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## **Section 2.**

# **Classification and Diagnosis of Diabetes**

# Classification

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to autoimmune  $\beta$ -cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood)
2. Type 2 diabetes (due to a non-autoimmune progressive loss of adequate  $\beta$ -cell insulin secretion frequently on the background of insulin resistance and metabolic syndrome)
3. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
4. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)

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Table 2.1—Staging of type 1 diabetes (12,16)

	Stage 1	Stage 2	Stage 3
Characteristics	<ul style="list-style-type: none"><li>• Autoimmunity</li><li>• Normoglycemia</li><li>• Presymptomatic</li></ul>	<ul style="list-style-type: none"><li>• Autoimmunity</li><li>• Dysglycemia</li><li>• Presymptomatic</li></ul>	<ul style="list-style-type: none"><li>• Autoimmunity</li><li>• Overt hyperglycemia</li><li>• Symptomatic</li></ul>
Diagnostic criteria	<ul style="list-style-type: none"><li>• Multiple islet autoantibodies</li><li>• No IGT or IFG</li></ul>	<ul style="list-style-type: none"><li>• Islet autoantibodies (usually multiple)</li><li>• Dysglycemia: IFG and/or IGT</li><li>• FPG 100–125 mg/dL (5.6–6.9 mmol/L)</li><li>• 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L)</li><li>• A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C</li></ul>	<ul style="list-style-type: none"><li>• Autoantibodies may become absent</li><li>• Diabetes by standard criteria</li></ul>

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose.

# CLASSIFICATION AND DIAGNOSIS OF DIABETES

**Table 2.2—Criteria for the diagnosis of diabetes**

FPG  $\geq 126$  mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.\*

OR

2-h PG  $\geq 200$  mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.\*

OR

A1C  $\geq 6.5\%$  (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.\*

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose  $\geq 200$  mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. \*In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

## A1C

- 2.1a To avoid misdiagnosis or missed diagnosis, the A1C test should be performed using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT) assay. **B**
- 2.1b Point-of-care A1C testing for diabetes screening and diagnosis should be restricted to U.S. Food and Drug Administration–approved devices at laboratories proficient in performing testing of moderate complexity or higher by trained personnel. **B**

## A1C (continued)

- 2.2** Marked discordance between measured A1C and plasma glucose levels should raise the possibility of A1C assay interference and consideration of using an assay without interference or plasma blood glucose criteria to diagnose diabetes. **B**
- 2.3** In conditions associated with an altered relationship between A1C and glycemia, such as hemoglobinopathies including sickle cell disease, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes. **B**

## A1C (continued)

- 2.4 Adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to oral glucose tolerance testing as a screen for diabetes. **A**

## Type 1 Diabetes

- 2.5** Screening for presymptomatic type 1 diabetes using screening tests that detect autoantibodies to insulin, glutamic acid decarboxylase (GAD), islet antigen 2, or zinc transporter 8 is currently recommended in the setting of a research study or can be considered an option for first-degree family members of a proband with type 1 diabetes. **B**
- 2.6** Development of and persistence of multiple islet autoantibodies is a risk factor for clinical diabetes and may serve as an indication for intervention in the setting of a clinical trial or screening for stage 2 type 1 diabetes. **B**



## Prediabetes and Type 2 Diabetes

- 2.7 Screening for prediabetes and type 2 diabetes with an informal assessment of risk factors or validated risk calculator should be done in asymptomatic adults. **B**
- 2.8 Testing for prediabetes and/or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity (BMI  $\geq 25$  kg/m<sup>2</sup> or  $\geq 23$  kg/m<sup>2</sup> in Asian American individuals) who have one or more risk factors (**Table 2.3**). **B**
- 2.9 For all people, screening should begin at age 35 years. **B**

## Prediabetes and Type 2 Diabetes (continued)

- 2.10 If tests are normal, repeat screening recommended at a minimum of 3-year intervals is reasonable, sooner with symptoms or change in risk (i.e., weight gain). **C**
- 2.11 To screen for prediabetes and type 2 diabetes, fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and A1C are each appropriate (**Table 2.2** and **Table 2.5**). **B**
- 2.12 When using oral glucose tolerance testing as a screen for diabetes, adequate carbohydrate intake (at least 150 g/day) should be assured for 3 days prior to testing. **A**
- 2.13 In people with prediabetes and type 2 diabetes, identify and treat cardiovascular disease risk factors. **A**

## Prediabetes and Type 2 Diabetes (continued)

- 2.14** Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents with overweight (BMI  $\geq$ 85th percentile) or obesity (BMI  $\geq$ 95th percentile) and who have one or more risk factors for diabetes. (See **Table 2.4** for evidence grading of risk factors.) **B**
- 2.15** People with HIV should be screened for diabetes and prediabetes with a fasting glucose test before starting antiretroviral therapy, at the time of switching antiretroviral therapy, and 3–6 months after starting or switching antiretroviral therapy. If initial screening results are normal, fasting glucose should be checked annually. **E**

## CLASSIFICATION AND DIAGNOSIS OF DIABETES

**Table 2.3—Criteria for screening for diabetes or prediabetes in asymptomatic adults**

1. Testing should be considered in adults with overweight or obesity (BMI  $\geq 25$  kg/m<sup>2</sup> or  $\geq 23$  kg/m<sup>2</sup> in Asian American individuals) who have one or more of the following risk factors:
  - First-degree relative with diabetes
  - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
  - History of CVD
  - Hypertension ( $\geq 140/90$  mmHg or on therapy for hypertension)
  - HDL cholesterol level  $<35$  mg/dL (0.90 mmol/L) and/or a triglyceride level  $>250$  mg/dL (2.82 mmol/L)
  - Individuals with polycystic ovary syndrome
  - Physical inactivity
  - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

2. People with prediabetes (A1C  $\geq 5.7\%$  [39 mmol/mol], IGT, or IFG) should be tested yearly.

3. People who were diagnosed with GDM should have lifelong testing at least every 3 years.

4. For all other people, testing should begin at age 35 years.

5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

6. People with HIV

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

## CLASSIFICATION AND DIAGNOSIS OF DIABETES

**Table 2.4—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting**

Screening should be considered in youth\* who have overweight ( $\geq 85$ th percentile) or obesity ( $\geq 95$ th percentile) **A** and who have one or more additional risk factors based on the strength of their association with diabetes:

- Maternal history of diabetes or GDM during the child's gestation **A**
- Family history of type 2 diabetes in first- or second-degree relative **A**
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander) **A**
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight) **B**

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

# CLASSIFICATION AND DIAGNOSIS OF DIABETES

**Table 2.5—Criteria defining prediabetes\***

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)

OR

2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

OR

A1C 5.7–6.4% (39–47 mmol/mol)

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

diabetes.org/socrisktest

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Are you at risk for type 2 diabetes?

**Diabetes Risk Test:**

1. How old are you? .....  
Less than 40 years (0 points)  
40-49 years (1 point)  
50-59 years (2 points)  
60 years or older (3 points)

2. Are you a man or a woman? .....  
Man (1 point)      Woman (0 points)

3. If you are a woman, have you ever been diagnosed with gestational diabetes? .....  
Yes (1 point)      No (0 points)

4. Do you have a mother, father, sister or brother with diabetes? .....  
Yes (1 point)      No (0 points)

5. Have you ever been diagnosed with high blood pressure? .....  
Yes (1 point)      No (0 points)

6. Are you physically active? .....  
Yes (0 points)      No (1 point)

7. What is your weight category? .....  
*See chart at right.*

WRITE YOUR SCORE IN THE BOX.

ADD UP YOUR SCORE.

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

1 point    2 points    3 points

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

Adapted from Bang et al., Ann Intern Med. 191:779-783, 2009. Original algorithm has excluded without pre-diabetes as part of the model.

**If you scored 5 or higher:**

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

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, Native Americans, Asian Americans, and Native Hawaiians and Pacific Islanders.

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

**Lower Your Risk**

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

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

Visit [diabetes.org](https://diabetes.org) or call 1-800-DIABETES (800-542-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

## Cystic Fibrosis-Related Diabetes

- 2.16 Annual screening for cystic fibrosis–related diabetes with an oral glucose tolerance test should begin by age 10 years in all people with cystic fibrosis not previously diagnosed with cystic fibrosis–related diabetes . **B**
- 2.17 A1C is not recommended as a screening test for cystic fibrosis–related diabetes. **B**
- 2.18 People with cystic fibrosis–related diabetes should be treated with insulin to attain individualized glycemic goals. **A**
- 2.19 Beginning 5 years after the diagnosis of cystic fibrosis–related diabetes, annual monitoring for complications of diabetes is recommended. **E**



## Posttransplantation Diabetes Mellitus

- 2.20 After organ transplantation, screening for hyperglycemia should be done. A formal diagnosis of posttransplantation diabetes mellitus is best made once the individual is stable on an immunosuppressive regimen and in the absence of an acute infection. **B**
- 2.21 The oral glucose tolerance test is the preferred test to make a diagnosis of posttransplantation diabetes mellitus. **B**
- 2.22 Immunosuppressive regimens shown to provide the best outcomes for patient and graft survival should be used, irrespective of posttransplantation diabetes mellitus risk. **E**

## Monogenic Diabetes Syndromes

- 2.23** Regardless of current age, all people diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes. **A**
- 2.24** Children and young adults who do not have typical characteristics of type 1 or type 2 diabetes and who often have a family history of diabetes in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity onset diabetes of the young. **A**
- 2.25** In both instances, consultation with a center specializing in diabetes genetics is recommended to understand the significance of genetic mutations and how best to approach further evaluation, treatment, and genetic counseling. **E**

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**Table 2.6—Most common causes of monogenic diabetes (171)**

	Gene	Inheritance	Clinical features
<b>MODY</b>	<i>HNF1A</i>	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [5 mmol/L]); sensitive to sulfonylureas
	<i>HNF4A</i>	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas
	<i>HNF1B</i>	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
	<i>GCK</i>	AD	GCK-MODY: higher glucose threshold (set point) for glucose-stimulated insulin secretion, causing stable, nonprogressive elevated fasting blood glucose; typically, does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [3 mmol/L])
<b>Neonatal diabetes</b>	<i>KCNJ11</i>	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	<i>INS</i>	AD	Permanent: IUGR; insulin requiring
	<i>ABCC8</i>	AD	Permanent or transient: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 ( <i>PLAGL1</i> , <i>HYMA1</i> )	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication, or maternal methylation defect; may be treatable with medications other than insulin
	<i>GATA6</i>	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	<i>EIF2AK3</i>	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	<i>EIF2B1</i>	AD	Permanent diabetes: can be associated with fluctuating liver function (172)
	<i>FOXP3</i>	X-linked	Permanent: immunodysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome: autoimmune diabetes, autoimmune thyroid disease, exfoliative dermatitis; insulin requiring

AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction; OGTT, oral glucose tolerance test; UPD6, uniparental disomy of chromosome 6; 2-h PG, 2-h plasma glucose.

Classification and Diagnosis of Diabetes:

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

- Diabetes diagnosed within the first 6 months of life (with occasional cases presenting later, mostly INS and ABCC8 mutations)
- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, no obesity, lacking other metabolic features, especially with strong family history of diabetes)
- Stable, mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), stable A1C between 5.6% and 7.6% (between 38 and 60 mmol/mol), especially if no obesity

## Gestational Diabetes Mellitus

- 2.26a In individuals who are planning pregnancy, screen those with risk factors **B** and consider testing all individuals of childbearing potential for undiagnosed diabetes. **E**
- 2.26b Before 15 weeks of gestation, test individuals with risk factors **B** and consider testing all individuals **E** for undiagnosed diabetes at the first prenatal visit using standard diagnostic criteria if not screened preconception.
- 2.26c Individuals of childbearing potential identified as having diabetes should be treated as such. **A**

## Gestational Diabetes Mellitus (continued)

- 2.26d Before 15 weeks of gestation, screen for abnormal glucose metabolism to identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes, are more likely to need insulin, and are at high risk of a later gestational diabetes mellitus diagnosis. **B** Treatment may provide some benefit. **E**
- 2.26e Screen for early abnormal glucose metabolism using fasting glucose of 110–125 mg/dL (6.1 mmol/L) or A1C 5.9–6.4% (41–47 mmol/mol). **B**
- 2.27 Screen for gestational diabetes mellitus at 24–28 weeks of gestation in pregnant individuals not previously found to have diabetes or high-risk abnormal glucose metabolism detected earlier in the current pregnancy. **A**

## Gestational Diabetes Mellitus (continued)

- 2.28 Screen individuals with gestational diabetes mellitus for prediabetes or diabetes at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. **B**
- 2.29 Individuals with a history of gestational diabetes mellitus should have lifelong screening for the development of diabetes or prediabetes at least every 3 years. **B**
- 2.30 Individuals with a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes. **A**

GDM diagnosis (**Table 2.7**) can be accomplished with either of two strategies:

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



# CLASSIFICATION AND DIAGNOSIS OF DIABETES

**Table 2.7—Screening for and diagnosis of GDM**

**One-step strategy**

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

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

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

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

**Two-step strategy**

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

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

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

The diagnosis of GDM is made when at least two\* of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria [251]):

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

GDM, gestational diabetes mellitus; GLT, glucose load test; OGTT, oral glucose tolerance test. \*American College of Obstetricians and Gynecologists notes that one elevated value can be used for diagnosis (247).

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## **Section 3.**

### **Prevention or Delay of Type 2 Diabetes and Associated Comorbidities**



## Overall Recommendation

- 3.1** Monitor for the development of type 2 diabetes in those with prediabetes at least annually; modified based on individual risk/benefit assessment. **E**

## Lifestyle Behavior Change for Diabetes Prevention

- 3.2 Refer adults with overweight/obesity at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and  $\geq 150$  min/week of moderate intensity physical activity. **A**
- 3.3 A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. **B**

## Lifestyle Behavior Change for Diabetes Prevention (continued)

- 3.4** Given the cost-effectiveness of lifestyle behavior modification programs for diabetes prevention, such diabetes prevention programs should be offered to adults at high risk of type 2 diabetes. **A** Diabetes prevention programs should be covered by third-party payers, and inconsistencies in access should be addressed.
- 3.5** Based on patient preference, certified technology-assisted diabetes prevention programs may be effective in preventing type 2 diabetes and should be considered. **B**

## Pharmacologic Interventions

- 3.6** Metformin therapy for the prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the Diabetes Prevention Program, especially those aged 25–59 years with BMI  $\geq 35$  kg/m<sup>2</sup>, higher fasting plasma glucose (e.g.,  $\geq 110$  mg/dL), and higher A1C (e.g.,  $\geq 6.0\%$ ), and in individuals with prior gestational diabetes mellitus. **A**
- 3.7** Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated individuals, especially in those with anemia or peripheral neuropathy. **B**

## Prevention of Vascular Disease and Mortality

- 3.8 Prediabetes is associated with heightened cardiovascular risk; therefore, screening for and treatment of modifiable risk factors for cardiovascular disease are suggested. **B**
- 3.9 Statin therapy may increase the risk of type 2 diabetes in people at high risk of developing type 2 diabetes. In such individuals, glucose status should be monitored regularly and diabetes prevention approaches reinforced. It is not recommended that statins be discontinued. **B**
- 3.10 In people with a history of stroke and evidence of insulin resistance and prediabetes, pioglitazone may be considered to lower the risk of stroke or myocardial infarction. However, this benefit needs to be balanced with the increased risk of weight gain, edema, and fracture. **A** Lower doses may mitigate the risk of adverse effects. **C**

## Patient-Centered Care Goals

- 3.11 In adults with overweight/obesity at high risk of type 2 diabetes, care goals should include weight loss or prevention of weight gain, minimizing the progression of hyperglycemia, and attention to cardiovascular risk and associated comorbidities. **B**
- 3.12 Pharmacotherapy (e.g., for weight management, minimizing the progression of hyperglycemia, cardiovascular risk reduction) may be considered to support person-centered care goals. **B**
- 3.13 More intensive preventive approaches should be considered in individuals who are at particularly high risk of progression to diabetes, including individuals with BMI  $\geq 35$  kg/m<sup>2</sup>, those at higher glucose levels (e.g., fasting plasma glucose 110–125 mg/dL, 2-h postchallenge glucose 173–199 mg/dL, A1C  $\geq 6.0\%$ ), and individuals with a history of gestational diabetes mellitus. **A**



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## **Section 6.**

# **Glycemic Targets**

## Glycemic Assessment

- 6.1 Assess glycemic status (A1C or other glycemic measurement such as time in range or glucose management indicator) at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control). E
- 6.2 Assess glycemic status at least quarterly and as needed in patients whose therapy has recently changed and/or who are not meeting glycemic goals. E

# Estimated Average Glucose

Table 6.1—Estimated average glucose (eAG)		
A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)
Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at <a href="http://professional.diabetes.org/eAG">professional.diabetes.org/eAG</a> . *These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, or no diabetes. The correlation between A1C and average glucose was 0.92 (13,14). Adapted from Nathan et al. (13).		

Glycemic Targets:  
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# Standardized CGM Metrics

Table 6.2—Standardized CGM metrics for clinical care		
1. Number of days CGM device is worn (recommend 14 days)		
2. Percentage of time CGM device is active (recommend 70% of data from 14 days)		
3. Mean glucose		
4. Glucose management indicator		
5. Glycemic variability (%CV) target ≤36%*		
6. TAR: % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2 hyperglycemia	
7. TAR: % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1 hyperglycemia	
8. TIR: % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range	
9. TBR: % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1 hypoglycemia	
10. TBR: % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2 hypoglycemia	
CGM, continuous glucose monitoring; CV, coefficient of variation; TAR, time above range; TBR, time below range; TIR, time in range. *Some studies suggest that lower %CV targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas. Adapted from Battelino et al. (35).		

Glycemic Targets:  
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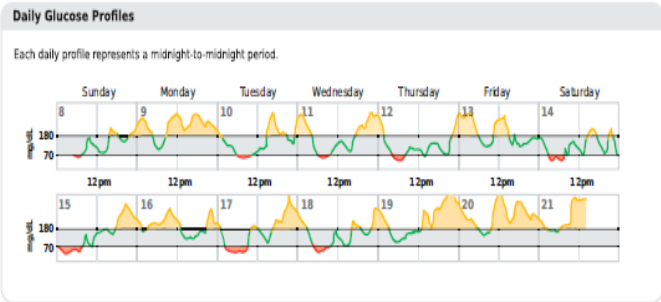
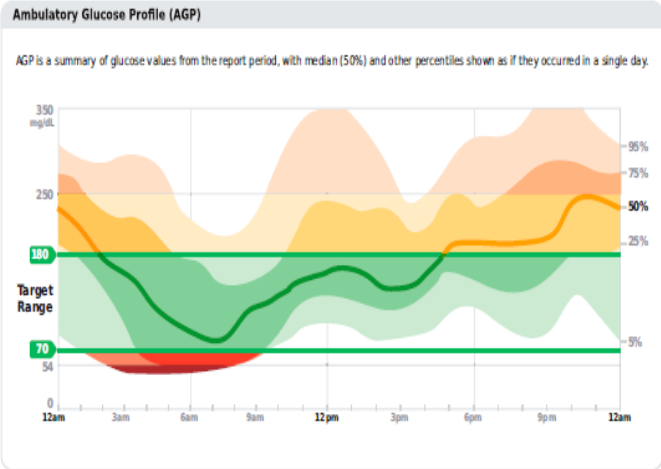
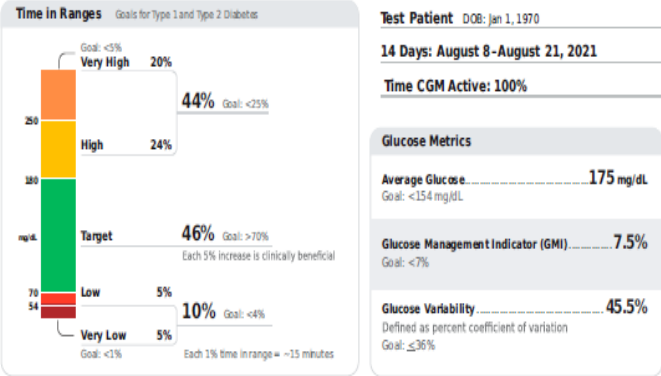
## Glucose Assessment by Continuous Glucose Monitoring

- 6.3 Standardized, single-page glucose reports from continuous glucose monitoring (CGM) devices with visual cues, such as the ambulatory glucose profile, should be considered as a standard summary for all CGM devices. **E**
- 6.4 Time in range is associated with the risk of microvascular complications and can be used for assessment of glycemic control. Additionally, time below range and time above range are useful parameters for the evaluation of the treatment plan (Table 6.2). **C**

GLYCEMIC TARGETS



AGP Report: Continuous Glucose Monitoring



Glycemic Targets:  
*Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S97-S110*

## Glycemic Goals

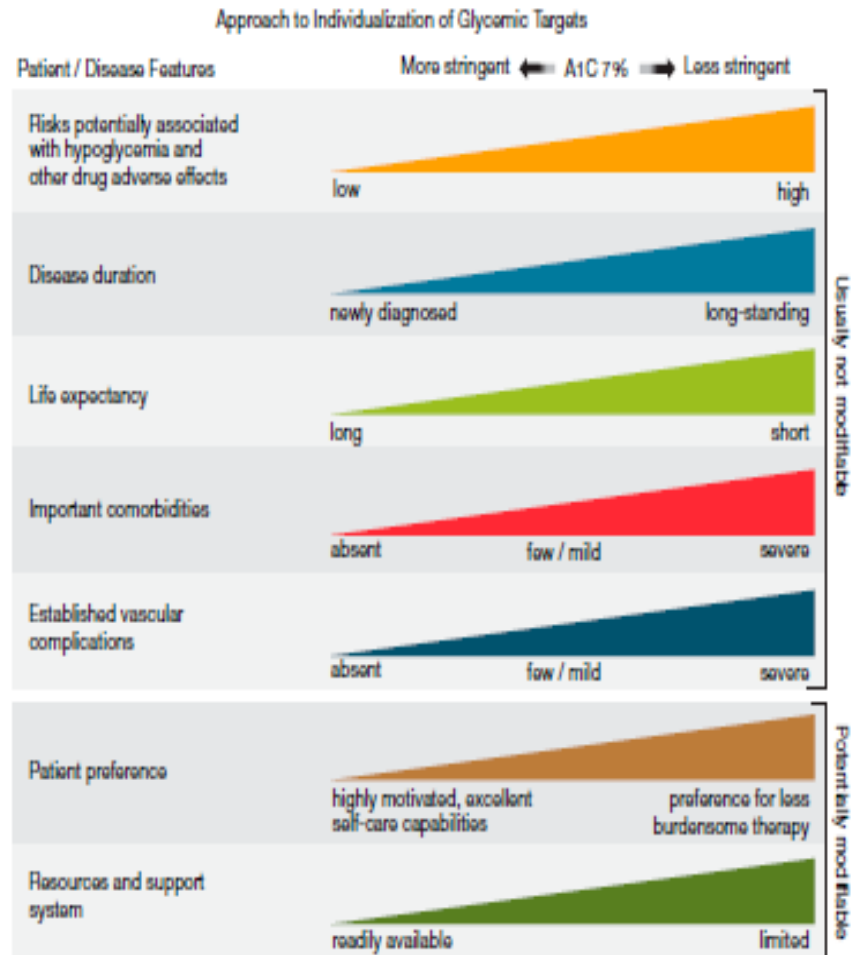
- 6.5a An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. **A**
- 6.5b If using ambulatory glucose profile/glucose management indicator to assess glycemia, a parallel goal for many nonpregnant adults is time in range of >70% with time below range <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% time in range with <1% time below range is recommended. (See Fig. 6.1 and Table 6.2.). **B**
- 6.6 On the basis of health care professional judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. **B**

## Glycemic Goals (continued)

- 6.7 Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits. Health care professionals should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriate stringent A1C targets. **B**
- 6.8 Reassess glycemic targets based on the individualized criteria in Fig. 6.2. **E**
- 6.9 Reassess Setting a glycemic goal during consultations is likely to improve patient outcomes. **E**



## GLYCEMIC TARGETS



Glycemic Targets:

*Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S97-S110*

## Cardiovascular Disease and Type 2 Diabetes

As outlined in more detail in Section 9, “Pharmacologic Approaches to Glycemic Treatment,” and Section 10, “Cardiovascular Disease and Risk Management,” the cardiovascular benefits of SGLT2 inhibitors or GLP-1 receptor agonists are not contingent upon A1C lowering; therefore, initiation can be considered in people with type 2 diabetes and CVD independent of the current A1C or A1C goal or metformin therapy. Based on these considerations, the following two strategies are offered (70):

1. If already on dual therapy or multiple glucose-lowering therapies and not on an SGLT2 inhibitor or GLP-1 receptor agonist, consider switching to one of these agents with proven cardiovascular benefit.
2. Introduce SGLT2 inhibitors or GLP-1 receptor agonists in people with CVD at A1C goal (independent of metformin) for cardiovascular benefit, independent of baseline A1C or individualized A1C target.

**Table 6.3—Summary of glycemic recommendations for many nonpregnant adults with diabetes**

A1C	<7.0% (53 mmol/mol)* #
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

\*More or less stringent glycemic goals may be appropriate for individual patients. #CGM may be used to assess glycemic target as noted in Recommendation 6.5b and Fig. 6.1. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations (as per Fig. 6.2). †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in people with diabetes.

# Hypoglycemia

- 6.10 Occurrence and risk for hypoglycemia should be reviewed at every encounter and investigated as indicated. Awareness of hypoglycemia should be considered using validated tools. **C**
- 6.11 Glucose (approximately 15–20 g) is the preferred treatment for the conscious individual with blood glucose <70 mg/dL (3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Fifteen minutes after treatment, if blood glucose monitoring (BGM) shows continued hypoglycemia, the treatment should be repeated. Once the BGM or glucose pattern is trending up, the individual should consume a meal or snack to prevent recurrence of hypoglycemia. **B**

## Hypoglycemia (continued)

- 6.12 Glucagon should be prescribed for all individuals at increased risk of level 2 or 3 hypoglycemia, so that it is available should it be needed. Caregivers, school personnel, or family members providing support to these individuals should know where it is and when and how to administer it. Glucagon administration is not limited to health care professionals. **E**
- 6.13 Hypoglycemia unawareness or one or more episodes of level 3 hypoglycemia should trigger hypoglycemia avoidance education and reevaluation and adjustment of the treatment plan to decrease hypoglycemia. **E**

## Hypoglycemia (continued)

- 6.13 Hypoglycemia unawareness or one or more episodes of level 3 hypoglycemia should trigger hypoglycemia avoidance education and reevaluation and adjustment of the treatment plan to decrease hypoglycemia. **E**
- 6.14 Insulin-treated patients with hypoglycemia unawareness, one level 3 hypoglycemic event, or a pattern of unexplained level 2 hypoglycemia should be advised to raise their glycemic targets to strictly avoid hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. **A**
- 6.15 Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if impaired or declining cognition is found. **B**



Table 6.4—Classification of hypoglycemia

	Glycemic criteria/description
Level 1	Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L)
Level 2	Glucose <54 mg/dL (3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia

Reprinted from Agiostratidou et al. (74).

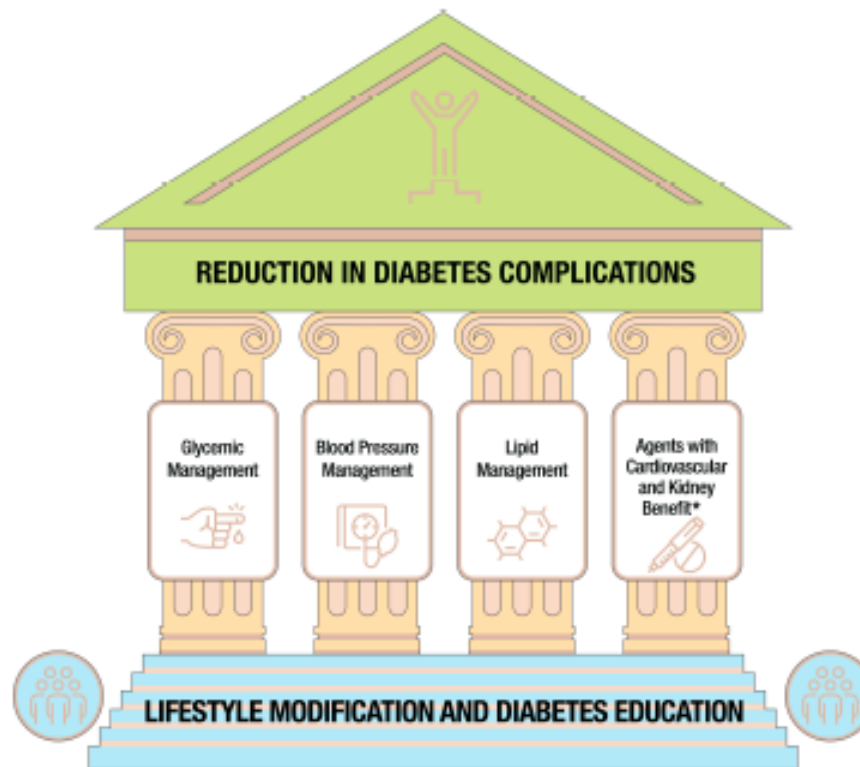
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## **Section 10.**

# **Cardiovascular Disease and Risk Management**



**Figure 10.1**—Multifactorial approach to reduction in risk of diabetes complications. \*Risk reduction interventions to be applied as individually appropriate.

Cardiovascular Disease and Risk Management:  
*Standards of Care in Diabetes - 2023. Diabetes Care* 2023;46(Suppl. 1):S158-S190

## Screening and Diagnosis

- 10.1** measured at every routine clinical visit. When possible, individuals found to have elevated blood pressure (systolic blood pressure 120–129 mmHg and diastolic <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. **A** Hypertension is defined as a systolic blood pressure  $\geq 130$  mmHg or a diastolic blood pressure  $\geq 80$  mmHg based on an average of  $\geq 2$  measurements obtained on  $\geq 2$  occasions. **A** Individuals with blood pressure  $\geq 180/110$  mmHg and cardiovascular disease could be diagnosed with hypertension at a single visit. **E**
- 10.2** All people with hypertension and diabetes should monitor their blood pressure at home. **A**

## Treatment Goals

- 10.3** For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. **B**
- 10.4** People with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated  $\geq 130/80$  mmHg. The on-treatment target blood pressure goal is  $<130/80$  mmHg, if it can be safely attained. **B**

## Treatment Goals (continued)

- 10.5** In pregnant individuals with diabetes and chronic hypertension, a blood pressure threshold of 140/90 mmHg for initiation or titration of therapy is associated with better pregnancy outcomes than reserving treatment for severe hypertension, with no increase in risk of small-for-gestational age birth weight. **A** There are limited data on the optimal lower limit, but therapy should be lessened for blood pressure <90/60 mmHg. **E** A blood pressure target of 110–135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension. **A**

# Randomized controlled trials of intensive versus standard hypertension treatment strategies

Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S158-S190*

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP (35)	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	SBP target: <120 mmHg Achieved (mean) SBP/DBP: 119.3/64.4 mmHg	SBP target: 130–140 mmHg Achieved (mean) SBP/DBP: 135/70.5 mmHg	<ul style="list-style-type: none"> <li>No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death</li> <li>Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment</li> <li>Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities</li> </ul>
ADVANCE (36)	11,140 participants with T2D aged ≥55 years with prior evidence of CVD or multiple cardiovascular risk factors	Intervention: a single-pill, fixed-dose combination of perindopril and indapamide Achieved (mean) SBP/DBP: 136/73 mmHg	Control: placebo Achieved (mean) SBP/DBP: 141.6/75.2 mmHg	<ul style="list-style-type: none"> <li>Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%)</li> <li>6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (242)</li> </ul>
HOT (37)	18,790 participants, including 1,501 with diabetes	DBP target: ≤80 mmHg Achieved (mean): 81.1 mmHg, ≤80 group; 85.2 mmHg, ≤90 group	DBP target: ≤90 mmHg	<ul style="list-style-type: none"> <li>In the overall trial, there was no cardiovascular benefit with more intensive targets</li> <li>In the subpopulation with diabetes, an intensive DBP target was associated with a significantly reduced risk (51%) of CVD events</li> </ul>
SPRINT (43)	9,361 participants without diabetes	SBP target: <120 mmHg Achieved (mean): 121.4 mmHg	SBP target: <140 mmHg Achieved (mean): 136.2 mmHg	<ul style="list-style-type: none"> <li>Intensive SBP target lowered risk of the primary composite outcome 25% (MI, ACS, stroke, heart failure, and death due to CVD)</li> <li>Intensive target reduced risk of death 27%</li> <li>Intensive therapy increased risks of electrolyte abnormalities and AKI</li> </ul>
STEP (34)	8,511 participants aged 60–80 years, including 1,627 with diabetes	SBP target: <130 mmHg Achieved (mean): 127.5 mmHg	SBP target: <150 mmHg Achieved (mean): 135.3 mmHg	<ul style="list-style-type: none"> <li>Intensive SBP target lowered risk of the primary composite outcome 26% (stroke, ACS [acute MI and hospitalization for unstable angina], acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes)</li> <li>Intensive target reduced risk of cardiovascular death 28%</li> <li>Intensive therapy increased risks of hypotension</li> </ul>

ACCORD BP, Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial; ACS, acute coronary syndrome; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; AKI, acute kidney injury; CVD, cardiovascular disease; DBP, diastolic blood pressure; HOT, Hypertension Optimal Treatment trial; MI, myocardial infarction; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; STEP, Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients; T2D, type 2 diabetes.

# Treatment Strategies—Lifestyle Intervention

- 10.6** For people with blood pressure  $>120/80$  mmHg, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. **A**

# Treatment Strategies—Pharmacologic Interventions

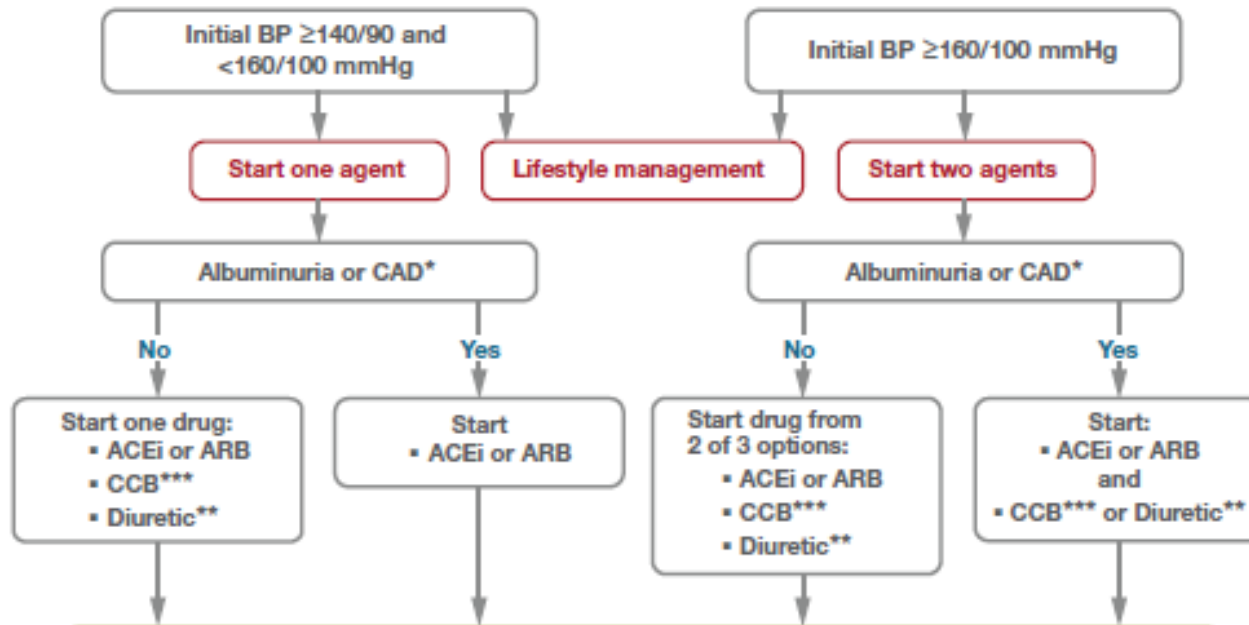
- 10.7 Individuals with confirmed office-based blood pressure  $\geq 130/80$  mmHg qualify for initiation and titration of pharmacologic therapy to achieve the recommended blood pressure goal of  $<130/80$  mmHg. **A**
- 10.8 Individuals with confirmed office-based blood pressure  $\geq 160/100$  mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in people with diabetes. **A**
- 10.9 Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in people with diabetes. **A** ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. **A**



## Treatment Strategies—Pharmacologic Interventions (continued)

- 10.10** Multiple-drug therapy is generally required to achieve blood pressure targets. However, combinations of ACE inhibitors and angiotensin receptor blockers and combinations of ACE inhibitors or angiotensin receptor blockers with direct renin inhibitors should not be used. **A**
- 10.12** An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in people with diabetes and urinary albumin-to-creatinine ratio  $\geq 300$  mg/g creatinine **A** or 30–299 mg/g creatinine. **B** If one class is not tolerated, the other should be substituted. **B**
- 10.12** For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. **B**

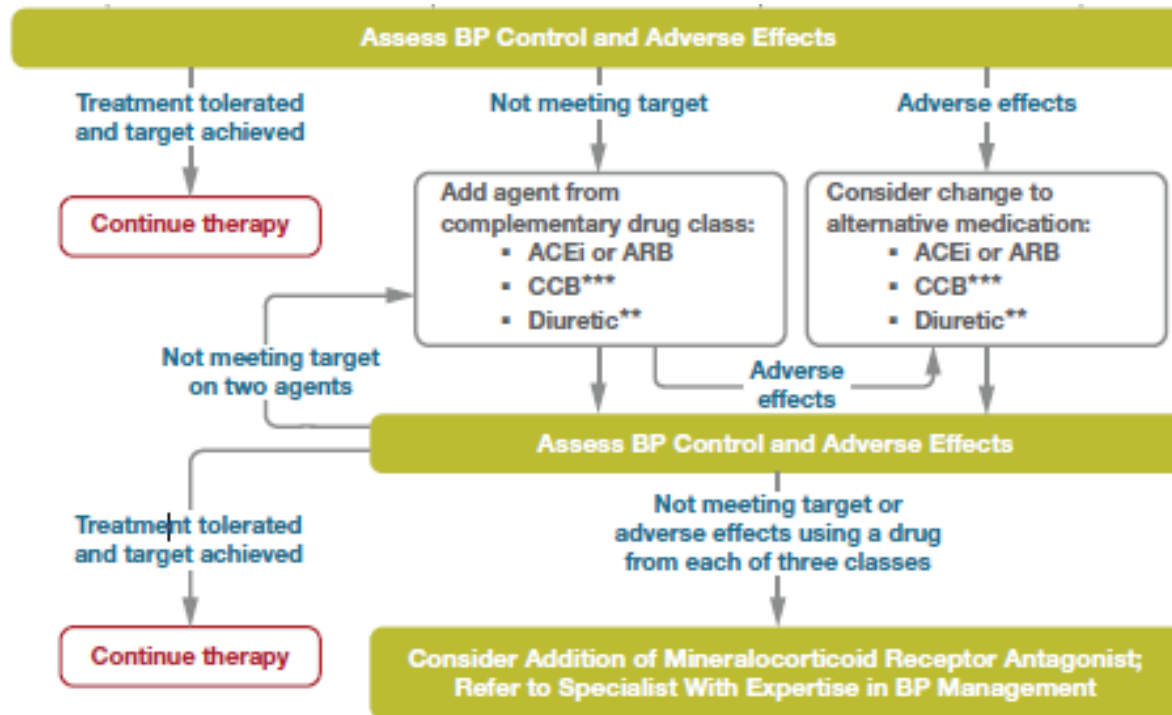
## Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes



**Recommendations  
for the Treatment of  
Confirmed  
Hypertension in  
People with  
Diabetes (1 of 2)**

Cardiovascular Disease and Risk Management:

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## Recommendations for the Treatment of Confirmed Hypertension in People with Diabetes (2 of 2)

# Treatment Strategies—Resistant Hypertension

- 10.13** Individuals with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. **A**

## Lipid Management—Lifestyle Intervention

- 10.14** Lifestyle modification focusing on weight loss (if indicated); application of a Mediterranean or Dietary Approaches to Stop Hypertension (DASH) eating pattern; reduction of saturated fat and trans fat; increase of dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols intake; and increased physical activity should be recommended to improve the lipid profile and reduce the risk of developing atherosclerotic cardiovascular disease in people with diabetes. **A**
- 10.15** Intensify lifestyle therapy and optimize glycemic control for patients with elevated triglyceride levels ( $\geq 150$  mg/dL [ $1.7$  mmol/L]) and/or low HDL cholesterol ( $< 40$  mg/dL [ $1.0$  mmol/L] for men,  $< 50$  mg/dL [ $1.3$  mmol/L] for women). **C**

## Lipid Management—Ongoing Therapy and Monitoring with Lipid Panel

- 10.16** In adults not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and every 5 years thereafter if under the age of. **E**
- 10.17** Obtain a lipid profile at initiation of statins or other lipid-lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter as it may help to monitor the response to therapy and inform medication taking. **E**

## Statin Treatment—Primary Prevention

- 10.18 For people with diabetes aged 40–75 years without atherosclerotic cardiovascular disease, use moderate-intensity statin therapy in addition to lifestyle therapy. **A**
- 10.19 For people with diabetes aged 20–39 years with additional atherosclerotic cardiovascular disease risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy. **C**
- 10.20 For people with diabetes aged 40–75 at higher cardiovascular risk, including those with one or more atherosclerotic cardiovascular disease risk factors, it is recommended to use high-intensity statin therapy to reduce LDL cholesterol by  $\geq 50\%$  of baseline and to target an LDL cholesterol goal of  $< 70$  mg/dL. **B**

## **Statin Treatment—Primary Prevention (continued)**

- 10.21** For people with diabetes aged 40–75 years at higher cardiovascular risk, especially those with multiple atherosclerotic cardiovascular disease risk factors and an LDL cholesterol  $\geq 70$  mg/dL, it may be reasonable to add ezetimibe or a PCSK9 inhibitor to maximum tolerated statin therapy. **C**
- 10.22** In adults with diabetes aged >75 years already on statin therapy, it is reasonable to continue statin treatment. **C**
- 10.23** In adults with diabetes aged >75 years, it may be reasonable to initiate moderate-intensity statin therapy after discussion of potential benefits and risks. **B**
- 10.24** Statin therapy is contraindicated in pregnancy. **B**



## Statin Treatment—Secondary Prevention

- 10.25 For people of all ages with diabetes and atherosclerotic cardiovascular disease, highintensity statin therapy should be added to lifestyle therapy. **A**
- 10.26 For people with diabetes and atherosclerotic cardiovascular disease, treatment with highintensity statin therapy is recommended to target an LDL cholesterol reduction of  $\geq 50\%$  from baseline and an LDL cholesterol goal of  $< 55$  mg/dL. Addition of ezetimibe or a PCSK9 inhibitor with proven benefit in this population is recommended if this goal is not achieved on maximum tolerated statin therapy. **B**
- 10.27 For individuals who do not tolerate the intended intensity, the maximum tolerated statin dose should be used. **E**

Table 10.2—High-intensity and moderate-intensity statin therapy*	
High-intensity statin therapy (lowers LDL cholesterol by $\geq 50\%$ )	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 1–4 mg
*Once-daily dosing. XL, extended release.	

# Treatment of Other Lipoprotein Fractions or Targets

- 10.28** For individuals with fasting triglyceride levels  $\geq 500$  mg/dL, evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. **C**
- 10.29** In adults with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175–499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise triglycerides. **C**
- 10.30** In individuals with atherosclerotic cardiovascular disease or other cardiovascular risk factors on a statin with controlled LDL cholesterol but elevated triglycerides (135–499 mg/dL), the addition of icosapent ethyl can be considered to reduce cardiovascular risk. **A**

## Other Combination Therapy

- 10.31 Statin plus fibrate combination therapy has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. **A**
- 10.32 Statin plus niacin combination therapy has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. **A**

## Antiplatelet Agents

- 10.33 Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease. **A**
- 10.34 For individuals with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**
- 10.35 Dual antiplatelet therapy (with low-dose aspirin and a P2Y<sub>12</sub> inhibitor) is reasonable for a year after an acute coronary syndrome and may have benefits beyond this period. **A**
- 10.36 Long-term treatment with dual antiplatelet therapy should be considered for individuals with prior coronary intervention, high ischemic risk, and low bleeding risk to prevent major adverse cardiovascular events. **A**

## Antiplatelet Agents (continued)

- 10.37** Combination therapy with aspirin plus low-dose rivaroxaban should be considered for individuals with stable coronary and/or peripheral artery disease and low bleeding risk to prevent major adverse limb and cardiovascular events. **A**
- 10.38** Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding. **A**

## Cardiovascular Disease—Screening

- 10.39** In asymptomatic individuals, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. **A**
- 10.40** Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). **E**

# Cardiovascular Disease—Treatment

- 10.41** Among people with type 2 diabetes who have established atherosclerotic cardiovascular disease or established kidney disease, a sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit (Table 10.3B and Table 10.3C) is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimens. **A**
- 10.41a** In people with type 2 diabetes and established atherosclerotic cardiovascular disease, multiple atherosclerotic cardiovascular disease risk factors, or diabetic kidney disease, a sodium–glucose cotransporter 2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. **A**



## Cardiovascular Disease—Treatment (continued)

- 10.41b** In people with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease, a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. **A**
- 10.41c** In people with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease, combined therapy with a sodium–glucose cotransporter 2 inhibitor with demonstrated cardiovascular benefit and a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit may be considered for additive reduction in the risk of adverse cardiovascular and kidney events. **A**

## Cardiovascular Disease—Treatment (continued)

- 10.42a** In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, a sodium–glucose cotransporter 2 inhibitor with proven benefit in this patient population is recommended to reduce risk of worsening heart failure and cardiovascular death. **A**
- 10.42b** In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, a sodium–glucose cotransporter 2 inhibitor with proven benefit in this patient population is recommended to improve symptoms, physical limitations, and quality of life. **A**

## Cardiovascular Disease—Treatment (continued)

- 10.43 For people with type 2 diabetes and chronic kidney disease with albuminuria treated with maximum tolerated doses of ACE inhibitor or angiotensin receptor blocker, addition of finerenone is recommended to improve cardiovascular outcomes and reduce the risk of chronic kidney disease progression. **A**
- 10.44 In people with known atherosclerotic cardiovascular disease, particularly coronary artery disease, ACE inhibitor or angiotensin receptor blocker therapy is recommended to reduce the risk of cardiovascular events. **A**
- 10.45 In people with prior myocardial infarction, b-blockers should be continued for 3 years after the event. **B**

# Cardiovascular Disease—Treatment (continued)

- 10.46 Treatment of individuals with heart failure with reduced ejection fraction should include a b-blocker with proven cardiovascular outcomes benefit, unless otherwise contraindicated. **A**
- 10.47 In people with type 2 diabetes with stable heart failure, metformin may be continued for glucose lowering if estimated glomerular filtration rate remains  $>30$  mL/min/1.73 m<sup>2</sup> but should be avoided in unstable or hospitalized individuals with heart failure. **B**

## Table 10.3A

**Table 10.3A—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: DPP-4 inhibitors**

	SAVOR-TIMI 53 (224) (n = 16,492)	EXAMINE (235) (n = 5,380)	TECOS (226) (n = 14,671)	CARMELINA (193,236) (n = 6,979)	CAROLINA (193,237) (n = 6,042)
Intervention	Saxagliptin/placebo	Alogliptin/placebo	Sitagliptin/placebo	Linaagliptin/placebo	Linagliptin/ glimepiride
Main inclusion criteria	Type 2 diabetes and history of or multiple risk factors for CVD	Type 2 diabetes and ACS within 15–90 days before randomization	Type 2 diabetes and preexisting CVD	Type 2 diabetes and high CV and renal risk	Type 2 diabetes and high CV risk
AIC inclusion criteria (%)	≥6.5	6.5–11.0	6.5–8.0	6.5–10.0	6.5–8.5
Age (years)†	65.1	61.0	65.4	65.8	64.0
Race (% White)	75.2	72.7	67.9	80.2	73.0
Sex (% male)	66.9	67.9	70.7	62.9	60.0
Diabetes duration (years)†	10.3	7.1	11.6	14.7	6.2
Median follow-up (years)	2.1	1.5	3.0	2.2	6.3
Statin use (%)	78	91	80	71.8	64.1
Metformin use (%)	70	66	82	54.8	82.5
Prior CVD/CHF (%)	78/13	100/28	74/18	57/26.8	34.5/4.5
Mean baseline A1C (%)	8.0	8.0	7.2	7.9	7.2
Mean difference in A1C between groups at end of treatment (%)	−0.3†	−0.3†	−0.3†	−0.36†	0
Year started/ reported	2010/2013	2009/2013	2008/2015	2013/2018	2010/2019
Primary outcome§	3-point MACE 1.00 (0.89–1.12)	3-point MACE 0.96 (95% UL ≤1.16)	4-point MACE 0.98 (0.89–1.08)	3-point MACE 1.02 (0.89–1.17)	3-point MACE 0.98 (0.84–1.14)
Key secondary outcome§	Expanded MACE 1.02 (0.94–1.11)	4-point MACE 0.95 (95% UL ≤1.14)	3-point MACE 0.99 (0.89–1.10)	Kidney composite (ESRD, sustained ≥40% decrease in eGFR, or renal death) 1.04 (0.89–1.22)	4-point MACE 0.99 (0.86–1.14)
Cardiovascular death§	1.03 (0.87–1.22)	0.85 (0.66–1.10)	1.03 (0.89–1.19)	0.96 (0.81–1.14)	1.00 (0.81–1.24)
MI§	0.95 (0.80–1.12)	1.08 (0.88–1.33)	0.95 (0.81–1.11)	1.12 (0.90–1.40)	1.03 (0.82–1.29)
Stroke§	1.11 (0.88–1.39)	0.91 (0.55–1.50)	0.97 (0.79–1.19)	0.91 (0.67–1.23)	0.86 (0.66–1.12)
HF hospitalization§	1.27 (1.07–1.51)	1.19 (0.90–1.58)	1.00 (0.83–1.20)	0.90 (0.74–1.08)	1.21 (0.92–1.59)
Unstable angina hospitalization§	1.19 (0.89–1.60)	0.90 (0.60–1.37)	0.90 (0.70–1.16)	0.87 (0.57–1.31)	1.07 (0.74–1.54)
All-cause mortality§	1.11 (0.96–1.27)	0.88 (0.71–1.09)	1.01 (0.90–1.14)	0.98 (0.84–1.13)	0.91 (0.78–1.06)
Worsening nephropathy§	1.08 (0.88–1.32)	—	—	Kidney composite (see above)	—

—, not assessed/reported; ACS, acute coronary syndrome; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GLP-1, glucagon-like peptide 1; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; UL, upper limit. Data from this table was adapted from Cefalu et al. (238) in the January 2018 issue of *Diabetes Care*. †Age was reported as means in all trials except EXAMINE, which reported medians; diabetes duration was reported as means in all trials except SAVOR-TIMI 53 and EXAMINE, which reported medians. ‡Significant difference in A1C between groups ( $P < 0.05$ ). §Outcomes reported as hazard ratio (95% CI). ||Worsening nephropathy is defined as a doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine  $>6.0$  mg/dL (530 mmol/L) in SAVOR-TIMI 53. Worsening nephropathy was a prespecified exploratory adjudicated outcome in SAVOR-TIMI 53.

## Table 10.3A—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: DPP-4 inhibitors

Cardiovascular  
Disease and Risk  
Management:  
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**Table 10.3B—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: GLP-1 receptor agonists**

	ELIXA (208) (n = 6,068)	LEADER (203) (n = 9,340)	SUSTAIN-6 (204)* (n = 3,297)	EXSCEL (209) (n = 14,752)	REWIND (207) (n = 9,901)	PIONEER-6 (205) (n = 3,183)
Intervention	Lixisenatide/placebo	Liraglutide/placebo	Semaglutide s.c. injection/placebo	Exenatide QW/placebo	Dulaglutide/placebo	Semaglutide oral/placebo
Main inclusion criteria	Type 2 diabetes and history of ACS (<180 days)	Type 2 diabetes and preexisting CVD, CKD, or HF at ≥50 years of age or CV risk at ≥60 years of age	Type 2 diabetes and preexisting CVD, HF, or CKD at ≥50 years of age or CV risk at ≥60 years of age	Type 2 diabetes with or without preexisting CVD	Type 2 diabetes and prior ASCVD event or risk factors for ASCVD	Type 2 diabetes and high CV risk (age of ≥50 years with established CVD or CKD, or age of ≥60 years with CV risk factors only)
A1C inclusion criteria (%)	5.5–11.0	≥7.0	≥7.0	6.5–10.0	≤9.5	None
Age (years)†	60.3	64.3	64.6	62	66.2	66
Race (% White)	75.2	77.5	83.0	75.8	75.7	72.3
Sex (% male)	69.3	64.3	60.7	62	53.7	68.4
Diabetes duration (years)†	9.3	12.8	13.9	12	10.5	14.9
Median follow-up (years)	2.1	3.8	2.1	3.2	5.4	1.3
Statin use (%)	93	72	73	74	66	85.2 (all lipid-lowering)
Metformin use (%)	66	76	73	77	81	77.4
Prior CVD/CHF (%)	100/22	81/18	60/24	73.1/16.2	32/9	84.7/12.2
Mean baseline A1C (%)	7.7	8.7	8.7	8.0	7.4	8.2
Mean difference in A1C between groups at end of treatment (%)	−0.3†^	−0.4†	−0.7 or −1.0^	−0.53†^	−0.61†	−0.7
Year started/reported	2010/2015	2010/2016	2013/2016	2010/2017	2011/2019	2017/2019
Primary outcome§	4-point MACE 1.02 (0.89–1.17)	3-point MACE 0.87 (0.78–0.97)	3-point MACE 0.74 (0.58–0.95)	3-point MACE 0.91 (0.83–1.00)	3-point MACE 0.88 (0.79–0.99)	3-point MACE 0.79 (0.57–1.11)

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**Table 10.3B—  
Cardiovascular and  
cardiorenal outcomes  
trials of available  
antihyperglycemic  
medications completed  
after the issuance  
of the FDA 2008  
guidelines: GLP-1  
receptor agonists (1 of 2)**

Cardiovascular  
Disease and Risk  
Management:  
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Table 10.3B—Continued	ELIXA (208) (n = 6,068)	LEADER (203) (n = 9,340)	SUSTAIN-6 (204)* (n = 3,297)	EXSCEL (209) (n = 14,752)	REWIND (207) (n = 9,901)	PIONEER-6 (205) (n = 3,183)
Key secondary outcome§	Expanded MACE 1.02 (0.90–1.11)	Expanded MACE 0.88 (0.81–0.96)	Expanded MACE 0.74 (0.62–0.89)	Individual components of MACE (see below)	Composite microvascular outcome (eye or renal outcome) 0.87 (0.79–0.95)	Expanded MACE or HF hospitalization 0.82 (0.61–1.10)
Cardiovascular death§	0.98 (0.78–1.22)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.91 (0.78–1.06)	0.49 (0.27–0.92)
MI§	1.03 (0.87–1.22)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	0.96 (0.79–1.15)	1.18 (0.73–1.90)
Stroke§	1.12 (0.79–1.58)	0.86 (0.71–1.06)	0.61 (0.38–0.99)	0.85 (0.70–1.03)	0.76 (0.61–0.95)	0.74 (0.35–1.57)
HF hospitalization§	0.96 (0.75–1.23)	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	0.93 (0.77–1.12)	0.86 (0.48–1.55)
Unstable angina hospitalization§	1.11 (0.47–2.62)	0.98 (0.76–1.26)	0.82 (0.47–1.44)	1.05 (0.94–1.18)	1.14 (0.84–1.54)	1.56 (0.60–4.01)
All-cause mortality§	0.94 (0.78–1.13)	0.85 (0.74–0.97)	1.05 (0.74–1.50)	0.86 (0.77–0.97)	0.90 (0.80–1.01)	0.51 (0.31–0.84)
Worsening nephropathy§	—	0.78 (0.67–0.92)	0.64 (0.46–0.88)	—	0.85 (0.77–0.93)	—

—, not assessed/reported; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; GLP-1, glucagon-like peptide 1; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction. Data from this table was adapted from Cefalu et al. (238) in the January 2018 issue of *Diabetes Care*. \*Powered to rule out a hazard ratio of 1.8; superiority hypothesis not prespecified. †Age was reported as means in all trials; diabetes duration was reported as means in all trials except EXSCEL, which reported medians. ‡Significant difference in A1C between groups ( $P < 0.05$ ). ††A1C change of 0.66% with 0.5 mg and 1.05% with 1 mg dose of semaglutide. §Outcomes reported as hazard ratio (95% CI). ||Worsening nephropathy is defined as the new onset of urine albumin-to-creatinine ratio  $>300$  mg/g creatinine or a doubling of the serum creatinine level and an estimated glomerular filtration rate of  $<45$  mL/min/1.73 m<sup>2</sup>, the need for continuous renal replacement therapy, or death from renal disease in LEADER and SUSTAIN-6 and as new macroalbuminuria, a sustained decline in estimated glomerular filtration rate of 30% or more from baseline, or chronic renal replacement therapy in REWIND. Worsening nephropathy was a prespecified exploratory adjudicated outcome in LEADER, SUSTAIN-6, and REWIND.

Table 10.3B—  
Cardiovascular and  
cardiorenal outcomes  
trials of available  
antihyperglycemic  
medications completed  
after the issuance  
of the FDA 2008  
guidelines: GLP-1 receptor  
agonists (2 of 2)

Cardiovascular  
Disease and Risk  
Management:  
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	EMPA-REG OUTCOME (8) (n = 7,020)	CANVAS Program (9) (n = 10,142)	DECLARE-TIMI 58 (196) (n = 17,360)	CREDENCE (194) (n = 4,401)	DAPA-CKD (197,239) (n = 4,304; 2,906 with diabetes)	VERTIS CV (201,240) (n = 8,246)	DAPA-HF (11) (n = 4,744; 1,968 with diabetes)	EMPEROR-Reduced (200) (n = 3,730; 1,856 with diabetes)	EMPEROR-Preserved (189,241) (n = 5,988; 2,938 with diabetes)	DELIVER (199) (n = 6,263; 2,807 with diabetes)
Intervention	Empagliflozin/placebo	Canagliflozin/placebo	Dapagliflozin/placebo	Canagliflozin/placebo	Dapagliflozin/placebo	Ertugliflozin/placebo	Dapagliflozin/placebo	Empagliflozin/placebo*	Empagliflozin/placebo	Dapagliflozin/placebo
Main inclusion criteria	Type 2 diabetes and preexisting CVD	Type 2 diabetes and preexisting CVD at ≥30 years of age or ≥2 CV risk factors at ≥50 years of age	Type 2 diabetes and established ASCVD or multiple risk factors for ASCVD	Type 2 diabetes and albuminuric kidney disease	Albuminuric kidney disease, with or without diabetes	Type 2 diabetes and ASCVD	NYHA class II, III, or IV heart failure and an ejection fraction ≤40%, with or without diabetes	NYHA class II, III, or IV heart failure and an ejection fraction ≤40%, with or without diabetes	NYHA class I, II, or III heart failure and an ejection fraction >40%	NYHA class I, II, or IV heart failure and an ejection fraction >40% with or without diabetes
A1C inclusion criteria (%)	7.0–10.0	7.0–10.5	≥6.5	6.5–12	—	7.0–10.5	—	—	—	—
Age (years)†	68.1	68.3	64.0	63	61.8	64.4	66	67.2, 66.5	71.8, 71.9	71.7
Race (% White)	72.4	78.3	79.6	66.6	53.2	87.8	70.3	71.1, 69.8	76.3, 75.4	71.2
Sex (% male)	71.5	64.2	62.6	66.1	66.9	70	76.6	76.5, 75.6	55.4, 55.3	56.1
Diabetes duration (years)†	57% >10	13.5	11.0	15.8	—	12.9	—	—	—	—
Median follow-up (years)	3.1	3.6	4.2	2.6	2.4	3.5	1.5	1.3	2.2	2.3
Statins use (%)	77	75	75 (statin or ezetimibe use)	69	64.9	—	—	—	68.1, 68.8	—
Metformin use (%)	74	77	82	57.8	29	—	51.2% (of people with diabetes)	—	—	—
Prior CVD/CHF (%)	99/10	66.6/34.4	40/10	50.4/14.8	37.4/10.9	99.9/23.1	100% with CHF	100% with CHF	100% with CHF	100% with CHF
Mean baseline A1C (%)	8.1	8.2	8.3	8.3	7.1% (7.8% in those with diabetes)	8.2	—	—	—	6.6
Mean difference in A1C between groups at end of treatment (%)	−0.3*	−0.58#	−0.43#	−0.31	—	−0.48 to −0.5	—	—	—	—
Year started/reported	2010/2015	2009/2017	2013/2018	2017/2019	2017/2020	2013/2020	2017/2019	2017/2020	2017/2020	2018/2022

Continued on p. S179

# Table 10.3C— Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: SGLT2 inhibitors

Cardiovascular  
Disease and Risk  
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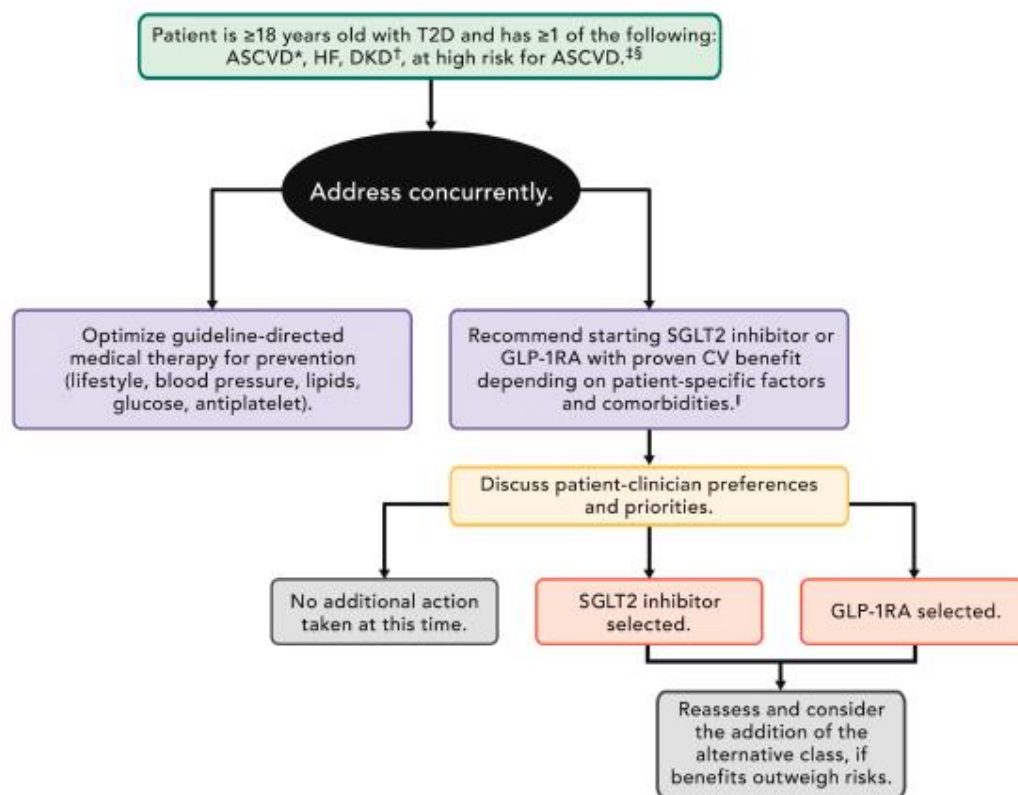
Table 10.3C—Continued

	EMPA-REG OUTCOME (8) (n = 7,020)	CANVAS Program (9) (n = 30,142)	DECLARE-TIMI 58 (196) (n = 17,360)	CREDENCE (194) (n = 4,401)	DAPA-CKD (197,239) (n = 4,304; 2,906 with diabetes)	VERTIS CV (201,340) (n = 8,246)	DAPA-HF (11) (n = 4,744; 1,983 with diabetes)	EMPEROR-Reduced (200) (n = 3,730; 1,856 with diabetes)	EMPEROR-Preserved (189,241) (n = 5,988; 2,938 with diabetes)	DELIVER (199) (n = 6,263; 2,807 with diabetes)
Primary outcome§	3-point MACE 0.86 (0.74–0.99)	3-point MACE 0.86 (0.75–0.97)	3-point MACE 0.98 (0.84–1.03) CV death or HF hospitalization 0.83 (0.73–0.95)	ESRD, doubling of creatinine, or death from renal or CV cause 0.70 (0.59–0.82)	≥50% decline in eGFR, ESRD, or death from renal or CV cause 0.61 (0.51–0.72)	3-point MACE 0.97 (0.85–1.11)	Worsening heart failure or death from CV causes 0.74 (0.65–0.85) Results did not differ by diabetes status	CV death or HF hospitalization 0.75 (0.65–0.86)	CV death or HF hospitalization 0.79 (0.69–0.90)	Worsening HF or CV death 0.82 (0.73–0.92)
Key secondary outcome§	4-point MACE 0.89 (0.78–1.01)	All-cause and CV mortality (see below)	Death from any cause 0.93 (0.82–1.04) Renal composite (≥40% decrease in eGFR rate to <60 mL/min/1.73 m <sup>2</sup> , now ESRD, or death from renal or CV causes 0.76 (0.67–0.87)	CV death or HF hospitalization 0.89 (0.77–0.83) 3-point MACE 0.80 (0.67–0.95)	≥50% decline in eGFR, ESRD, or death from renal cause 0.56 (0.45–0.68) CV death or HF hospitalization 0.71 (0.55–0.92) Death from any cause 0.89 (0.53–0.88)	CV death or HF hospitalization 0.88 (0.75–1.03) CV death 0.92 (0.77–1.11) Renal death, renal replacement therapy, or doubling of creatinine 0.81 (0.63–1.04)	CV death or HF hospitalization 0.75 (0.65–0.85)	Total HF hospitalizations 0.70 (0.58–0.85) Mean slope of change in eGFR 1.73 (1.10–2.37)	All HF hospitalizations (first and recurrent) 0.73 (0.61–0.88) Rate of decline in eGFR (–1.25 vs. –2.82 mL/min/1.73 m <sup>2</sup> ; P < 0.001)	Total number worsening HF and CV deaths 0.77 (0.67–0.89) Change in KCCQ TSS at month 8 1.11 (1.08–1.21) Mean change in KCCQ TSS 2.4 (1.5–3.4) All-cause mortality 0.94 (0.83–1.07)
Cardiovascular death§	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.82–1.17)	0.78 (0.61–1.00)	0.81 (0.58–1.12)	0.92 (0.77–1.11)	0.82 (0.69–0.98)	0.92 (0.75–1.12)	0.91 (0.76–1.09)	0.88 (0.74–1.05)
MI§	0.87 (0.70–1.09)	0.89 (0.73–1.09)	0.89 (0.77–1.01)	—	—	1.04 (0.86–1.26)	—	—	—	—
Stroke§	1.18 (0.89–1.56)	87 (0.69–1.09)	1.01 (0.84–1.21)	—	—	1.06 (0.82–1.37)	—	—	—	—
HF hospitalization§	0.65 (0.50–0.85)	67 (0.52–0.87)	0.73 (0.61–0.88)	0.61 (0.47–0.80)	—	0.70 (0.54–0.90)	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.73 (0.61–0.88)	0.77 (0.67–0.89)
Unstable angina hospitalization§	0.99 (0.74–1.34)	—	—	—	—	—	—	—	—	—
All-cause mortality§	0.68 (0.57–0.82)	87 (0.74–1.01)	0.93 (0.82–1.04)	0.83 (0.68–1.02)	0.69 (0.53–0.88)	0.93 (0.80–1.08)	0.83 (0.71–0.97)	0.92 (0.77–1.10)	1.00 (0.87–1.15)	0.94 (0.83–1.07)
Worsening nephropathy§	0.61 (0.53–0.70)	0.60 (0.47–0.77)	0.53 (0.43–0.66)	(See primary outcome)	(See primary outcome)	(See secondary outcomes)	0.71 (0.44–1.16)	Composite renal outcome 0.50 (0.32–0.77)	Composite renal outcome** 0.95 (0.73–1.24)	—

—, not assessed/reported; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; KCCQ TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; MACE, major adverse cardiovascular event; MI, myocardial infarction; SGLT2, sodium–glucose cotransporter 2; NYFA, New York Heart Association. Data from this table was adapted from Cefalu et al. (238) in the January 2018 issue of *Diabetes Care*. \*Baseline characteristics for EMPEROR-Reduced displayed as empagliflozin, placebo. †Age was reported as means in all trials; diabetes duration was reported as means in all trials except EMPA-REG OUTCOME, which reported as percentage of population with diabetes duration >10 years, and DECLARE-TIMI 58, which reported median. ‡Significant difference in A1C between groups (P < 0.05). ††A1C change of 0.30 in EMPA-REG OUTCOME is based on pooled results for both doses (i.e., 0.24% for 10 mg and 0.36% for 25 mg of empagliflozin). §Outcomes reported as hazard ratio (95% CI). ||Definitions of worsening nephropathy differed between trials. \*\*Composite outcome in EMPEROR-Preserved: time to first occurrence of chronic dialysis, renal transplantation; sustained reduction of ≥40% in eGFR, sustained eGFR <15 mL/min/1.73 m<sup>2</sup> for individuals with baseline eGFR ≥30 mL/min/1.73 m<sup>2</sup>.

# Table 10.3C— Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: SGLT2 inhibitors

Cardiovascular  
Disease and Risk  
Management:  
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**Figure 10.3—Approach to risk reduction with SGLT2 inhibitor or GLP-1 receptor agonist therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy**

Cardiovascular  
Disease and Risk  
Management:  
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