EL 3; SS]

529. **Edghill EL, Flanagan SE, Patch AM, et al.** Insulin mutation screening in 1,044 patients with diabetes: mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood. *Diabetes*. 2008;57:1034-1042. [EL 3; SS]

530. **Pearson ER, Flechtner I, Njølstad PR, et al.** Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med*. 2006;355:467-477. [EL 2; PCS]

531. **Vaxillaire M, Froguel P.** Monogenic diabetes in the young, pharmacogenetics and relevance to multifactorial forms of type 2 diabetes. *Endocr Rev*. 2008;29:254-264. [EL 4; review NE]

532. **American Diabetes Association.** Type 2 diabetes in children and adolescents. *Diabetes Care*. 2000;23:381-389. [EL 4; guidelines NE]

533. **Fajans SS, Bell GI, Polonsky KS.** Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. *N Engl J Med*. 2001;345:971-980. [EL 4; review NE]

534. **Herman WH, Fajans SS, Ortiz FJ, et al.** Abnormal insulin secretion, not insulin resistance, is the genetic or primary defect of MODY in the RW pedigree. *Diabetes*. 1994;43:40-46. [EL 3; SS]

535. **Holmkvist J, Almgren P, Lyssenko V, et al.** Common variants in maturity-onset diabetes of the young genes and future risk of type 2 diabetes. *Diabetes*. 2008;57:1738-44. [EL 3; SS]

536. **Nyunt O, Wu JY, McGown IN, et al.** Investigating maturity onset diabetes of the young. *Clin Biochem Rev*. 2009;30:67-74. [EL 4; review NE]

537. **Weng J, Ekelund M, Lehto M, et al.** Screening for MODY mutations, GAD antibodies, and type 1 diabetes-associated HLA genotypes in women with gestational diabetes mellitus. *Diabetes Care*. 2002;25:68-71. [EL 3; SS]

538. **Plotnick LP, Clark LM, Brancati FL, Erlinger T.** Safety and effectiveness of insulin pump therapy in children and adolescents with type 1 diabetes. *Diabetes Care*. 2003;26:1142-1146. [EL 3; SS]

539. **Litton J, Rice A, Friedman N, Oden J, Lee MM, Freemark M.** Insulin pump therapy in toddlers and preschool children with type 1 diabetes mellitus. *J Pediatr*. 2002;141:490-5. [EL 2; PCS]

540. **Johnson SB, Kelly M, Henretta JC, Cunningham WR, Tomer A, Silverstein JH.** A longitudinal analysis of adherence and health status in childhood diabetes. *J Pediatr Psychol*. 1992;17:537-553. [EL 3; SS]

541. **Jones KL, Arslanian S, Peterokova VA, Park JS, Tomlinson MJ.** Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care*. 2002;25:89-94. [EL 1; RCT]

542. **Zeitler P, Hirst K, Pyle L, et al.** A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med*. 2012;366:2247-2256. [EL 1; RCT]

543. **Ziegler R, Heidtmann B, Hilgard D, Hofer S, Rosenbauer J, Holl R.** Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes. *Pediatr Diabetes*. 2011;12:11-17. [EL 3; SS]

544. **Beck RW, Buckingham B, Miller K, et al.** Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes. *Diabetes Care*. 2009;32:1947-1953. [EL 2; PCS]

545. **Pickup JC, Freeman SC, Sutton AJ.** Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ*. 2011;343:d3805. [EL 1; MRCT]

546. **Pettitt DJ, Baird HR, Aleck KA, Bennett PH, Knowler WC.** Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. *N Engl J Med*. 1983;308:242-245. [EL 2; PCS]

547. **Dabelea D, Hanson RL, Lindsay RS, et al.** Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes*. 2000;49:2208-2211. [EL 3; CCS]

548. **Knowler WC, Pettitt DJ, Saad MF, Bennett PH.** Diabetes mellitus in the Pima Indians: incidence, risk factors and pathogenesis. *Diabetes Metab Rev*. 1990;6:1-27. [EL 3; SS]

549. **Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennett PH, Knowler WC.** Congenital susceptibility to NIDDM. Role of intrauterine environment. *Diabetes*. 1988;37:622-628. [EL 3; SS]

550. **Jovanovic L, Savas H, Mehta M, Trujillo A, Pettitt DJ.** Frequent monitoring of A1C during pregnancy as a treatment tool to guide therapy. *Diabetes Care*. 2011;34:53-54. [EL 2; PCS]

551. **HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, et al.** Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008;358:1991-2002. [EL 2; PCS]

552. World Health Organization. Definition, diagnosis, classification of diabetes and its complications. Report of a WHO Consultation. Part 1: Diagnosis and classification of diabetes mellitus. Geneva, Switzerland: World Health Organization; 1999. [EL 4; consensus NE]

553. **Pettitt DJ, Jovanovic L.** Low birth weight as a risk factor for gestational diabetes, diabetes, and impaired glucose tolerance during pregnancy. *Diabetes Care*. 2007;30 Suppl 2:S147-S149. [EL 4; review NE]

554. **Catalano PM, Presley L, Minium J, Hauguel-de Mouzon S.** Fetuses of obese mothers develop insulin resistance in utero. *Diabetes Care*. 2009;32:1076-1080. [EL 3; PCS]

555. **Hales CN, Barker DJ, Clark PM, et al.** Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ*. 1991;303:1019-1022. [EL 3; SS]

556. **Jovanovic-Peterson L, ed.** *Medical Management of Pregnancy Complicated by Diabetes*. 4th ed. Alexandria, VA: American Diabetes Association; 2009. [EL 4; review NE]

557. **Metzger BE, Gabbe SG, Persson B, et al.** International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 2010;33:676-682. [EL 4; CPG]

558. **Cypryk K, Sobczak M, Pertyńska-Marczewska M, et al.** Pregnancy complications and perinatal outcome in diabetic women treated with Humalog (insulin lispro) or regular human insulin during pregnancy. *Med Sci Monit*. 2004;10:PI29-PI32. [EL 2; NRCT]

559. **Lapolla A, Dalfra MG, Spezia R, et al.** Outcome of pregnancy in type 1 diabetic patients treated with insulin lispro or regular insulin: an Italian experience. *Acta Diabetol*. 2008;45:61-66. [EL 3; retrospective study SS]

560. **Masson EA, Patmore JE, Brash PD, et al.** Pregnancy outcome in Type 1 diabetes mellitus treated with insulin lispro (Humalog). *Diabet Med*. 2003;20:46-50. [EL 3; retrospective study SS]

561. **Mathiesen ER, Kinsley B, Amiel SA, et al.** Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. *Diabetes Care*. 2007;30:771-776. [EL 1; RCT]

562. **Sciacca L, Marotta V, Insalaco F, et al.** Use of insulin detemir during pregnancy. *Nutr Metab Cardiovasc Dis*. 2010;20:e15-e16. [EL 3; SCR]

563. **Lapolla A, Di Cianni G, Bruttomesso D, et al.** Use of insulin detemir in pregnancy: a report on 10 Type 1 diabetic women. *Diabet Med*. 2009;26:1181-1182. [EL 3; retrospective study SS]

564. **Mathiesen ER, Damm P, Jovanovic L, et al.** Basal insulin analogues in diabetic pregnancy: a literature review and baseline results of a randomised, controlled trial in type 1 diabetes. *Diabetes Metab Res Rev*. 2011;27:543-551. [EL 1; RCT, not blinded]

565. **Mathiesen ER, Hod M, Ivanisevic M, et al.** Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. *Diabetes Care*. 2012;35:2012-2017. [EL 1; RCT, not blinded]

566. **Little RR, Rohlfing CL, Tennill AL, et al.** Measurement of Hba(1C) in patients with chronic renal failure. *Clin Chim Acta*. 2013;418:73-76. [EL 2; PCS]

567. **Davidson PC, Bode BW, Steed RD, Hebblewhite HR.** A cause-and-effect-based mathematical curvilinear model that predicts the effects of self-monitoring of blood glucose frequency on hemoglobin A1c and is suitable for statistical correlations. *J Diabetes Sci Technol*. 2007;1:850-856. [EL 3; SS]

568. **Miller KM, Beck RW, Bergenstal RM, et al.** Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. *Diabetes Care*. 2013;36:2009-2014. [EL 2; RCCS]

569. **Minder AE, Albrecht D, Schafer J, Zulewski H.** Frequency of blood glucose testing in well educated patients with diabetes mellitus type 1: How often is enough? *Diabetes Res Clin Pract*. 2013;101:57-61. [EL 3; CSS]

570. **Davis SN, Horton ES, Battelino T, Rubin RR, Schulman KA, Tamborlane WV.** STAR 3 randomized controlled trial to compare sensor-augmented insulin pump therapy with multiple daily injections in the treatment of type 1 diabetes: research design, methods, and baseline characteristics of enrolled subjects. *Diabetes Technol Ther*. 2010;12:249-255. [EL 1; RCT]

571. **Pearce KL, Noakes M, Keogh J, Clifton PM.** Effect of carbohydrate distribution on postprandial glucose peaks with the use of continuous glucose monitoring in type 2 diabetes. *Am J Clin Nutr*. 2008;87:638-644. [EL 1; RCT]

572. **Bruttomesso D, Costa S, Baritussio A.** Continuous subcutaneous insulin infusion (CSII) 30 years later: still the best option for insulin therapy. *Diabetes Metab Res Rev*. 2009;25:99-111. [EL 4; review NE]

573. **HSBC Global Research.** Diabetes: Proprietary survey on insulin pumps and continuous blood glucose monitoring. 2005. [EL 3; SS]

574. U.S. Food & Drug Administration. General Hospital and Personal Use Medical Devices Panel 2010 Insulin Infusion Pumps Panel Information. 2010. [EL 4; review NE]

575. **Pettis RJ, Harvey AJ.** Microneedle delivery: clinical studies and emerging medical applications. *Ther Deliv.* 2012;3:357-371. [EL 4; NE]

576. **Hanaire H.** External insulin pump treatment in the day-to-day management of diabetes: benefits and future prospectives. *Diabetes Metab.* 2011;37 Suppl 4:S40-S47. [EL 4; NE]

577. **Vaughn DE, Muchmore DB.** Use of recombinant human hyaluronidase to accelerate rapid insulin analogue absorption: experience with subcutaneous injection and continuous infusion. *Endocr Pract.* 2011;17:914-921. [EL 4; NE]

578. **Cengiz E, Weinzimer SA, Sherr JL, et al.** Acceleration of insulin pharmacodynamic profile by a novel insulin infusion site warming device. *Pediatr Diabetes.* 2013;14:168-173. [EL 2; PCS]

579. **O'Neal DN, Adhya S, Jenkins A, Ward G, Welsh JB, Voskanyan G.** Feasibility of adjacent insulin infusion and continuous glucose monitoring via the Medtronic Combo-Set. *J Diabetes Sci Technol.* 2013;7:381-288. [EL 3; CCS]

580. **Bergenstal RM, Klonoff DC, Garg SK, et al.** Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med.* 2013;369:224-232. [EL 1; RCT, not blinded]

581. **Grunberger G, Abelseth JM, Bailey TS, et al.** Consensus statement by the American Association of Clinical Endocrinologists/American College of Endocrinology Insulin Pump Management Task Force. *Endocr Pract.* 2014;20:463-489. [EL 4; NE]

582. **American Diabetes Association.** Continuous subcutaneous insulin infusion. *Diabetes Care.* 2004;27 Suppl 1:S110. [EL 4; review NE]

583. **American Association of Diabetics Educators.** Insulin pump therapy: Guidelines for successful outcomes from its Consensus Summit. 2008. Available at: https://www.diabeteseducator.org/export/sites/aade/_resources/pdf/Insulin_Pump_White_Paper.pdf [EL 4; CPG NE]

584. **Eugster EA, Francis G, Lawson-Wilkins Drug and Therapeutics Committee.** Position statement: Continuous subcutaneous insulin infusion in very young children with type 1 diabetes. *Pediatrics.* 2006;118:e1244-e1249. [EL 4; position NE]

585. **Phillip M, Battelino T, Rodriguez H, et al.** Use of insulin pump therapy in the pediatric age-group: consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2007;30:1653-1662. [EL 4; consensus NE]

586. **Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R.** Insulin pump therapy: a meta-analysis. *Diabetes Care.* 2003;26:1079-1087. [EL 1; MRCT]

587. **Jeitler K, Horvath K, Berghold A, et al.** Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. *Diabetologia.* 2008;51:941-951. [EL 1; MRCT]

588. **Fatourechi MM, Kudva YC, Murad MH, Elamin MB, Tabini CC, Montori VM.** Clinical review: Hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. *J Clin Endocrinol Metab.* 2009;94:729-740. [EL 1; MRCT]

589. **Pickup JC, Sutton AJ.** Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med.* 2008;25:765-774. [EL 1; MRCT]

590. **Raskin P, Bode BW, Marks JB, et al.** Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: a randomized, parallel-group, 24-week study. *Diabetes Care.* 2003;26:2598-2603. [EL 1; RCT, not blinded]

591. **Wainstein J, Metzger M, Boaz M, et al.** Insulin pump therapy vs. multiple daily injections in obese type 2 diabetic patients. *Diabet Med.* 2005;22:1037-46. [EL 1; RCT, not blinded, small sample size]

592. **Herman WH, Ilag LL, Johnson SL, et al.** A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. *Diabetes Care.* 2005;28:1568-1573. [EL 1; RCT, not blinded]

593. **Berthe E, Lireux B, Coffin C, et al.** Effectiveness of intensive insulin therapy by multiple daily injections and continuous subcutaneous infusion: a comparison study in type 2 diabetes with conventional insulin regimen failure. *Horm Metab Res.* 2007;39:224-229. [EL 1; RCT, small sample size, not blinded]

594. **Parkner T, Møller MK, Chen JW, et al.** Overnight CSII as supplement to oral antidiabetic drugs in type 2 diabetes. *Diabetes Obes Metab.* 2008;10:556-563. [EL 3; CCS]

595. **Noh YH, Lee SM, Kim EJ, et al.** Improvement of cardiovascular risk factors in patients with type 2 diabetes after long-term continuous subcutaneous insulin infusion. *Diabetes Metab Res Rev.* 2008;24:384-391. [EL 3; CCS]

596. **Reznik Y, Cohen O, Aronson R, et al.** Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. *Lancet.* 2014;384:1265-1272. [EL 1; RCT, not blinded]

597. **Jennings AM, Lewis KS, Murdoch S, Talbot JF, Bradley C, Ward JD.** Randomized trial comparing continuous subcutaneous insulin infusion and conventional insulin therapy in type II diabetic patients poorly controlled with sulfonylureas. *Diabetes Care.* 1991;14:738-744. [EL 1; RCT, small sample size, not blinded]

598. **St Charles ME, Sadri H, Minshall ME, Tunis SL.** Health economic comparison between continuous subcutaneous insulin infusion and multiple daily injections of insulin for the treatment of adult type 1 diabetes in Canada. *Clin Ther.* 2009;31:657-667. [EL 3; SS]

599. **St Charles M, Lynch P, Graham C, Minshall ME.** A cost-effectiveness analysis of continuous subcutaneous insulin injection versus multiple daily injections in type 1 diabetes patients: a third-party US payer perspective. *Value Health.* 2009;12:674-686. [EL 3; SS]

600. **Cummins E, Royle P, Snaith A, et al.** Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. *Health Technol Assess.* 2010;14:iii-iv, xi-xvi, 1-181. [EL 3; SS]

601. **Cohen O, Keidar N, Simchen M, Weisz B, Dolitsky M, Sivan E.** Macrosomia in well controlled CSII treated Type I diabetic pregnancy. *Gynecol Endocrinol.* 2008;24:611-613. [EL 3; retrospective review SS]

602. **Roze S, Valentine WJ, Zakrzewska KE, Palmer AJ.** Health-economic comparison of continuous subcutaneous insulin infusion with multiple daily injection for the treatment of Type 1 diabetes in the UK. *Diabet Med.* 2005;22:1239-1245. [EL 3; SS]

603. **Kamble S, Schulman KA, Reed SD.** Cost-effectiveness of sensor-augmented pump therapy in adults with type 1 diabetes in the United States. *Value Health.* 2012;15:632-638. [EL 1; RCT, posthoc analysis]

604. **Nørgaard K, Sohlberg A, Goodall G.** [Cost-effectiveness of continuous subcutaneous insulin infusion therapy for type 1 diabetes]. *Ugeskr Laeger.* 2010;172:2020-2025. [EL 3; SS]

605. **National Diabetes Education Program.** Diabetes Healthsense. Bethesda, MD: National Institutes of Health; 2014. Available at: http://ndep.nih.gov/resources/diabetes-healthsense/. [EL 4; NE]

606. **Smith SA, Poland GA.** Use of influenza and pneumococcal vaccines in people with diabetes. *Diabetes Care.* 2000;23:95-108. [EL 4; NE]

607. **Lau D, Eurich DT, Majumdar SR, Katz A, Johnson JA.** Working-age adults with diabetes experience greater susceptibility to seasonal influenza: a population-based cohort study. *Diabetologia.* 2014;57:690-698. [EL 3; SS]

608. **McKane CK, Marmarelis M, Mendu ML, Moromizato T, Gibbons FK, Christopher KB.** Diabetes mellitus and community-acquired bloodstream infections in the critically ill. *J Crit Care.* 2014;29:70-76. [EL 3; CSS]

609. **Tsakiridou E, Makris D, Chatzipantazi V, et al.** Diabetes and hemoglobin a1c as risk factors for nosocomial infections in critically ill patients. *Crit Care Res Pract.* 2013;2013:279479. [EL 2; PCS]

610. **Adamuz J, Viasus D, Jiménez-Martínez E, et al.** Incidence, timing and risk factors associated with 1-year mortality after hospitalization for community-acquired pneumonia. *J Infect.* 2014;68:534-541. [EL 2; PCS]

611. **Colquhoun AJ, Nicholson KG, Botha JL, Raymond NT.** Effectiveness of influenza vaccine in reducing hospital admissions in people with diabetes. *Epidemiol Infect.* 1997;119:335-341. [EL 2; RCCS]

612. **Grohskopf LA, Olsen SJ, Sokolow LZ, et al.** Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP) -- United States, 2014-15 influenza season. *MMWR Morb Mortal Wkly Rep.* 2014;63:691-697. [EL 4; NE]

613. **Centers for Disease Control and Prevention.** Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2012;61:816-819. [EL 4; NE]

614. **Tomczyk S, Bennett NM, Stoecker C, et al.** Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2014;63:822-825. [EL 4; NE]

615. **Centers for Disease Control and Prevention.** Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2011;60:1709-1711. [EL 4; NE]

616. **Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE.** Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care.* 2000;23:934-942. [EL 1; meta-analysis]

617. **Rotella F, Mannucci E.** Depression as a risk factor for diabetes: a meta-analysis of longitudinal studies. *J Clin Psychiatry.* 2013;74:31-37. [EL 2; MNRCT]

618. **Pan A, Lucas M, Sun Q, et al.** Increased mortality risk in women with depression and diabetes mellitus. *Arch Gen Psychiatry.* 2011;68:42-50. [EL 2; PCS]

619. **Kivimäki M, Hamer M, Batty GD, et al.** Antidepressant medication use, weight gain, and risk of type 2 diabetes: a population-based study. *Diabetes Care.* 2010;33:2611-2616. [EL 3; SS]

620. **Heiskanen TH, Koivumaa-Honkanen HT, Niskanen LK, et al.** Depression and major weight gain: a 6-year prospective follow-up of outpatients. *Compr Psychiatry.* 2013;54:599-604. [EL 2; PCS]

621. **Serretti A, Mandelli L.** Antidepressants and body weight: a comprehensive review and meta-analysis. *J Clin Psychiatry.* 2010;71:1259-1272. [EL 2; NRCT]

622. **Katon WJ, Lin EH, Von Korff M, et al.** Collaborative care for patients with depression and chronic illnesses. *N Engl J Med.* 2010;363:2611-2620. [EL 1; RCT, single-blinded]

623. **Liu X, Ji J, Sundquist K, Sundquist J, Hemminki K.** The impact of type 2 diabetes mellitus on cancer-specific survival: a follow-up study in Sweden. *Cancer.* 2012;118:1353-1361. [EL 3; SS]

624. **Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ.** Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med.* 2003;348:1625-1638. [EL 2; PCS]

625. **Campbell PT, Newton CC, Patel AV, Jacobs EJ, Gapstur SM.** Diabetes and cause-specific mortality in a prospective cohort of one million U.S. adults. *Diabetes Care.* 2012;35:1835-1844. [EL 2; PCS]

626. **Handelsman Y, Leroith D, Bloomgarden ZT, et al.** Diabetes and cancer--an AACE/ACE consensus statement. *Endocr Pract.* 2013;19:675-693. [EL 4; NE]

627. **Schouten LJ, Rivera C, Hunter DJ, et al.** Height, body mass index, and ovarian cancer: a pooled analysis of 12 cohort studies. *Cancer Epidemiol Biomarkers Prev.* 2008;17:902-912. [EL 2; MNRCT]

628. **Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M.** Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet.* 2008;371:569-578. [EL 2; MNRCT]

629. **Olsen CM, Green AC, Whiteman DC, Sadeghi S, Kolahdooz F, Webb PM.** Obesity and the risk of epithelial ovarian cancer: a systematic review and meta-analysis. *Eur J Cancer.* 2007;43:690-709. [EL 2; MNRCT]

630. **Druesne-Pecollo N, Touvier M, Barrandon E, et al.** Excess body weight and second primary cancer risk after breast cancer: a systematic review and meta-analysis of prospective studies. *Breast Cancer Res Treat.* 2012;135:647-654. [EL 2; MNRCT]

631. **Crosbie EJ, Zwahlen M, Kitchener HC, Egger M, Renehan AG.** Body mass index, hormone replacement therapy, and endometrial cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2010;19:3119-3130. [EL 2; MNRCT]

632. **Giovannucci E, Rimm EB, Liu Y, et al.** Body mass index and risk of prostate cancer in U.S. health professionals. *J Natl Cancer Inst.* 2003;95:1240-1244. [EL 3; SS]

633. **Allott EH, Masko EM, Freedland SJ.** Obesity and prostate cancer: weighing the evidence. *Eur Urol*. 2013;63:800-809. [EL 4; NE]

634. **Vucenik I, Stains JP.** Obesity and cancer risk: evidence, mechanisms, and recommendations. *Ann N Y Acad Sci*. 2012;1271:37-43. [EL 4; NE]

635. **Kasper JS, Giovannucci E.** A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2006;15:2056-2062. [EL 2; MNRCT]

636. **El-Serag HB, Hampel H, Javadi F.** The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol*. 2006;4:369-380. [EL 2; MNRCT]

637. **Huxley R, Ansary-Moghaddam A, Berrington de González A, Barzi F, Woodward M.** Type II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer*. 2005;92:2076-2083. [EL 2; MNRCT]

638. **Friberg E, Orsini N, Mantzoros CS, Wolk A.** Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia*. 2007;50:1365-1374. [EL 2; MNRCT]

639. **Larsson SC, Orsini N, Wolk A.** Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst*. 2005;97:1679-1687. [EL 2; MNRCT]

640. **Larsson SC, Mantzoros CS, Wolk A.** Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer*. 2007;121:856-862. [EL 2; MNRCT]

641. **Fierz Y, Novosyadlyy R, Vijayakumar A, Yakar S, LeRoith D.** Insulin-sensitizing therapy attenuates type 2 diabetes-mediated mammary tumor progression. *Diabetes*. 2010;59:686-693. [EL 4; NE]

642. **Novosyadlyy R, Lann DE, Vijayakumar A, et al.** Insulin-mediated acceleration of breast cancer development and progression in a nonobese model of type 2 diabetes. *Cancer Res*. 2010;70:741-751. [EL 4; NE]

643. **Nunez NP, Oh WJ, Rozenberg J, et al.** Accelerated tumor formation in a fatless mouse with type 2 diabetes and inflammation. *Cancer Res*. 2006;66:5469-5476. [EL 4; NE]

644. **Vander Heiden MG, Cantley LC, Thompson CB.** Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science*. 2009;324:1029-1033. [EL 4; NE]

645. **Vander Heiden MG, Plas DR, Rathmell JC, Fox CJ, Harris MH, Thompson CB.** Growth factors can influence cell growth and survival through effects on glucose metabolism. *Mol Cell Biol*. 2001;21:5899-5912. [EL 4; NE]

646. **Christofk HR, Vander Heiden MG, Harris MH, et al.** The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. *Nature*. 2008;452:230-233. [EL 4; NE]

647. **Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ.** Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. *Diabetes Care*. 2010;33:322-326. [EL 2; PCS]

648. **Decensi A, Puntoni M, Goodwin P, et al.** Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. *Cancer Prev Res (Phila)*. 2010;3:1451-1461. [EL 2; MNRCT]

649. **Stevens RJ, Ali R, Bankhead CR, et al.** Cancer outcomes and all-cause mortality in adults allocated to metformin: systematic review and collaborative meta-analysis of randomised clinical trials. *Diabetologia*. 2012;55:2593-2603. [EL 1; MRCT]

650. **Noto H, Goto A, Tsujimoto T, Noda M.** Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. *PLoS One*. 2012;7:e33411. [EL 2; MNRCT]

651. **Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC.** Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes*. 2013;62:2595-2604. [EL 3; SS]

652. **Egan AG, Blind E, Dunder K, et al.** Pancreatic safety of incretin-based drugs--FDA and EMA assessment. *N Engl J Med*. 2014;370:794-797. [EL 4; NE]

653. **Engel SS, Round E, Golm GT, Kaufman KD, Goldstein BJ.** Safety and tolerability of sitagliptin in type 2 diabetes: pooled analysis of 25 clinical studies. *Diabetes Ther*. 2013;4:119-145. [EL 1; MRCT]

654. **Garg R, Chen W, Pendergrass M.** Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. *Diabetes Care*. 2010;33:2349-2354. [EL 3; SS]

655. **Dore DD, Seeger JD, Arnold Chan K.** Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Med Res Opin*. 2009;25:1019-1027. [EL 3; SS]

656. **Dore DD, Bloomgren GL, Wenten M, et al.** A cohort study of acute pancreatitis in relation to exenatide use. *Diabetes Obes Metab*. 2011;13:559-566. [EL 2; PCS]

657. Victoza (liraglutide rDNA origin) injection prescribing information. Princeton, NJ: Novo Nordisk, Inc; 2013. [EL 4; NE]

658. **Gerstein HC, Bosch J, Dagenais GR, et al.** Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012;367:319-328. [EL 1; RCT]

659. Farxiga (dapagliflozin) prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; 2014. [EL 4; NE]

660. Invokana (canagliflozin) prescribing information. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2013. [EL 4; NE]

661. American Diabetes Association. Frequently Asked Questions About Commercial Driver's Licenses. Alexandria, VA: American Diabetes Association; 2014. Available at: http://www.diabetes.org/living-with-diabetes/know-your-rights/discrimination/drivers-licenses/commercial-drivers-and-diabetes-discrimination/faqs-about-commercial-drivers-licenses.html. [EL 4; NE]

662. **Jordan JL.** The Federal Air Surgeon's Column: Insulin-Dependency in Aviation Washington, DC: Federal Aviation Administration; 2012. Available at: http://www.faa.gov/other_visit/aviation_industry/designees_delegations/designee_types/ame/fasmb/editorials_jj/insulindependency/. [EL 4; NE]

663. **Bieber-Tregear M, Funmilayo D, Connor D, Tregear S, Tiller M.** Diabetes and Commercial Motor Vehicle Driver Safety. McLean, VA: MANILA Consulting Group, Inc.; 2011. Available at: http://ntl.bts.gov/lib/39000/39400/39416/2010_Diabetes_Update_Final_May_27_2011.pdf. [EL 4; NE]

664. **Hemmelgarn B, Lévesque LE, Suissa S.** Anti-diabetic drug use and the risk of motor vehicle crash in the elderly. *Can J Clin Pharmacol*. 2006;13:e112-e120. [EL 2; RCCS]

665. **McGwin G Jr, Sims RV, Pulley L, Roseman JM.** Diabetes and automobile crashes in the elderly. A population-based case-control study. *Diabetes Care*. 1999;22:220-227. [EL 2; RCCS]

666. **Koepsell TD, Wolf ME, McCloskey L, et al.** Medical conditions and motor vehicle collision injuries in older adults. *J Am Geriatr Soc*. 1994;42:695-700. [EL 2; RCCS]

667. **Holman RR, Farmer AJ, Davies MJ, et al.** Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med*. 2009;361:1736-1747. [EL 1; RCT, not blinded]

668. **Liu SC, Tu YK, Chien MN, Chien KL.** Effect of anti-diabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis. *Diabetes Obes Metab*. 2012;14:810-820. [EL 1; MRCT]

669. **Sieber WK, Robinson CF, Birdsey J, et al.** Obesity and other risk factors: the National Survey of U.S. Long-Haul Truck Driver Health and Injury. *Am J Ind Med*. 2014;57:615-626. [EL 3; SS]

670. **Xie W, Chakrabarty S, Levine R, Johnson R, Talmage JB.** Factors associated with obstructive sleep apnea among commercial motor vehicle drivers. *J Occup Environ Med*. 2011;53:169-173. [EL 2; RCCS]

671. **Borgia P, Forastiere F, Rapiti E, et al.** Mortality among taxi drivers in Rome: a cohort study. *Am J Ind Med*. 1994;25:507-517. [EL 3; SS]