10. Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2023*

Diabetes Care 2023;46(Suppl. 1):S158–S190 | https://doi.org/10.2337/dc23-S010

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The American Diabetes Association (ADA) "Standards of Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee, are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations and a full list of Professional Practice Committee members, please refer to Introduction and Methodology. Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, "Children and Adolescents."

Atherosclerotic cardiovascular disease (ASCVD)—defined as coronary heart disease (CHD), cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin—is the leading cause of morbidity and mortality for individuals with diabetes and results in an estimated $37.3 billion in cardiovascular-related spending per year associated with diabetes (1). Common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for ASCVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing ASCVD in people with diabetes. Furthermore, large benefits are seen when multiple cardiovascular risk factors are addressed simultaneously. Under the current paradigm of aggressive risk factor modification in people with diabetes, there is evidence that measures of 10-year CHD risk among U.S. adults with diabetes have improved significantly over the past decade (2) and that ASCVD morbidity and mortality have decreased (3,4).

Heart failure is another major cause of morbidity and mortality from cardiovascular disease. Recent studies have found that rates of incident heart failure hospitalization (adjusted for age and sex) were twofold higher in people with diabetes compared with those without (5,6). People with diabetes may have heart failure with preserved ejection fraction (HFpEF) or with reduced ejection fraction (HFrEF). Hypertension is often a precursor of heart failure of either type, and ASCVD can coexist with either type (7), whereas prior myocardial infarction (MI) is often a major factor in HFrEF. Rates of heart failure hospitalization have been improved in recent trials including people with type 2 diabetes, most of whom also had ASCVD, with sodium–glucose cotransporter 2 (SGLT2) inhibitors (8–11).

A recent meta-analysis indicated that SGLT2 inhibitors reduce the risk of heart failure hospitalization, cardiovascular mortality, and all-cause mortality in people with (secondary prevention) and without (primary prevention) cardiovascular disease (12).

For prevention and management of both ASCVD and heart failure, cardiovascular risk factors should be systematically assessed at least annually in all people with diabetes. These risk factors include duration of diabetes, obesity/overweight, hypertension, dyslipidemia, smoking, a family history of premature coronary disease, chronic kidney disease (CKD), and the presence of albuminuria. Modifiable abnormal risk factors should be treated as described in these guidelines. Notably, the majority of evidence supporting interventions to reduce cardiovascular risk in diabetes comes from trials of people with type 2 diabetes. No randomized trials have been specifically designed to assess the impact of cardiovascular risk reduction strategies in people with type 1 diabetes. Therefore, the recommendations for cardiovascular risk factor modification for people with type 1 diabetes are extrapolated from data obtained in people with type 2 diabetes

and are similar to those for people with type 2 diabetes.

As depicted in **Fig. 10.1**, a comprehensive approach to the reduction in risk of diabetes-related complications is recommended. Therapy that includes multiple, concurrent evidence-based approaches to care will provide complementary reduction in the risks of microvascular, kidney, neurologic, and cardiovascular complications. Management of glycemia, blood pressure, and lipids and the incorporation of specific therapies with cardiovascular and kidney outcomes benefit (as individually appropriate) are considered fundamental elements of global risk reduction in diabetes.

THE RISK CALCULATOR

The American College of Cardiology/American Heart Association ASCVD risk calculator (Risk Estimator Plus) is generally a useful tool to estimate 10-year risk of a first ASCVD event (available online at tools.acc.org/ASCVD-Risk-Estimator-Plus). The calculator includes diabetes as a risk factor, since diabetes itself confers increased risk for ASCVD, although it should be acknowledged that these risk calculators do not account for the duration of diabetes or the presence of diabetes complications,

such as albuminuria. Although some variability in calibration exists in various subgroups, including by sex, race, and diabetes, the overall risk prediction does not differ in those with or without diabetes (13–16), validating the use of risk calculators in people with diabetes. The 10-year risk of a first ASCVD event should be assessed to better stratify ASCVD risk and help guide therapy, as described below.

Recently, risk scores and other cardiovascular biomarkers have been developed for risk stratification of secondary prevention patients (i.e., those who are already high risk because they have ASCVD) but are not yet in widespread use (17,18). With newer, more expensive lipid-lowering therapies now available, use of these risk assessments may help target these new therapies to "higher risk" ASCVD patients in the future.

HYPERTENSION/BLOOD PRESSURE CONTROL

Hypertension is defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥80 mmHg (19). This is in agreement with the definition of hypertension by the American College of Cardiology and American Heart Association (19). Hypertension is common among people with either type 1 or type 2 diabetes. Hypertension is a major risk factor for both ASCVD and microvascular complications. Moreover, numerous studies have shown that antihypertensive therapy reduces ASCVD events, heart failure, and microvascular complications. Please refer to the American Diabetes Association position statement "Diabetes and Hypertension" for a detailed review of the epidemiology, diagnosis, and treatment of hypertension (20) and recent updated hypertension guideline recommendations (19,21,22).

Screening and Diagnosis

Recommendations

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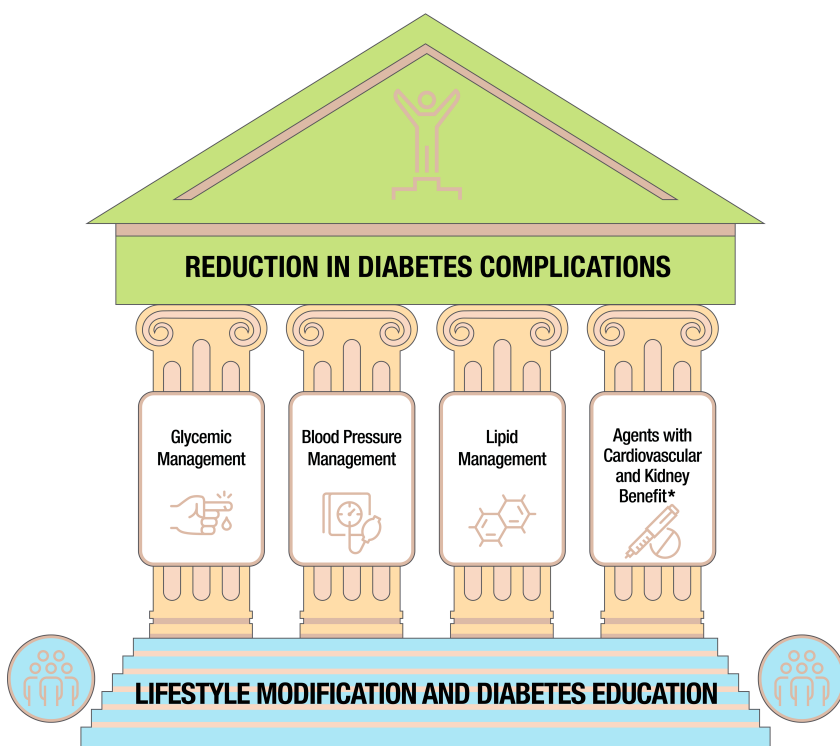
Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications. *Risk reduction interventions to be applied as individually appropriate.

The figure shows a temple/building graphic with:
- Roof: a figure with arms raised
- Top banner: **REDUCTION IN DIABETES COMPLICATIONS**
- Four pillars: Glycemic Management | Blood Pressure Management | Lipid Management | Agents with Cardiovascular and Kidney Benefit*
- Base: **LIFESTYLE MODIFICATION AND DIABETES EDUCATION**

on a separate day, to diagnose hypertension. **A** Hypertension is defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥80 mmHg based on an average of ≥2 measurements obtained on ≥2 occasions. **A** Individuals with blood pressure ≥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**

Blood pressure should be measured at every routine clinical visit by a trained individual and should follow the guidelines established for the general population: measurement in the seated position, with feet on the floor and arm supported at heart level, after 5 min of rest. Cuff size should be appropriate for the upper-arm circumference. Elevated values should preferably be confirmed on a separate day; however, in individuals with cardiovascular disease and blood pressure ≥180/110 mmHg, it is reasonable to diagnose hypertension at a single visit (21). Postural changes in blood pressure and pulse may be evidence of autonomic neuropathy and therefore require adjustment of blood pressure targets. Orthostatic blood pressure measurements should be checked on initial visit and as indicated.

Home blood pressure self-monitoring and 24-h ambulatory blood pressure monitoring may provide evidence of white coat hypertension, masked hypertension, or other discrepancies between office and "true" blood pressure (23,24). In addition to confirming or refuting a diagnosis of hypertension, home blood pressure assessment may be useful to monitor antihypertensive treatment. Studies of individuals without diabetes found that home measurements may better correlate with ASCVD risk than office measurements (23,24). Moreover, home blood pressure monitoring may improve patient medication taking and thus help reduce cardiovascular risk (25).

Treatment Goals

Recommendations

10.3 For people 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 ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. **B**

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 clinical trials have demonstrated unequivocally that treatment of hypertension reduces cardiovascular events as well as microvascular complications (26–32). There has been controversy on the recommendation of a specific blood pressure goal in people with diabetes. The committee recognizes that there has been no randomized controlled trial to specifically demonstrate a decreased incidence of cardiovascular events in people with diabetes by targeting a blood pressure <130/80 mmHg. The recommendation to support a blood pressure goal of <130/80 mmHg in people with diabetes is consistent with guidelines from the American College of Cardiology and American Heart Association (20), the International Society of Hypertension (21), and the European Society of Cardiology (22). The committee's recommendation for the blood pressure target of <130/80 mmHg derives primarily from the collective evidence of the following randomized controlled trials. The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that treatment to a target systolic blood pressure of <120 mmHg decreases cardiovascular event rates by 25% in high-risk patients, although people with diabetes were excluded from this trial (33). The recently completed Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial included nearly 20% of people with diabetes and noted decreased cardiovascular events with treatment of hypertension to a blood pressure target of <130 mmHg (34). While the ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial (ACCORD BP) did not confirm that targeting a systolic blood pressure of <120 mmHg in people with diabetes results in decreased cardiovascular event rates, the prespecified secondary outcome of stroke was reduced by 41% with intensive treatment (35). The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial revealed that treatment with perindopril/indapamide to an achieved systolic blood pressure of ~135 mmHg significantly decreased cardiovascular event rates compared with a placebo treatment with an achieved blood pressure of 140 mmHg (36). Therefore, it is recommended that people with diabetes who have hypertension should be treated to blood pressure targets of <130/80 mmHg. Notably, there is an absence of high-quality data available to guide blood pressure targets in people with type 1 diabetes, but a similar blood pressure target of <130/80 mmHg is recommended in people with type 1 diabetes. As discussed below, treatment should be individualized and treatment should not be targeted to <120/80 mmHg, as a mean achieved blood pressure of <120/80 mmHg is associated with adverse events.

Randomized Controlled Trials of Intensive Versus Standard Blood Pressure Control

SPRINT provides the strongest evidence to support lower blood pressure goals in patients at increased cardiovascular risk, although this trial excluded people with diabetes (33). The trial enrolled 9,361 patients with a systolic blood pressure of

≥130 mmHg and increased cardiovascular risk and treated to a systolic blood pressure target of <120 mmHg (intensive treatment) versus a target of <140 mmHg (standard treatment). The primary composite outcome of myocardial infarction (MI), coronary syndromes, stroke, heart failure, or death from cardiovascular causes was reduced by 25% in the intensive treatment group. The achieved systolic blood pressures in the trial were 121 mmHg and 136 mmHg in the intensive versus standard treatment group, respectively. Adverse outcomes, including hypotension, syncope, electrolyte abnormality, and acute kidney injury were more common in the intensive treatment arm; risk of adverse outcomes needs to be weighed against the cardiovascular benefit of more intensive blood pressure lowering.

ACCORD BP provides the strongest direct assessment of the benefits and risks of intensive blood pressure control in people with type 2 diabetes (35). In the study, a total of 4,733 with type 2 diabetes were assigned to intensive therapy (targeting a systolic blood pressure <120 mmHg) or standard therapy (targeting a systolic blood pressure <140 mmHg). The mean achieved systolic blood pressures were 119 mmHg and 133 mmHg in the intensive versus standard group, respectively. The primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes was not significantly reduced in the intensive treatment group. The prespecified secondary outcome of stroke was significantly reduced by 41% in the intensive treatment group. Adverse events attributed to blood pressure treatment, including hypotension, syncope, bradycardia, hyperkalemia, and elevations in serum creatinine occurred more frequently in the intensive treatment arm than in the standard therapy arm (**Table 10.1**).

Of note, the ACCORD BP and SPRINT trials targeted a similar systolic blood pressure <120 mmHg, but in contrast to SPRINT, the primary composite cardiovascular end point was nonsignificantly reduced in ACCORD BP. The results have been interpreted to be generally consistent between both trials, but ACCORD BP was viewed as underpowered due to the composite primary end point being less sensitive to blood pressure regulation (33).

The more recent STEP trial assigned 8,511 patients aged 60–80 years with

hypertension to a systolic blood pressure target of 110 to <130 mmHg (intensive treatment) or a target of 130 to <150 mmHg (34). In this trial, the primary composite outcome of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes was reduced by 26% in the intensive treatment group. In this trial, 18.9% of patients in the intensive treatment arm and 19.4% in the standard treatment arm had a diagnosis of type 2 diabetes. Hypotension occurred more frequently in the intensive treatment group (3.4%) compared with the standard treatment group (2.6%), without significant differences in other adverse events, including dizziness, syncope, or fractures.

In ADVANCE, 11,140 people with type 2 diabetes were randomized to receive either treatment with fixed combination perindopril/indapamide or matching placebo (36). The primary end point, a composite of cardiovascular death, nonfatal stroke infarction, or worsening renal or diabetic eye disease, was reduced by 9% in the combination treatment. The achieved systolic blood pressure was ~135 mmHg in the treatment group and 140 mmHg in the placebo group.

The Hypertension Optimal Treatment (HOT) trial enrolled 18,790 patients and targeted diastolic blood pressure <90 mmHg, <85 mmHg, or <80 mmHg (37). The cardiovascular event rates, defined as fatal or nonfatal MI, fatal and nonfatal strokes, and all other cardiovascular events, were not significantly different between diastolic blood pressure targets (≤90 mmHg, ≤85 mmHg, and ≤80 mmHg), although the lowest incidence of cardiovascular events occurred with an achieved diastolic blood pressure of 82 mmHg. However, in people with diabetes, there was a significant 51% reduction in the treatment group with a target diastolic blood pressure of <80 mmHg compared with a target diastolic blood pressure of <90 mmHg.

Meta-analyses of Trials
To clarify optimal blood pressure targets in people with diabetes, multiple meta-analyses have been performed. One of the largest meta-analyses included 73,913 people with diabetes. Compared with a less tight blood pressure control, allocation to a tighter blood pressure control

significantly reduced the risk of stroke by 31% but did not reduce the risk of MI (38). Another meta-analysis of 19 trials including 44,989 patients showed that a mean blood pressure of 133/76 mmHg is associated with a 14% risk reduction for major cardiovascular events compared with a mean blood pressure of 140/81 mmHg (32). This benefit was greatest in people with diabetes. An analysis of trials including people with type 2 diabetes and impaired glucose tolerance with achieved systolic blood pressures of <135 mmHg in the intensive blood pressure treatment group and <140 mmHg in the standard treatment group revealed a 10% reduction in all-cause mortality and a 17% reduction in stroke (30). More intensive reduction to <130 mmHg was associated with a further reduction in stroke but not other cardiovascular events.

Several meta-analyses stratified clinical trials by mean baseline blood pressure or mean blood pressure attained in the intervention (or intensive treatment) arm. Based on these analyses, antihypertensive treatment appears to be most beneficial when mean baseline blood pressure is ≥140/90 mmHg (19,26,27,29–31). Among trials with lower baseline or attained blood pressure, antihypertensive treatment reduced the risk of stroke, retinopathy, and albuminuria, but effects on other ASCVD outcomes and heart failure were not evident.

Individualization of Treatment Targets
Patients and clinicians should engage in a shared decision-making process to determine individual blood pressure targets (19). This approach acknowledges that the benefits and risks of intensive blood pressure targets are uncertain and may vary across patients and is consistent with a patient-focused approach to care that values patient priorities and health care professional judgment (39). Secondary analyses of ACCORD BP and SPRINT suggest that clinical factors can help determine individuals more likely to benefit and less likely to be harmed by intensive blood pressure control (40,41).

Absolute benefit from blood pressure reduction correlated with absolute baseline cardiovascular risk in SPRINT and in earlier clinical trials conducted at higher baseline blood pressure levels (13,41). Extrapolation of these studies suggests that people with diabetes may also be more likely to benefit from intensive blood

Table 10.1—Randomized controlled trials of intensive versus standard hypertension treatment strategies

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	• No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death • Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment • Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities
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	• 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%) • 6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (242)
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	• In the overall trial, there was no cardiovascular benefit with more intensive targets • In the subpopulation with diabetes, an intensive DBP target was associated with a significantly reduced risk (51%) of CVD events
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	• Intensive SBP target lowered risk of the primary composite outcome 25% (MI, ACS, stroke, heart failure, and death due to CVD) • Intensive target reduced risk of death 27% • Intensive therapy increased risks of electrolyte abnormalities and AKI
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	• 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) • Intensive target reduced risk of cardiovascular death 28% • Intensive therapy increased risks of hypotension

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.

pressure control when they have high absolute cardiovascular risk. This approach is consistent with guidelines from the American College of Cardiology and American Heart Association, which also advocate a blood pressure target of <130/80 mmHg for all people, with or without diabetes (20).

Potential adverse effects of antihypertensive therapy (e.g., hypotension, syncope, falls, acute kidney injury, and electrolyte abnormalities) should also be taken into account (33,35,42,43). Individuals with older age, CKD, and frailty have been shown to be at higher risk of adverse effects of intensive blood

pressure control (43). In addition, individuals with orthostatic hypotension, substantial comorbidity, functional limitations, or polypharmacy may be at high risk of adverse effects, and some patients may prefer higher blood pressure targets to enhance quality of life. However, in ACCORD BP, it was found that intensive

blood pressure lowering decreased the risk of cardiovascular events irrespective of baseline diastolic blood pressure in patients who also received standard glycemic control (44). Therefore, the presence of low diastolic blood pressure is not necessarily a contraindication to more intensive blood pressure management in the context of otherwise standard care.

Pregnancy and Antihypertensive Medications

There are few randomized controlled trials of antihypertensive therapy in pregnant individuals with diabetes. A 2014 Cochrane systematic review of antihypertensive therapy for mild to moderate chronic hypertension that included 49 trials and over 4,700 women did not find any conclusive evidence for or against blood pressure treatment to reduce the risk of preeclampsia for the mother or effects on perinatal outcomes such as preterm birth, small-for-gestational-age infants, or fetal death (45). The Control of Hypertension in Pregnancy Study (CHIPS) (46) enrolled mostly women with chronic hypertension. In CHIPS, targeting a diastolic blood pressure of 85 mmHg during pregnancy was associated with reduced likelihood of developing accelerated maternal hypertension and no demonstrable adverse outcome for infants compared with targeting a higher diastolic blood pressure. The mean systolic blood pressure achieved in the more intensively treated group was 133.1 ± 0.5 mmHg, and the mean diastolic blood pressure achieved in that group was 85.3 ± 0.3 mmHg. A similar approach is supported by the International Society for the Study of Hypertension in Pregnancy, which specifically recommends use of antihypertensive therapy to maintain systolic blood pressure between 110 and 140 mmHg and diastolic blood pressure between 80 and 85 mmHg (47).

The more recent Chronic Hypertension and Pregnancy (CHAP) trial assigned pregnant individuals with mild chronic hypertension to antihypertensive medications to target a blood pressure goal of <140/90 mmHg (active treatment group) or to control treatment, in which antihypertensive therapy was withheld unless severe hypertension (systolic pressure ≥160 mmHg or diastolic pressure ≥105 mmHg) developed (control group) (48). The primary outcome, a composite of preeclampsia with severe features,

medically indicated preterm birth at <35 weeks of gestation, placental abruption, or fetal/neonatal death, occurred in 30.2% of female participants in the active treatment group vs. 37.0% in the control group (P < 0.001). The mean systolic blood pressure between randomization and delivery was 129.5 mmHg in the active treatment group and 132.6 mmHg in the control group.

Current evidence supports controlling blood pressure to 110–135/85 mmHg to reduce the risk of accelerated maternal hypertension but also to minimize impairment of fetal growth. During pregnancy, treatment with ACE inhibitors, angiotensin receptor blockers (ARBs), and spironolactone are contraindicated as they may cause fetal damage. Special consideration should be taken for individuals of childbearing potential, and people intending to become pregnant should switch from an ACE inhibitor/ARB or spironolactone to an alternative antihypertensive medication approved during pregnancy. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, and long-acting nifedipine, while hydralzine may be considered in the acute management of hypertension in pregnancy or severe preeclampsia (49). Diuretics are not recommended for blood pressure control in pregnancy but may be used during late-stage pregnancy if needed for volume control (49,50). The American College of Obstetricians and Gynecologists also recommends that postpartum individuals with gestational hypertension, preeclampsia, and superimposed preeclampsia have their blood pressures observed for 72 h in the hospital and for 7–10 days postpartum. Long-term follow-up is recommended for these individuals as they have increased lifetime cardiovascular risk (51). See Section 15, "Management of Diabetes in Pregnancy," for additional information.

Treatment Strategies

Lifestyle Intervention

> **Recommendation**
>
> **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**

Lifestyle management is an important component of hypertension treatment because it lowers blood pressure, enhances the effectiveness of some antihypertensive medications, promotes other aspects of metabolic and vascular health, and generally leads to few adverse effects. Lifestyle therapy consists of reducing excess body weight through caloric restriction (see Section 8, "Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes"), at least 150 min of moderate-intensity aerobic activity per week (see Section 3, "Prevention or Delay of Type 2 Diabetes and Associated Comorbidities"), restricting sodium intake (<2,300 mg/day), increasing consumption of fruits and vegetables (8–10 servings per day) and low-fat dairy products (2–3 servings per day), avoiding excessive alcohol consumption (no more than 2 servings per day in men and no more than 1 serving per day in women) (52), and increasing activity levels (53) (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes").

These lifestyle interventions are reasonable for individuals with diabetes and mildly elevated blood pressure (systolic >120 mmHg or diastolic >80 mmHg) and should be initiated along with pharmacologic therapy when hypertension is diagnosed (**Fig. 10.2**) (53). A lifestyle therapy plan should be developed in collaboration with the patient and discussed as part of diabetes management. Use of internet or mobile-based digital platforms to reinforce healthy behaviors may be considered as a component of care, as these interventions have been found to enhance the efficacy of medical therapy for hypertension (54,55).

Pharmacologic Interventions

> **Recommendations**
>
> **10.7** Individuals with confirmed office-based blood pressure ≥130/80 mmHg qualify for initiation and titration of pharmacologic therapy to achieve

Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes

REASSESS REGULARLY (3-6 MONTHS)

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┌─────────────────────────┐         ┌─────────────────────────┐
│ Initial BP ≥130/80 and  │         │ Initial BP ≥160/100 mmHg│
│     <160/100 mmHg       │         │                         │
└─────────────────────────┘         └─────────────────────────┘

  Start one agent    Lifestyle management     Start two agents

┌──────────────────┐                ┌──────────────────┐
│ Albuminuria or   │                │ Albuminuria or   │
│     CAD*         │                │     CAD*         │
└──────────────────┘                └──────────────────┘
   No        Yes                       No         Yes
```

Start one drug:
- ACEi or ARB
- CCB***
- Diuretic**

Start
- ACEi or ARB

Start drug from 2 of 3 options:
- ACEi or ARB
- CCB***
- Diuretic**

Start:
- ACEi or ARB and
- CCB*** or Diuretic**

Assess BP Control and Adverse Effects

Treatment tolerated and target achieved   Not meeting target   Adverse effects

Continue therapy

Add agent from complementary drug class:
- ACEi or ARB
- CCB***
- Diuretic**

Consider change to alternative medication:
- ACEi or ARB
- CCB***
- Diuretic**

Not meeting target on two agents   Adverse effects

Assess BP Control and Adverse Effects

Treatment tolerated and target achieved

Not meeting target or adverse effects using a drug from each of three classes

Continue therapy

Consider Addition of Mineralocorticoid Receptor Antagonist; Refer to Specialist With Expertise in BP Management
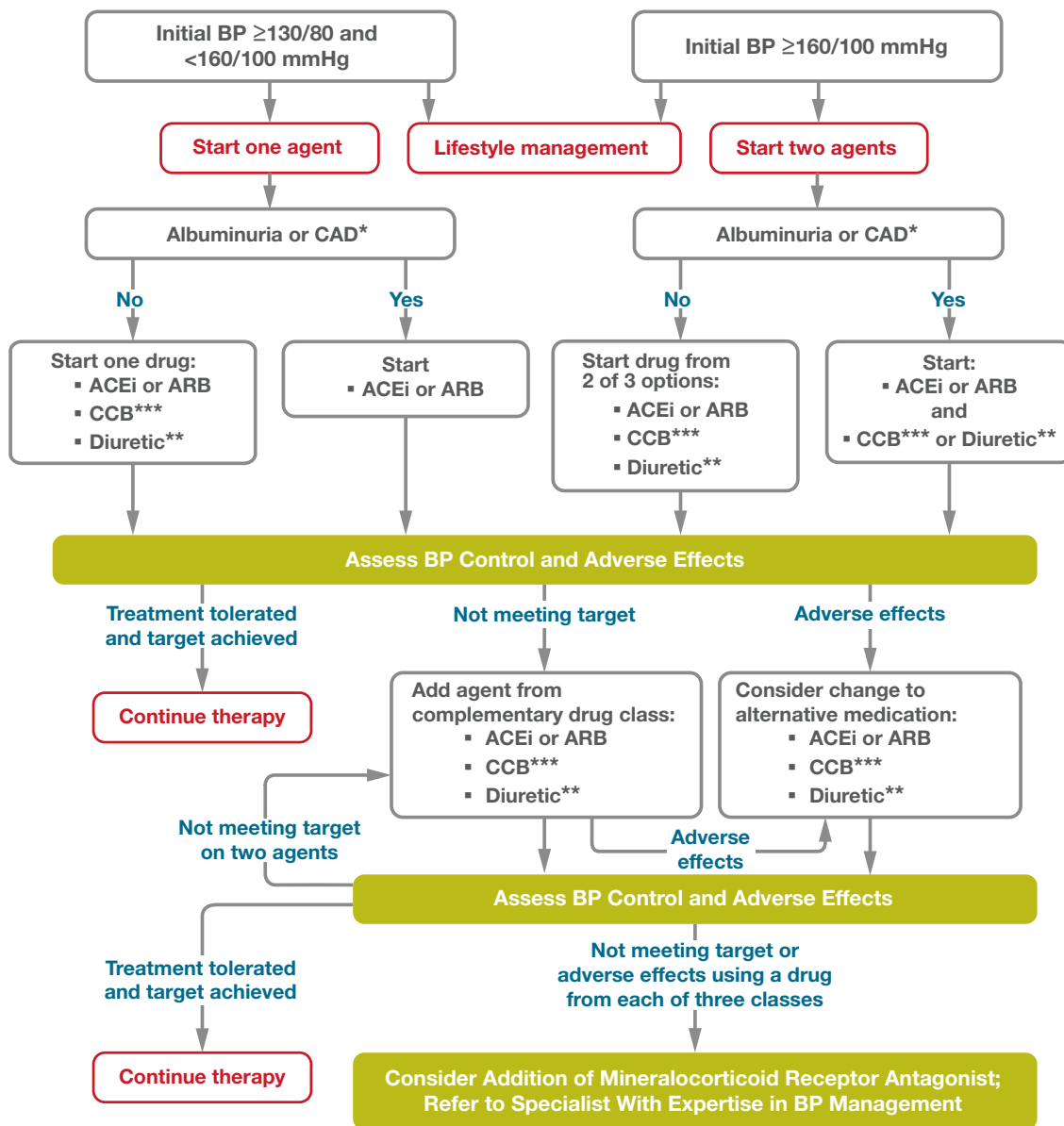
Figure 10.2—Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested to treat hypertension for people with coronary artery disease (CAD) or urine albumin-to-creatinine ratio 30–299 mg/g creatinine and strongly recommended for individuals with urine albumin-to-creatinine ratio ≥300 mg/g creatinine. **Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. ***Dihydropyridine calcium channel blocker (CCB). BP, blood pressure. Adapted from de Boer et al. (20).

the recommended blood pressure goal of <130/80 mmHg. **A**

10.8 Individuals with confirmed office-based blood pressure ≥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**

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**

10.11 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 ≥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**

Initial Number of Antihypertensive Medications. Initial treatment for people with diabetes depends on the severity of hypertension (**Fig. 10.2**). Those with blood pressure between 130/80 mmHg and 160/100 mmHg may begin with a single drug. For patients with blood pressure ≥160/100 mmHg, initial pharmacologic treatment with two antihypertensive medications is recommended in order to more effectively achieve adequate blood pressure control (56–58). Single-pill antihypertensive combinations may improve medication taking in some patients (59).

Classes of Antihypertensive Medications. Initial treatment for hypertension should include any of the drug classes demonstrated to reduce cardiovascular events in people with diabetes: ACE inhibitors (60,61), ARBs (60,61), thiazide-like diuretics (62), or dihydropyridine calcium channel blockers (63). In people with diabetes and established coronary artery disease, ACE inhibitors or ARBs are recommended first-line therapy for hypertension (64–66). For patients with albuminuria (urine albumin-to-creatinine ratio [UACR] ≥30 mg/g), initial treatment should include an ACE inhibitor or ARB to

reduce the risk of progressive kidney disease (20) (**Fig. 10.2**). In patients receiving ACE inhibitor or ARB therapy, continuation of those medications as kidney function declines to estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 may provide cardiovascular benefit without significantly increasing the risk of end-stage kidney disease (67). In the absence of albuminuria, risk of progressive kidney disease is low, and ACE inhibitors and ARBs have not been found to afford superior cardioprotection when compared with thiazide-like diuretics or dihydropyridine calcium channel blockers (68). β-Blockers are indicated in the setting of prior MI, active angina, or HfrEF but have not been shown to reduce mortality as blood pressure-lowering agents in the absence of these conditions (28,69,70).

Multiple-Drug Therapy. Multiple-drug therapy is often required to achieve blood pressure targets (**Fig. 10.2**), particularly in the setting of diabetic kidney disease. However, the use of both ACE inhibitors and ARBs in combination, or the combination of an ACE inhibitor or ARB and a direct renin inhibitor, is contraindicated given the lack of added ASCVD benefit and increased rate of adverse events—namely, hyperkalemia, syncope, and acute kidney injury (AKI) (71–73). Titration of and/or addition of further blood pressure medications should be made in a timely fashion to overcome therapeutic inertia in achieving blood pressure targets.

Bedtime Dosing. Although prior analyses of randomized clinical trials found a benefit to evening versus morning dosing of antihypertensive medications (74,75), these results have not been reproduced in subsequent trials. Therefore, preferential use of antihypertensives at bedtime is not recommended (76).

Hyperkalemia and Acute Kidney Injury. Treatment with ACE inhibitors or ARBs can cause AKI and hyperkalemia, while diuretics can cause AKI and either hypokalemia or hyperkalemia (depending on mechanism of action) (77,78). Detection and management of these abnormalities is important because AKI and hyperkalemia each increase the risks of cardiovascular events and death (79). Therefore, serum creatinine and potassium should be monitored during treatment with an ACE inhibitor, ARB, or diuretic, particularly

among patients with reduced glomerular filtration who are at increased risk of hyperkalemia and AKI (77,78,80).

Resistant Hypertension

> **Recommendation**
>
> 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**

Resistant hypertension is defined as blood pressure ≥140/90 mmHg despite a therapeutic strategy that includes appropriate lifestyle management plus a diuretic and two other antihypertensive drugs with complementary mechanisms of action at adequate doses. Prior to diagnosing resistant hypertension, a number of other conditions should be excluded, including missed doses of antihypertensive medications, white coat hypertension, and secondary hypertension. In general, barriers to medication taking (such as cost and side effects) should be identified and addressed (**Fig. 10.2**). Mineralocorticoid receptor antagonists, including spironolactone and eplerenone, are effective for management of resistant hypertension in people with type 2 diabetes when added to existing treatment with an ACE inhibitor or ARB, thiazide-like diuretic, or dihydropyridine calcium channel blocker (81). In addition, mineralocorticoid receptor antagonists reduce albuminuria in people with diabetic nephropathy (82–84). However, adding a mineralocorticoid receptor antagonist to a regimen including an ACE inhibitor or ARB may increase the risk for hyperkalemia, emphasizing the importance of regular monitoring for serum creatinine and potassium in these patients, and long-term outcome studies are needed to better evaluate the role of mineralocorticoid receptor antagonists in blood pressure management.

LIPID MANAGEMENT
Lifestyle Intervention

> **Recommendations**
>
> 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 (≥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**

Lifestyle intervention, including weight loss in people with overweight or obesity (when appropriate) (85), increased physical activity, and medical nutrition therapy, allows some patients to reduce ASCVD risk factors. Nutrition intervention should be tailored according to each patient's age, pharmacologic treatment, lipid levels, and medical conditions.

Recommendations should focus on application of a Mediterranean (83) or Dietary Approaches to Stop Hypertension (DASH) eating pattern, reducing saturated and *trans* fat intake and increasing plant stanols/sterols, n-3 fatty acids, and viscous fiber (such as in oats, legumes, and citrus) intake (86,87). Glycemic control may also beneficially modify plasma lipid levels, particularly in patients with very high triglycerides and poor glycemic control. See Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes," for additional nutrition information.

Ongoing Therapy and Monitoring With Lipid Panel

Recommendations

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 40 years, or more frequently if indicated. **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**

In adults with diabetes, it is reasonable to obtain a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) at the time of diagnosis, at the initial medical evaluation, and at least every 5 years thereafter in patients <40 years of age. In younger people with longer duration of disease (such as those with youth-onset type 1 diabetes), more frequent lipid profiles may be reasonable. A lipid panel should also be obtained immediately before initiating statin therapy. Once a patient is taking a statin, LDL cholesterol levels should be assessed 4–12 weeks after initiation of statin therapy, after any change in dose, and on an individual basis (e.g., to monitor for medication taking and efficacy). If LDL cholesterol levels are not responding in spite of medication taking, clinical judgment is recommended to determine the need for and timing of lipid panels. In individual patients, the highly variable LDL cholesterol–lowering response seen with statins is poorly understood (88). Clinicians should attempt to find a dose or alternative statin that is tolerable if side effects occur. There is evidence for benefit from even extremely low, less than daily statin doses (89).

STATIN TREATMENT
Primary Prevention

Recommendations

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 ≥50% of baseline and to target an LDL cholesterol goal of <70 mg/dL. **B**

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 ≥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. **B**

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. **C**

10.24 Statin therapy is contraindicated in pregnancy. **B**

Secondary Prevention

Recommendations

10.25 For people of all ages with diabetes and atherosclerotic cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy. **A**

10.26 For people with diabetes and atherosclerotic cardiovascular disease, treatment with high-intensity statin therapy is recommended to target an LDL cholesterol reduction of ≥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 ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)
Atorvastatin 40–80 mg Rosuvastatin 20–40 mg	Atorvastatin 10–20 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.

Initiating Statin Therapy Based on Risk

People with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of ASCVD. Multiple clinical trials have demonstrated the beneficial effects of statin therapy on ASCVD outcomes in subjects with and without CHD (90,91). Subgroup analyses of people with diabetes in larger trials (92–96) and trials in people with diabetes (97,98) showed significant primary and secondary prevention of ASCVD events and CHD death in people with diabetes. Meta-analyses, including data from over 18,000 people with diabetes from 14 randomized trials of statin therapy (mean follow-up 4.3 years), demonstrate a 9% proportional reduction in all-cause mortality and 13% reduction in vascular mortality for each 1 mmol/L (39 mg/dL) reduction in LDL cholesterol (99). The cardiovascular benefit in this large meta-analysis did not depend on baseline LDL cholesterol levels and was linearly related to the LDL cholesterol reduction without a low threshold beyond which there was no benefit observed (99).

Accordingly, statins are the drugs of choice for LDL cholesterol lowering and cardioprotection. **Table 10.2** shows the two statin dosing intensities that are recommended for use in clinical practice: high-intensity statin therapy will achieve approximately a ≥50% reduction in LDL cholesterol, and moderate-intensity statin regimens achieve 30–49% reductions in LDL cholesterol. Low-dose statin therapy is generally not recommended in people with diabetes but is sometimes the only dose of statin that a patient can tolerate. For patients who do not tolerate the intended intensity of statin, the maximum tolerated statin dose should be used.

As in those without diabetes, absolute reductions in ASCVD outcomes (CHD death and nonfatal MI) are greatest in people with high baseline ASCVD risk (known ASCVD and/or very high LDL cholesterol levels), but the overall benefits of statin therapy in people with diabetes at moderate or even low risk for ASCVD are convincing (100,101). The relative benefit of lipid-lowering therapy has been uniform across most subgroups tested (91,99), including subgroups that varied with respect to age and other risk factors.

Primary Prevention (People Without ASCVD)

For primary prevention, moderate-dose statin therapy is recommended for those aged ≥40 years (93,100,101), although high-intensity therapy should be considered in the context of additional ASCVD risk factors. The evidence is strong for people with diabetes aged 40–75 years, an age-group well represented in statin trials showing benefit. Since cardiovascular risk is enhanced in people with diabetes, as noted above, patients who also have multiple other coronary risk factors have increased risk, equivalent to that of those with ASCVD. Therefore, current guidelines recommend that in people with diabetes who are at higher cardiovascular risk, especially those with one or more ASCVD risk factors, high-intensity statin therapy should be prescribed to reduce LDL cholesterol by ≥50% from baseline and to target an LDL cholesterol of <70 mg/dL (102–104). Since in clinical practice it is frequently difficult to ascertain the baseline LDL cholesterol level prior to statin therapy initiation, in those individuals, a focus on an LDL cholesterol target level of <70 mg/dL rather than the percent reduction in LDL cholesterol is recommended. In those individuals, it may also be reasonable to add ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy to maximum tolerated statin therapy if needed to reduce LDL cholesterol levels by ≥50% and to achieve the recommended LDL cholesterol target of <70 mg/dL (14).

The evidence is lower for patients aged >75 years; relatively few older people with diabetes have been enrolled in primary prevention trials. However, heterogeneity by age has not been seen in the relative benefit of lipid-lowering therapy in trials that included older participants (91,98,99), and because older age confers higher risk, the absolute benefits are actually greater (91,105). Moderate-intensity statin therapy is recommended in people with diabetes who are ≥75 years of age. However, the risk-benefit profile should be routinely evaluated in this population, with downward titration of dose performed as needed. See Section 13, "Older Adults," for more details on clinical considerations for this population.

Age <40 Years and/or Type 1 Diabetes. Very little clinical trial evidence exists for people with type 2 diabetes under the age of 40 years or for people with type 1 diabetes of any age. For pediatric recommendations, see Section 14, "Children and Adolescents." In the Heart Protection Study (lower age limit 40 years), the subgroup of ~600 people with type 1 diabetes had a proportionately similar, although not statistically significant, reduction in risk to that in people with type 2 diabetes (93). Even though the data are not definitive, similar statin treatment approaches should be considered for people with type 1 or type 2 diabetes, particularly in the presence of other cardiovascular risk factors. Patients <40 years of age have lower risk of developing a cardiovascular event over a 10-year horizon; however, their lifetime risk of developing cardiovascular disease and suffering an MI, stroke, or cardiovascular death is high. For people who are <40 years of age and/or have type 1 diabetes with other ASCVD risk factors, it is recommended that the patient and health care professional discuss the relative benefits and risks and consider the use of moderate-intensity statin therapy. Please refer to "Type 1 Diabetes Mellitus and Cardiovascular Disease: A Scientific Statement From the American Heart Association and American Diabetes Association" (106) for additional discussion.

Secondary Prevention (People With ASCVD)

Because cardiovascular event rates are increased in people with diabetes and

established ASCVD, intensive therapy is indicated and has been shown to be of benefit in multiple large meta-analyses and randomized cardiovascular outcomes trials (91,99,105,107,108). High-intensity statin therapy is recommended for all people with diabetes and ASCVD to target an LDL cholesterol reduction of ≥50% from baseline and an LDL cholesterol goal of <55 mg/dL. Based on the evidence discussed below, addition of ezetimibe or a PCSK9 inhibitor is recommended if this goal is not achieved on maximum tolerated statin therapy. These recommendations are based on the observation that high-intensity versus moderate-intensity statin therapy reduces cardiovascular event rates in high-risk individuals with established cardiovascular disease in randomized trials (95,107). In addition, the Cholesterol Treatment Trialists' Collaboration involving 26 statin trials, of which 5 compared high-intensity versus moderate-intensity statins (99), showed a 21% reduction in major cardiovascular events in people with diabetes for every 39 mg/dL of LDL cholesterol lowering, irrespective of baseline LDL cholesterol or patient characteristics (99). However, the best evidence to support lower LDL cholesterol targets in people with diabetes and established cardiovascular disease derives from multiple large randomized trials investigating the benefits of adding nonstatin agents to statin therapy. As discussed in detail below, these include combination treatment with statins and ezetimibe (105,109) or PCSK9 inhibitors (108,110–112). Each trial found a significant benefit in the reduction of ASCVD events that was directly related to the degree of further LDL cholesterol lowering. These large trials included a significant number of participants with diabetes and prespecified analyses on cardiovascular outcomes in people with and without diabetes (109,111,112). The decision to add a nonstatin agent should be made following a clinician-patient discussion about the net benefit, safety, and cost of combination therapy.

Combination Therapy for LDL Cholesterol Lowering

Statins and Ezetimibe

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a randomized controlled trial in 18,144 patients comparing the addition of ezetimibe to simvastatin therapy versus simvastatin alone (105). Individuals were ≥50 years of age, had experienced a recent acute coronary syndrome (ACS) and were treated for an average of 6 years. Overall, the addition of ezetimibe led to a 6.4% relative benefit and a 2% absolute reduction in major adverse cardiovascular events (atherosclerotic cardiovascular events), with the degree of benefit being directly proportional to the change in LDL cholesterol, which was 70 mg/dL in the statin group on average and 54 mg/dL in the combination group (105). In those with diabetes (27% of participants), the combination of moderate-intensity simvastatin (40 mg) and ezetimibe (10 mg) showed a significant reduction of major adverse cardiovascular events with an absolute risk reduction of 5% (40% vs. 45% cumulative incidence at 7 years) and a relative risk reduction of 14% (hazard ratio [HR] 0.86 [95% CI 0.78–0.94]) over moderate-intensity simvastatin (40 mg) alone (109).

Statins and PCSK9 Inhibitors

Placebo-controlled trials evaluating the addition of the PCSK9 inhibitors evolocumab and alirocumab to maximum tolerated doses of statin therapy in participants who were at high risk for ASCVD demonstrated an average reduction in LDL cholesterol ranging from 36 to 59%. These agents have been approved as adjunctive therapy for individuals with ASCVD or familial hypercholesterolemia who are receiving maximum tolerated statin therapy but require additional lowering of LDL cholesterol (113,114). No cardiovascular outcome trials have been performed to assess whether PCSK9 inhibitor therapy reduces ASCVD event rates in individuals without established cardiovascular disease (primary prevention).

The effects of PCSK9 inhibition on ASCVD outcomes was investigated in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, which enrolled 27,564 individuals with prior ASCVD and an additional high-risk feature who were receiving their maximum tolerated statin therapy (two-thirds were on high-intensity statin) but who still had LDL cholesterol ≥70 mg/dL or non-HDL cholesterol ≥100 mg/dL (108). Patients were randomized to receive subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg every month based on patient preference) versus placebo. Evolocumab reduced LDL cholesterol by 59% from a median of 92 to 30 mg/dL in the treatment arm.

During the median follow-up of 2.2 years, the composite outcome of cardiovascular death, MI, stroke, hospitalization for angina, or revascularization occurred in 11.3% vs. 9.8% of the placebo and evolocumab groups, respectively, representing a 15% relative risk reduction (*P* < 0.001). The combined end point of cardiovascular death, MI, or stroke was reduced by 20%, from 7.4 to 5.9% (*P* < 0.001). Evolocumab therapy also significantly reduced all strokes (1.5% vs. 1.9%; HR 0.79 [95% CI 0.66–0.95]; *P* = 0.01) and ischemic stroke (1.2% vs. 1.6%; HR 0.75 [95% CI 0.62–0.92]; *P* = 0.005) in the total population, with findings being consistent in individuals with or without a history of ischemic stroke at baseline (115). Importantly, similar benefits were seen in a prespecified subgroup of people with diabetes, comprising 11,031 patients (40% of the trial) (112).

In the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), 18,924 patients (28.8% of whom had diabetes) with recent acute coronary syndrome were randomized to the PCSK9 inhibitor alirocumab or placebo every 2 weeks in addition to maximum tolerated statin therapy, with alirocumab dosing titrated between 75 and 150 mg to achieve LDL cholesterol levels between 25 and 50 mg/dL (110). Over a median follow-up of 2.8 years, a composite primary end point (comprising death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospital admission) occurred in 903 patients (9.5%) in the alirocumab group and in 1,052 patients (11.1%) in the placebo group (HR 0.85 [95% CI 0.78–0.93]; *P* < 0.001). Combination therapy with alirocumab plus statin therapy resulted in a greater absolute reduction in the incidence of the primary end point in people with diabetes (2.3% [95% CI 0.4–4.2]) than in those with prediabetes (1.2% [0.0–2.4]) or normoglycemia (1.2% [–0.3 to 2.7]) (111).

In addition to monoclonal antibodies targeting PCSK9, the siRNA inclisiran has been developed and has recently become available in the U.S. In the Inclisiran for

Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol (ORION-10) and Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol (ORION-11) trials (116), individuals with established cardiovascular disease or ASCVD risk equivalent were randomized to receive inclisiran or placebo. Inclisiran allows less frequent administration compared with monoclonal antibodies and was administered on day 1, on day 90, and every 6 months in these trials. In the ORION-10 trial, 47.5% of patients in the inclisiran group and 42.4% in the placebo group had diabetes; in the ORION-11 trial, 36.5% of patients in the inclisiran group and 33.7% in the placebo group had diabetes. The coprimary end point of placebo-corrected percentage change in LDL cholesterol level from baseline to day 510 was 52.3% in the ORION-10 trial and 49.9% in the ORION-11 trial. In an exploratory analysis, the prespecified cardiovascular end point, defined as a cardiovascular basket of nonadjudicated terms, including those classified within cardiac death, and any signs or symptoms of cardiac arrest, nonfatal MI, or stroke, occurred in 7.4% of the inclisiran group and 10.2% of the placebo group in the ORION-10 trial and in 7.8% of the inclisiran group and 10.3% of the placebo group in the ORION-11 trial. A cardiovascular outcome trial using inclisiran in people with established cardiovascular disease is currently ongoing (117).

Statins and Bempedoic Acid

Bempedoic acid is a novel LDL cholesterol–lowering agent that is indicated as an adjunct to diet and maximum tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established ASCVD who require additional lowering of LDL cholesterol. A pooled analysis suggests that bempedoic acid therapy lowers LDL cholesterol levels by about 23% compared with placebo (118). At this time, there are no completed trials demonstrating a cardiovascular outcomes benefit to use of this medication; however, this agent may be considered for patients who cannot use or tolerate other evidence-based LDL cholesterol-lowering approaches, or for whom those other therapies are inadequately effective (119).

Treatment of Other Lipoprotein Fractions or Targets

Recommendations

10.28 For individuals with fasting triglyceride levels ≥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**

Hypertriglyceridemia should be addressed with dietary and lifestyle changes including weight loss and abstinence from alcohol (120). Severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL and especially >1,000 mg/dL) may warrant pharmacologic therapy (fibric acid derivatives and/or fish oil) and reduction in dietary fat to reduce the risk of acute pancreatitis. Moderate- or high-intensity statin therapy should also be used as indicated to reduce risk of cardiovascular events (see statin treatment). In people with moderate hypertriglyceridemia, lifestyle interventions, treatment of secondary factors, and avoidance of medications that might raise triglycerides are recommended.

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) enrolled 8,179 adults receiving statin therapy with moderately elevated triglycerides (135–499 mg/dL, median baseline of 216 mg/dL) who had either established cardiovascular disease (secondary prevention cohort) or diabetes plus at least one other cardiovascular risk

factor (primary prevention cohort) (121). Patients were randomized to icosapent ethyl 4 g/day (2 g twice daily with food) versus placebo. The trial met its primary end point, demonstrating a 25% relative risk reduction ($P < 0.001$) for the primary end point composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. This reduction in risk was seen in people with or without diabetes at baseline. The composite of cardiovascular death, nonfatal MI, or nonfatal stroke was reduced by 26% ($P < 0.001$). Additional ischemic end points were significantly lower in the icosapent ethyl group than in the placebo group, including cardiovascular death, which was reduced by 20% ($P = 0.03$). The proportions of patients experiencing adverse events and serious adverse events were similar between the active and placebo treatment groups. It should be noted that data are lacking with other n-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products (121). As an example, the addition of 4 g per day of a carboxylic acid formulation of the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (n-3 carboxylic acid) to statin therapy in patients with atherogenic dyslipidemia and high cardiovascular risk, 70% of whom had diabetes, did not reduce the risk of major adverse cardiovascular events compared with the inert comparator of corn oil (122).

Low levels of HDL cholesterol, often associated with elevated triglyceride levels, are the most prevalent pattern of dyslipidemia in people with type 2 diabetes. However, the evidence for the use of drugs that target these lipid fractions is substantially less robust than that for statin therapy (123). In a large trial in people with diabetes, fenofibrate failed to reduce overall cardiovascular outcomes (124).

Other Combination Therapy

Recommendations

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

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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**
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Statin and Fibrate Combination Therapy

Combination therapy (statin and fibrate) is associated with an increased risk for abnormal transaminase levels, myositis, and rhabdomyolysis. The risk of rhabdomyolysis is more common with higher doses of statins and renal insufficiency and appears to be higher when statins are combined with gemfibrozil (compared with fenofibrate) (125).

In the ACCORD study, in people with type 2 diabetes who were at high risk for ASCVD, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke compared with simvastatin alone. Prespecified subgroup analyses suggested heterogeneity in treatment effects with possible benefit for men with both a triglyceride level ≥204 mg/dL (2.3 mmol/L) and an HDL cholesterol level ≤34 mg/dL (0.9 mmol/L) (126).

Statin and Niacin Combination Therapy

The Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial randomized over 3,000 people (about one-third with diabetes) with established ASCVD, LDL cholesterol levels <180 mg/dL [4.7 mmol/L], low HDL cholesterol levels (men <40 mg/dL [1.0 mmol/L] and women <50 mg/dL [1.3 mmol/L]), and triglyceride levels of 150–400 mg/dL (1.7–4.5 mmol/L) to statin therapy plus extended-release niacin or placebo. The trial was halted early due to lack of efficacy on the primary ASCVD outcome (first event of the composite of death from CHD, nonfatal MI, ischemic stroke, hospitalization for an ACS, or symptom-driven coronary or cerebral revascularization) and a possible increase in ischemic stroke in those on combination therapy (127).

The much larger Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial also failed to show a benefit of adding niacin to background statin therapy (128). A total of 25,673 individuals with prior vascular disease were randomized to receive 2 g of extended-release niacin and 40 mg of laropiprant (an antagonist of the prostaglandin D2 receptor DP1 that has been shown to improve participation in niacin therapy) versus a matching placebo daily and followed for a median follow-up period of 3.9 years. There was no significant difference in the rate of coronary death, MI, stroke, or coronary revascularization with the addition of niacin–laropiprant versus placebo (13.2% vs. 13.7%; rate ratio 0.96; $P = 0.29$). Niacin–laropiprant was associated with an increased incidence of new-onset diabetes (absolute excess, 1.3 percentage points; $P < 0.001$) and disturbances in diabetes management among those with diabetes. In addition, there was an increase in serious adverse events associated with the gastrointestinal system, musculoskeletal system, skin, and, unexpectedly, infection and bleeding.

Therefore, combination therapy with a statin and niacin is not recommended given the lack of efficacy on major ASCVD outcomes and increased side effects.

Diabetes Risk With Statin Use

Several studies have reported a modestly increased risk of incident diabetes with statin use (129,130), which may be limited to those with diabetes risk factors. An analysis of one of the initial studies suggested that although statin use was associated with diabetes risk, the cardiovascular event rate reduction with statins far outweighed the risk of incident diabetes even for patients at highest risk for diabetes (131). The absolute risk increase was small (over 5 years of follow-up, 1.2% of participants on placebo developed diabetes and 1.5% on rosuvastatin developed diabetes) (131). A meta-analysis of 13 randomized statin trials with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of diabetes, so that (on average) treatment of 255 patients with statins for 4 years resulted in one additional case of diabetes while simultaneously preventing 5.4 vascular events among those 255 patients (130).

Lipid-Lowering Agents and Cognitive Function

Although concerns regarding a potential adverse impact of lipid-lowering agents on cognitive function have been raised, several lines of evidence point against this association, as detailed in a 2018 European Atherosclerosis Society Consensus Panel statement (132). First, there are three large randomized trials of statin versus placebo where specific cognitive tests were performed, and no differences were seen between statin and placebo (133–136). In addition, no change in cognitive function has been reported in studies with the addition of ezetimibe (105) or PCSK9 inhibitors (108,137) to statin therapy, including among patients treated to very low LDL cholesterol levels. In addition, the most recent systematic review of the U.S. Food and Drug Administration's (FDA's) postmarketing surveillance databases, randomized controlled trials, and cohort, case-control, and cross-sectional studies evaluating cognition in patients receiving statins found that published data do not reveal an adverse effect of statins on cognition (138). Therefore, a concern that statins or other lipid-lowering agents might cause cognitive dysfunction or dementia is not currently supported by evidence and should not deter their use in individuals with diabetes at high risk for ASCVD (138).

ANTIPLATELET AGENTS

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Recommendations

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 P2Y12 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**

10.37 Combination therapy with aspirin plus low-dose rivaroxaban

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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**

Risk Reduction

Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with previous MI or stroke (secondary prevention) and is strongly recommended. In primary prevention, however, among patients with no previous cardiovascular events, its net benefit is more controversial (129,140).

Previous randomized controlled trials of aspirin specifically in people with diabetes failed to consistently show a significant reduction in overall ASCVD end points, raising questions about the efficacy of aspirin for primary prevention in people with diabetes, although some sex differences were suggested (141–143).

The Antithrombotic Trialists' Collaboration published an individual patient–level meta-analysis (139) of the six large trials of aspirin for primary prevention in the general population. These trials collectively enrolled over 95,000 participants, including almost 4,000 with diabetes. Overall, they found that aspirin reduced the risk of serious vascular events by 12% (relative risk 0.88 [95% CI 0.82–0.94]). The largest reduction was for nonfatal MI, with little effect on CHD death (relative risk 0.95 [95% CI 0.78–1.15]) or total stroke.

Most recently, the ASCEND (A Study of Cardiovascular Events iN Diabetes) trial randomized 15,480 people with diabetes but no evident cardiovascular disease to aspirin 100 mg daily or placebo (144). The primary efficacy end point was vascular death, MI, or stroke or transient ischemic attack. The primary safety outcome was major bleeding (i.e., intracranial hemorrhage, sight-threatening bleeding in the eye, gastrointestinal

bleeding, or other serious bleeding). During a mean follow-up of 7.4 years, there was a significant 12% reduction in the primary efficacy end point (8.5% vs. 9.6%; P = 0.01). In contrast, major bleeding was significantly increased from 3.2 to 4.1% in the aspirin group (rate ratio 1.29; P = 0.003), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There were no significant differences by sex, weight, or duration of diabetes or other baseline factors including ASCVD risk score.

Two other large, randomized trials of aspirin for primary prevention, in people without diabetes (ARRIVE [Aspirin to Reduce Risk of Initial Vascular Events]) (145) and in the elderly (ASPREE [Aspirin in Reducing Events in the Elderly]) (146), which included 11% with diabetes, found no benefit of aspirin on the primary efficacy end point and an increased risk of bleeding. In ARRIVE, with 12,546 patients over a period of 60 months follow-up, the primary end point occurred in 4.29% vs. 4.48% of patients in the aspirin versus placebo groups (HR 0.96 [95% CI 0.81–1.13]; P = 0.60). Gastrointestinal bleeding events (characterized as mild) occurred in 0.97% of patients in the aspirin group vs. 0.46% in the placebo group (HR 2.11 [95% CI 1.36–3.28]; P = 0.0007). In ASPREE, including 19,114 individuals, for cardiovascular disease (fatal CHD, MI, stroke, or hospitalization for heart failure) after a median of 4.7 years of follow-up, the rates per 1,000 person-years were 10.7 vs. 11.3 events in aspirin vs. placebo groups (HR 0.95 [95% CI 0.83–1.08]). The rate of major hemorrhage per 1,000 person-years was 8.6 events vs. 6.2 events, respectively (HR 1.38 [95% CI 1.18–1.62]; P < 0.001).

Thus, aspirin appears to have a modest effect on ischemic vascular events, with the absolute decrease in events depending on the underlying ASCVD risk. The main adverse effect is an increased risk of gastrointestinal bleeding. The excess risk may be as high as 5 per 1,000 per year in real-world settings. However, for adults with ASCVD risk >1% per year, the number of ASCVD events prevented will be similar to the number of episodes of bleeding induced, although these complications do not have equal effects on long-term health (147).

Recommendations for using aspirin as primary prevention include both men and women aged ≥50 years with diabetes and at least one additional major risk

factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or CKD/albuminuria) who are not at increased risk of bleeding (e.g., older age, anemia, renal disease) (148–151). Noninvasive imaging techniques such as coronary calcium scoring may potentially help further tailor aspirin therapy, particularly in those at low risk (152,153). For people >70 years of age (with or without diabetes), the balance appears to have greater risk than benefit (144,146). Thus, for primary prevention, the use of aspirin needs to be carefully considered and may generally not be recommended. Aspirin may be considered in the context of high cardiovascular risk with low bleeding risk, but generally not in older adults. Aspirin therapy for primary prevention may be considered in the context of shared decision-making, which carefully weighs the cardiovascular benefits with the fairly comparable increase in risk of bleeding.

For people with documented ASCVD, use of aspirin for secondary prevention has far greater benefit than risk; for this indication, aspirin is still recommended (139).

Aspirin Use in People <50 Years of Age

Aspirin is not recommended for those at low risk of ASCVD (such as men and women aged <50 years with diabetes with no other major ASCVD risk factors) as the low benefit is likely to be outweighed by the risks of bleeding. Clinical judgment should be used for those at intermediate risk (younger patients with one or more risk factors or older patients with no risk factors) until further research is available. Patients' willingness to undergo long-term aspirin therapy should also be considered (154). Aspirin use in patients aged <21 years is generally contraindicated due to the associated risk of Reye syndrome.

Aspirin Dosing

Average daily dosages used in most clinical trials involving people with diabetes ranged from 50 mg to 650 mg but were mostly in the range of 100–325 mg/day. There is little evidence to support any specific dose but using the lowest possible dose may help to reduce side effects (155). In the ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness) trial of individuals with established cardiovascular disease, 38% of whom had

diabetes, there were no significant differences in cardiovascular events or major bleeding between patients assigned to 81 mg and those assigned to 325 mg of aspirin daily (156). In the U.S., the most common low-dose tablet is 81 mg. Although platelets from people with diabetes have altered function, it is unclear what, if any, effect that finding has on the required dose of aspirin for cardioprotective effects in people with diabetes. Many alternate pathways for platelet activation exist that are independent of thromboxane A_2 and thus are not sensitive to the effects of aspirin (157). "Aspirin resistance" has been described in people with diabetes when measured by a variety of ex vivo and in vitro methods (platelet aggregometry, measurement of thromboxane B_2) (158), but other studies suggest no impairment in aspirin response among people with diabetes (159). A trial suggested that more frequent dosing regimens of aspirin may reduce platelet reactivity in individuals with diabetes (160); however, these observations alone are insufficient to empirically recommend that higher doses of aspirin be used in this group at this time. Another meta-analysis raised the hypothesis that low-dose aspirin efficacy is reduced in those weighing >70 kg (161); however, the ASCEND trial found benefit of low-dose aspirin in those in this weight range, which would thus not validate this suggested hypothesis (144). It appears that 75–162 mg/day is optimal.

Indications for P2Y12 Receptor Antagonist Use

A P2Y12 receptor antagonist in combination with aspirin is reasonable for at least 1 year in patients following an ACS and may have benefits beyond this period. Evidence supports use of either ticagrelor or clopidogrel if no percutaneous coronary intervention was performed and clopidogrel, ticagrelor, or prasugrel if a percutaneous coronary intervention was performed (162). In people with diabetes and prior MI (1–3 years before), adding ticagrelor to aspirin significantly reduces the risk of recurrent ischemic events including cardiovascular and CHD death (163). Similarly, the addition of ticagrelor to aspirin reduced the risk of ischemic cardiovascular events compared with aspirin alone in people with diabetes and stable coronary artery disease (164,165). However, a higher incidence of major bleeding,

including intracranial hemorrhage, was noted with dual antiplatelet therapy. The net clinical benefit (ischemic benefit vs. bleeding risk) was improved with ticagrelor therapy in the large prespecified subgroup of patients with history of percutaneous coronary intervention, while no net benefit was seen in patients without prior percutaneous coronary intervention (165). However, early aspirin discontinuation compared with continued dual antiplatelet therapy after coronary stenting may reduce the risk of bleeding without a corresponding increase in the risks of mortality and ischemic events, as shown in a prespecified analysis of people with diabetes enrolled in the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial and a recent meta-analysis (166,167).

Combination Antiplatelet and Anticoagulation Therapy

Combination therapy with aspirin plus low dose rivaroxaban may be considered for people with stable coronary and/or peripheral artery disease to prevent major adverse limb and cardiovascular complications. In the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial of 27,395 individuals with established coronary artery disease and/or peripheral artery disease, aspirin plus rivaroxaban 2.5 mg twice daily was superior to aspirin plus placebo in the reduction of cardiovascular ischemic events including major adverse limb events. The absolute benefits of combination therapy appeared larger in people with diabetes, who comprised 10,341 of the trial participants (168,169). A similar treatment strategy was evaluated in the Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease (VOYAGER PAD) trial (170), in which 6,564 individuals with peripheral artery disease who had undergone revascularization were randomly assigned to receive rivaroxaban 2.5 mg twice daily plus aspirin or placebo plus aspirin. Rivaroxaban treatment in this group of patients was also associated with a significantly lower incidence of ischemic cardiovascular events, including major adverse limb events. However, an increased risk of major bleeding was noted

with rivaroxaban added to aspirin treatment in both COMPASS and VOYAGER PAD.

The risks and benefits of dual antiplatelet or antiplatelet plus anticoagulant treatment strategies should be thoroughly discussed with eligible patients, and shared decision-making should be used to determine an individually appropriate treatment approach. This field of cardiovascular risk reduction is evolving rapidly, as are the definitions of optimal care for patients with differing types and circumstances of cardiovascular complications.

CARDIOVASCULAR DISEASE

Screening

> **Recommendations**
>
> **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**

Treatment

> **Recommendations**
>
> **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 10.3***B* and **Table 10.3***C*) is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimens. **A**

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	Linagliptin/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
A1C 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 10.3B—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)

Continued o

Table 10.3B—Continued

Key secondary outcome§	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)
	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. ^AIC change of 0.66% with 0.5 mg and 1.05% with 1 mg dose of semaglutide. ‡Significant difference in A1C between groups (*P* < 0.05). §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 m², 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.

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**

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**

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**
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, β-blockers should be continued for 3 years after the event. **B**
10.46	Treatment of individuals with heart failure with reduced ejection fraction should include a β-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^2 but should be avoided in unstable or hospitalized individuals with heart failure. **B**

Cardiac Testing

Candidates for advanced or invasive cardiac testing include those with *1*) typical or atypical cardiac symptoms and *2*) an abnormal resting electrocardiogram (ECG). Exercise ECG testing without or with echocardiography may be used as the initial test. In adults with diabetes ≥40 years of age, measurement of coronary artery calcium is also reasonable for cardiovascular risk assessment. Pharmacologic stress echocardiography or nuclear imaging should be considered in individuals with diabetes in whom resting ECG abnormalities preclude exercise stress testing (e.g., left bundle branch block or ST-T abnormalities). In addition, individuals who require stress testing and are unable to exercise should undergo pharmacologic stress echocardiography or nuclear imaging.

Screening Asymptomatic Patients

The screening of asymptomatic patients with high ASCVD risk is not recommended (171), in part because these high-risk patients should already be receiving intensive medical therapy—an approach that provides benefit similar to invasive revascularization (172,173). There is also some evidence that silent ischemia may reverse over time, adding to the controversy concerning aggressive screening strategies (174). In prospective studies, coronary artery calcium has been established as an independent predictor of future ASCVD events in people with diabetes and is consistently superior to both the UK Prospective Diabetes Study (UKPDS) risk engine and the Framingham Risk Score in predicting risk in this population (175–177). However, a randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic people with type 2 diabetes and normal ECGs (178). Despite abnormal myocardial perfusion imaging in more than one in five patients, cardiac outcomes were essentially equal (and very low) in screened versus unscreened patients. Accordingly, indiscriminate screening is not considered cost-effective. Studies have found that a risk factor-based approach to the initial diagnostic evaluation and subsequent follow-up for coronary artery disease fails to identify which people with type 2 diabetes will have silent ischemia on screening tests (179,180).

Any benefit of newer noninvasive coronary artery disease screening methods, such as computed tomography calcium scoring and computed tomography angiography, to identify patient subgroups for different treatment strategies remains unproven in asymptomatic people with diabetes, though research is ongoing. Since asymptomatic people with diabetes with higher coronary disease burden have more future cardiac events (175,181,182), these additional imaging tests may provide reasoning for treatment intensification and/or guide informed patient decision-making and willingness for medication initiation and participation.

While coronary artery screening methods, such as calcium scoring, may improve cardiovascular risk assessment in people with type 2 diabetes (183), their routine use leads to radiation exposure and may result in unnecessary invasive testing such as coronary angiography and revascularization procedures. The ultimate balance of benefit, cost, and risks of such an approach in asymptomatic patients remains controversial, particularly in the modern setting of aggressive ASCVD risk factor control.

Lifestyle and Pharmacologic Interventions

Intensive lifestyle intervention focusing on weight loss through decreased caloric intake and increased physical activity as performed in the Action for Health in Diabetes (Look AHEAD) trial may be considered for improving glucose control, fitness, and some ASCVD risk factors (184). Patients at increased ASCVD risk should receive statin, ACE inhibitor, or ARB therapy if the patient has hypertension, and possibly aspirin, unless there are contraindications to a particular drug class. Clear benefit exists for ACE inhibitor or ARB therapy in people with diabetic kidney disease or hypertension, and these agents are recommended for hypertension management in people with known ASCVD (particularly coronary artery disease) (65,66,185). People with type 2 diabetes and CKD should be considered for treatment with finerenone to reduce cardiovascular outcomes and the risk of CKD progression (186–189). β-Blockers should be used in individuals with active angina or HFrEF and for 3 years after MI in those with preserved left ventricular function (190,191).

Glucose-Lowering Therapies and Cardiovascular Outcomes

In 2008, the FDA issued a guidance for industry to perform cardiovascular outcomes trials for all new medications for the treatment for type 2 diabetes amid concerns of increased cardiovascular risk (192). Previously approved diabetes medications were not subject to the guidance. Recently published cardiovascular outcomes trials have provided additional data on cardiovascular and renal outcomes in people with type 2 diabetes with cardiovascular disease or at high risk for cardiovascular disease (**Table 10.3A**, **Table 10.3B**, and **Table 10.3C**). An expanded review of the effects of glucose-lowering and other therapies

in people with CKD is included in Section 11, "Chronic Kidney Disease and Risk Management."

Cardiovascular outcomes trials of dipeptidyl peptidase 4 (DPP-4) inhibitors have all, so far, not shown cardiovascular benefits relative to placebo. In addition, the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Type 2 Diabetes) study demonstrated noninferiority between a DPP-4 inhibitor, linagliptin, and a sulfonylurea, glimepiride, on cardiovascular outcomes despite lower rates of hypoglycemia in the linagliptin treatment group (193). However, results from other new agents have provided a mix of results.

SGLT2 Inhibitor Trials

The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was a randomized, double-blind trial that assessed the effect of empagliflozin, an SGLT2 inhibitor, versus placebo on cardiovascular outcomes in 7,020 people with type 2 diabetes and existing cardiovascular disease. Study participants had a mean age of 63 years, 57% had diabetes for more than 10 years, and 99% had established cardiovascular disease. EMPA-REG OUTCOME showed that over a median follow-up of 3.1 years, treatment reduced the composite outcome of MI, stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group, HR in the empagliflozin group 0.86 [95% CI 0.74–0.99]; $P = 0.04$ for superiority) and cardiovascular death by 38% (absolute rate 3.7% vs. 5.9%, HR 0.62 [95% CI 0.49–0.77]; $P < 0.001$) (8).

Two large outcomes trials of the SGLT2 inhibitor canagliflozin have been conducted that separately assessed *1*) the cardiovascular effects of treatment in patients at high risk for major adverse cardiovascular events (9) and *2*) the impact of canagliflozin therapy on cardiorenal outcomes in people with diabetes-related CKD (194). First, the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program integrated data from two trials. The CANVAS trial that started in 2009 was partially unblinded prior to completion because of the need to file interim cardiovascular outcomes data for regulatory approval of the drug (195). Thereafter, the post approval CANVAS-Renal (CANVAS-R) trial was started in 2014. Combining both

trials, 10,142 participants with type 2 diabetes were randomized to canagliflozin or placebo and were followed for an average 3.6 years. The mean age of patients was 63 years, and 66% had a history of cardiovascular disease. The combined analysis of the two trials found that canagliflozin significantly reduced the composite outcome of cardiovascular death, MI, or stroke versus placebo (occurring in 26.9 vs. 31.5 participants per 1,000 patient-years; HR 0.86 [95% CI 0.75–0.97]). The specific estimates for canagliflozin versus placebo on the primary composite cardiovascular outcome were HR 0.88 (95% CI 0.75–1.03) for the CANVAS trial and 0.82 (0.66–1.01) for CANVAS-R, with no heterogeneity found between trials. Of note, there was an increased risk of lower-limb amputation with canagliflozin (6.3 vs. 3.4 participants per 1,000 patient-years; HR 1.97 [95% CI 1.41–2.75]) (9). Second, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial randomized 4,401 people with type 2 diabetes and chronic diabetes-related kidney disease (UACR >300 mg/g and eGFR 30 to <90 mL/min/1.73 m^2) to canagliflozin 100 mg daily or placebo (194). The primary outcome was a composite of end-stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular causes. The trial was stopped early due to conclusive evidence of efficacy identified during a prespecified interim analysis with no unexpected safety signals. The risk of the primary composite outcome was 30% lower with canagliflozin treatment when compared with placebo (HR 0.70 [95% CI 0.59–0.82]). Moreover, it reduced the prespecified end point of end-stage kidney disease alone by 32% (HR 0.68 [95% CI 0.54–0.86]). Canagliflozin was additionally found to have a lower risk of the composite of cardiovascular death, MI, or stroke (HR 0.80 [95% CI 0.67–0.95]), as well as lower risk of hospitalizations for heart failure (HR 0.61 [95% CI 0.47–0.80]) and of the composite of cardiovascular death or hospitalization for heart failure (HR 0.69 [95% CI 0.57–0.83]). In terms of safety, no significant increase in lower-limb amputations, fractures, acute kidney injury, or hyperkalemia was noted for canagliflozin relative to placebo in CREDENCE. An increased risk for diabetic ketoacidosis was noted, however, with 2.2 and 0.2 events per 1,000 patient-years noted

in the canagliflozin and placebo groups, respectively (HR 10.80 [95% CI 1.39–83.65]) (194).

The Dapagliflozin Effect on Cardiovascular Events-Thrombosis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial was another randomized, double-blind trial that assessed the effects of dapagliflozin versus placebo on cardiovascular and renal outcomes in 17,160 people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD (196). Study participants had a mean age of 64 years, with ∼40% of study participants having established ASCVD at baseline—a characteristic of this trial that differs from other large cardiovascular trials where a majority of participants had established cardiovascular disease. DECLARE-TIMI 58 met the prespecified criteria for noninferiority to placebo with respect to major adverse cardiovascular events but did not show a lower rate of major adverse cardiovascular events when compared with placebo (8.8% in the dapagliflozin group and 9.4% in the placebo group; HR 0.93 [95% CI 0.84–1.03]; $P = 0.17$). A lower rate of cardiovascular death or hospitalization for heart failure was noted (4.9% vs. 5.8%; HR 0.83 [95% CI 0.73–0.95]; $P = 0.005$), which reflected a lower rate of hospitalization for heart failure (HR 0.73 [95% CI 0.61–0.88]). No difference was seen in cardiovascular death between groups.

In the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial (197), 4,304 individuals with CKD (UACR 200–5,000 mg/g and eGFR 25–75 mL/min/1.73 m^2), with or without diabetes, were randomized to dapagliflozin 10 mg daily or placebo. The primary outcome was a composite of sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. Over a median follow-up period of 2.4 years, a primary outcome event occurred in 9.2% of participants in the dapagliflozin group and 14.5% of those in the placebo group. The risk of the primary composite outcome was significantly lower with dapagliflozin therapy compared with placebo (HR 0.61 [95% CI 0.51–0.72]), as were the risks for a renal composite outcome of sustained decline in eGFR of at least 50%, endstage kidney disease, or death from renal causes (HR 0.56 [95% CI 0.45–0.68]), and a composite of cardiovascular death

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

	EMPA-REG OUTCOME (8) (n = 7,020)	CANVAS Program (9) (n = 10,142)	DECLARE-TIMI 58 (196) (n = 17,160)	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; 1,983 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)
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 II, III, or IV heart failure and an ejection fraction >40%	NYHA class II, III, 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)†	63.1	63.3	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
Statin 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	65.6/14.4	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

Table 10.3C—Continued

	EMPA-REG OUTCOME (8) (n = 7,020)	CANVAS Program (9) (n = 10,142)	DECLARE-TIMI 58 (196) (n = 17,160)	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; 1,983 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 0.93 (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, ESKD, 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 m², new ESRD, or death from renal or CV causes 0.76 (0.67–0.87)	CV death or HF hospitalization 0.69 (0.57–0.83) 3-point MACE 0.80 (0.67–0.95)	≥50% decline in eGFR, ESKD, 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 0.69 (0.53–0.88)	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. −2.62 mL/min/1.73 m²; 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 (1.03–1.21) 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)	0.87 (0.69–1.09)	1.01 (0.84–1.21)	—	—	1.06 (0.82–1.37)	—	—	—	—
HF hospitalization§	0.65 (0.50–0.85)	0.67 (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)	0.87 (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; NYHA, 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 as means; diabetes duration was reported as median. ‡Significant difference in A1C between groups (P < 0.05). ^AIC 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 m² for individuals with baseline eGFR ≥30 mL/min/1.73 m².

or hospitalization for heart failure (HR 0.71 [95% CI 0.55–0.92]). The effects of dapagliflozin therapy were similar in individuals with and without type 2 diabetes.

Results of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced), Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved), Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in Patients With PRESERVED Ejection Fraction Heart Failure (PRESERVED-HF), and Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER), which assessed the effects of dapagliflozin and empagliflozin in individuals with established heart failure (11,189,198,199,200), are described below in GLUCOSE-LOWERING THERAPIES AND HEART FAILURE.

The Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) (201) was a randomized, double-blind trial that established the effects of ertugliflozin versus placebo on cardiovascular outcomes in 8,246 people with type 2 diabetes and established ASCVD. Participants were assigned to the addition of 5 mg or 15 mg of ertugliflozin or to placebo once daily to background standard care. Study participants had a mean age of 64.4 years and a mean duration of diabetes of 13 years at baseline and were followed for a median of 3.0 years. VERTIS CV met the prespecified criteria for noninferiority of ertugliflozin to placebo with respect to the primary outcome of major adverse cardiovascular events (11.9% in the pooled ertugliflozin group and 11.9% in the placebo group; HR 0.97 [95% CI 0.85–1.11]; $P < 0.001$). Ertugliflozin was not superior to placebo for the key secondary outcomes of death from cardiovascular causes or hospitalization for heart failure; death from cardiovascular causes; or the composite of death from renal causes, renal replacement therapy, or doubling of the serum creatinine level. The HR for a secondary outcome of hospitalization for heart failure (ertugliflozin vs. placebo) was 0.70 [95% CI 0.54–0.90], consistent with findings from other SGLT2 inhibitor cardiovascular outcomes trials.

Sotagliflozin, an SGLT1 and SGLT2 inhibitor not currently approved by the FDA in the U.S., lowers glucose via delayed glucose absorption in the gut in addition to increasing urinary glucose excretion and has been evaluated in the Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial (202). A total of 10,584 people with type 2 diabetes, CKD, and additional cardiovascular risk were enrolled in SCORED and randomized to sotagliflozin 200 mg once daily (uptitrated to 400 mg once daily if tolerated) or placebo. SCORED ended early due to a lack of funding; thus, changes to the prespecified primary end points were made prior to unblinding to accommodate a lower than anticipated number of end point events. The primary end point of the trial was the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure. After a median of 16 months of follow-up, the rate of primary end point events was reduced with sotagliflozin (5.6 events per 100 patient-years in the sotagliflozin group and 7.5 events per 100 patient-years in the placebo group [HR 0.74 (95% CI 0.63–0.88); $P < 0.001$]). Sotagliflozin also reduced the risk of the secondary end point of total number of hospitalizations for heart failure and urgent visits for heart failure (3.5% in the sotagliflozin group and 5.1% in the placebo group; HR 0.67 [95% CI 0.55–0.82]; $P < 0.001$) but not the secondary end point of deaths from cardiovascular causes. No significant between-group differences were found for the outcome of all-cause mortality or for a composite renal outcome comprising the first occurrence of long-term dialysis, renal transplantation, or a sustained reduction in eGFR. In general, the adverse effects of sotagliflozin were similar to those seen with use of SGLT2 inhibitors, but they also included an increased rate of diarrhea potentially related to the inhibition of SGLT1.

GLP-1 Receptor Agonist Trials
The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was a randomized, double-blind trial that assessed the effect of liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, versus placebo on cardiovascular outcomes in 9,340

people with type 2 diabetes at high risk for cardiovascular disease or with cardiovascular disease (203). Study participants had a mean age of 64 years and a mean duration of diabetes of nearly 13 years. Over 80% of study participants had established cardiovascular disease. After a median follow-up of 3.8 years, LEADER showed that the primary composite outcome (MI, stroke, or cardiovascular death) occurred in fewer participants in the treatment group (13.0%) when compared with the placebo group (14.9%) (HR 0.87 [95% CI 0.78–0.97]; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). Deaths from cardiovascular causes were significantly reduced in the liraglutide group (4.7%) compared with the placebo group (6.0%) (HR 0.78 [95% CI 0.66–0.93]; $P = 0.007$) (203).

Results from a moderate-sized trial of another GLP-1 receptor agonist, semaglutide, were consistent with the LEADER trial (204). Semaglutide is a once-weekly GLP-1 receptor agonist approved by the FDA for the treatment of type 2 diabetes. The Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) was the initial randomized trial powered to test noninferiority of semaglutide for the purpose of regulatory approval (204). In this study, 3,297 people with type 2 diabetes were randomized to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 2 years. The primary outcome (the first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke) occurred in 108 patients (6.6%) in the semaglutide group vs. 146 patients (8.9%) in the placebo group (HR 0.74 [95% CI 0.58–0.95]; $P < 0.001$). More patients discontinued treatment in the semaglutide group because of adverse events, mainly gastrointestinal. The cardiovascular effects of the oral formulation of semaglutide compared with placebo have been assessed in Peptide Innovation for Early Diabetes Treatment (PIONEER) 6, a preapproval trial designed to rule out an unacceptable increase in cardiovascular risk (205). In this trial of 3,183 people with type 2 diabetes and high cardiovascular risk followed for a median of 15.9 months, oral semaglutide was noninferior to placebo for the primary composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke (HR 0.79 [95% CI 0.57–1.11]; $P < 0.001$

for noninferiority) (205). The cardiovascular effects of this formulation of semaglutide will be further tested in a large, longer-term outcomes trial.

The Harmony Outcomes trial randomized 9,463 people with type 2 diabetes and cardiovascular disease to once-weekly subcutaneous albiglutide or matching placebo, in addition to their standard care (206). Over a median duration of 1.6 years, the GLP-1 receptor agonist reduced the risk of cardiovascular death, MI, or stroke to an incidence rate of 4.6 events per 100 person-years in the albiglutide group vs. 5.9 events in the placebo group (HR ratio 0.78, $P = 0.0006$ for superiority) (206). This agent is not currently available for clinical use.

The Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trial was a randomized, double-blind, placebo-controlled trial that assessed the effect of the once-weekly GLP-1 receptor agonist dulaglutide versus placebo on major adverse cardiovascular events in ~9,990 people with type 2 diabetes at risk for cardiovascular events or with a history of cardiovascular disease (207). Study participants had a mean age of 66 years and a mean duration of diabetes of ~10 years. Approximately 32% of participants had history of atherosclerotic cardiovascular events at baseline. After a median follow-up of 5.4 years, the primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes occurred in 12.0% and 13.4% of participants in the dulaglutide and placebo treatment groups, respectively (HR 0.88 [95% CI 0.79–0.99]; $P = 0.026$). These findings equated to incidence rates of 2.4 and 2.7 events per 100 person-years, respectively. The results were consistent across the subgroups of patients with and without history of CV events. Allcause mortality did not differ between groups ($P = 0.067$).

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial studied the once-daily GLP-1 receptor agonist lixisenatide on cardiovascular outcomes in people with type 2 diabetes who had had a recent acute coronary event (208). A total of 6,068 people with type 2 diabetes with a recent hospitalization for MI or unstable angina within the previous 180 days were randomized to receive lixisenatide or placebo in addition to standard care and were followed for a median of ~2.1 years. The primary

outcome of cardiovascular death, MI, stroke, or hospitalization for unstable angina occurred in 406 patients (13.4%) in the lixisenatide group vs. 399 (13.2%) in the placebo group (HR 1.2 [95% CI 0.89–1.17]), which demonstrated the noninferiority of lixisenatide to placebo ($P < 0.001$) but did not show superiority ($P = 0.81$).

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial also reported results with the once-weekly GLP-1 receptor agonist extended-release exenatide and found that major adverse cardiovascular events were numerically lower with use of extended-release exenatide compared with placebo, although this difference was not statistically significant (209). A total of 14,752 people with type 2 diabetes (of whom 10,782 [73.1%] had previous cardiovascular disease) were randomized to receive extended-release exenatide 2 mg or placebo and followed for a median of 3.2 years. The primary end point of cardiovascular death, MI, or stroke occurred in 839 patients (11.4%; 3.7 events per 100 person-years) in the exenatide group and in 905 patients (12.2%; 4.0 events per 100 person-years) in the placebo group (HR 0.91 [95% CI 0.83–1.00]; $P < 0.001$ for noninferiority), but exenatide was not superior to placebo with respect to the primary end point ($P = 0.06$ for superiority). However, all-cause mortality was lower in the exenatide group (HR 0.86 [95% CI 0.77–0.97]). The incidence of acute pancreatitis, pancreatic cancer, medullary thyroid carcinoma, and serious adverse events did not differ significantly between the two groups.

In summary, there are now numerous large randomized controlled trials reporting statistically significant reductions in cardiovascular events for three of the FDA-approved SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, with lesser benefits seen with ertugliflozin) and four FDA-approved GLP-1 receptor agonists (liraglutide, albiglutide [although that agent was removed from the market for business reasons], semaglutide [lower risk of cardiovascular events in a moderate-sized clinical trial but one not powered as a cardiovascular outcomes trial], and dulaglutide). Meta-analyses of the trials reported to date suggest that GLP-1 receptor agonists and SGLT2 inhibitors reduce risk of atherosclerotic major adverse cardiovascular events to a comparable degree in people with type 2

diabetes and established ASCVD (210,211). SGLT2 inhibitors also reduce risk of heart failure hospitalization and progression of kidney disease in people with established ASCVD, multiple risk factors for ASCVD, or albuminuric kidney disease (212,213). In people with type 2 diabetes and established ASCVD, multiple ASCVD risk factors, or diabetic kidney disease, an SGLT2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. For many patients, use of either an SGLT2 inhibitor or a GLP-1 receptor agonist to reduce cardiovascular risk is appropriate. Emerging data suggest that use of both classes of drugs will provide an additive cardiovascular and kidney outcomes benefit; thus, combination therapy with an SGLT2 inhibitor and a GLP-1 receptor agonist may be considered to provide the complementary outcomes benefits associated with these classes of medication. Evidence to support such an approach includes findings from AMPLITUDE-O (Effect of Efpeglenatide on Cardiovascular Outcomes), an outcomes trial of people with type 2 diabetes and either cardiovascular or kidney disease plus at least one other risk factor randomized to the investigational GLP-1 receptor agonist efpeglenatide or placebo (214). Randomization was stratified by current or potential use of SGLT2 inhibitor therapy, a class ultimately used by >15% of the trial participants. Over a median follow-up of 1.8 years, efpeglenatide therapy reduced the risk of incident major adverse cardiovascular events by 27% and of a composite renal outcome event by 32%. Importantly, the effects of efpeglenatide did not vary by use of SGLT2 inhibitors, suggesting that the beneficial effects of the GLP-1 receptor agonist were independent of those provided by SGLT2 inhibitor therapy (215). Efpeglenatide is currently not approved by the FDA for use in the U.S.

Glucose-Lowering Therapies and Heart Failure

As many as 50% of people with type 2 diabetes may develop heart failure (216). These conditions, which are each

associated with increased morbidity and mortality, commonly coincide, and independently contribute to adverse outcomes (217). Strategies to mitigate these risks are needed, and the heart failure–related risks and benefits of glucose-lowering medications should be considered carefully when determining a regimen of care for people with diabetes and either established heart failure or high risk for the development of heart failure.

Data on the effects of glucose-lowering agents on heart failure outcomes have demonstrated that thiazolidinediones have a strong and consistent relationship with increased risk of heart failure (218–220). Therefore, thiazolidinedione use should be avoided in people with symptomatic heart failure. Restrictions to use of metformin in people with medically treated heart failure were removed by the FDA in 2006 (221). Observational studies of people with type 2 diabetes and heart failure suggest that metformin users have better outcomes than individuals treated with other antihyperglycemic agents (222); however, no randomized trial of metformin therapy has been conducted in people with heart failure. Metformin may be used for the management of hyperglycemia in people with stable heart failure as long as kidney function remains within the recommended range for use (223).

Recent studies examining the relationship between DPP-4 inhibitors and heart failure have had mixed results. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) study showed that patients treated with the DPP-4 inhibitor saxagliptin were more likely to be hospitalized for heart failure than those given placebo (3.5% vs. 2.8%, respectively) (224). However, three other cardiovascular outcomes trials—Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) (225), Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (226), and the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) (193)—did not find a significant increase in risk of heart failure hospitalization with DPP-4 inhibitor use compared with placebo. No increased risk of heart failure hospitalization has been identified in the cardiovascular outcomes trials of the GLP-1 receptor

agonists lixisenatide, liraglutide, semaglutide, exenatide once-weekly, albiglutide, or dulaglutide compared with placebo (**Table 10.3***B*) (203,204,207–209).

Reduced incidence of heart failure has been observed with the use of SGLT2 inhibitors (8,194,196). In EMPA-REG OUTCOME, the addition of empagliflozin to standard care led to a significant 35% reduction in hospitalization for heart failure compared with placebo (8). Although the majority of patients in the study did not have heart failure at baseline, this benefit was consistent in patients with and without a history of heart failure (10). Similarly, in CANVAS and DECLARE-TIMI 58, there were 33% and 27% reductions in hospitalization for heart failure, respectively, with SGLT2 inhibitor use versus placebo (9,196). Additional data from the CREDENCE trial with canagliflozin showed a 39% reduction in hospitalization for heart failure, and 31% reduction in the composite of cardiovascular death or hospitalization for heart failure, in a diabetic kidney disease population with albuminuria (UACR >300 to 5,000 mg/g) (194). These combined findings from four large outcomes trials of three different SGLT2 inhibitors are highly consistent and clearly indicate robust benefits of SGLT2 inhibitors in the prevention of heart failure hospitalizations. The EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and CREDENCE trials suggested, but did not prove, that SGLT2 inhibitors would be beneficial in the treatment of people with established heart failure. More recently, the placebo-controlled DAPA-HF trial evaluated the effects of dapagliflozin on the primary outcome of a composite of worsening heart failure or cardiovascular death in patients with New York Heart Association (NYHA) class II, III, or IV heart failure and an ejection fraction of 40% or less. Of the 4,744 trial participants, 45% had a history of type 2 diabetes. Over a median of 18.2 months, the group assigned to dapagliflozin treatment had a lower risk of the primary outcome (HR 0.74 [95% CI 0.65–0.85]), lower risk of first worsening heart failure event (HR 0.70 [95% CI 0.59–0.83]), and lower risk of cardiovascular death (HR 0.82 [95% CI 0.69–0.98]) compared with placebo. The effect of dapagliflozin on the primary outcome was consistent regardless of the presence or absence of type 2 diabetes (11).

EMPEROR-Reduced assessed the effects of empagliflozin 10 mg once daily versus

placebo on a primary composite outcome of cardiovascular death or hospitalization for worsening heart failure in a population of 3,730 patients with NYHA class II, III, or IV heart failure and an ejection fraction of 40% or less (200). At baseline, 49.8% of participants had a history of diabetes. Over a median follow-up of 16 months, those in the empagliflozin-treated group had a reduced risk of the primary outcome (HR 0.75 [95% CI 0.65–0.86]; P < 0.001) and fewer total hospitalizations for heart failure (HR 0.70 [95% CI 0.58–0.85]; P < 0.001). The effect of empagliflozin on the primary outcome was consistent irrespective of diabetes diagnosis at baseline. The risk of a prespecified renal composite outcome (chronic dialysis, renal transplantation, or a sustained reduction in eGFR) was lower in the empagliflozin group than in the placebo group (1.6% in the empagliflozin group vs. 3.1% in the placebo group; HR 0.50 [95% CI 0.32–0.77]).

EMPEROR-Preserved, a randomized double-blinded placebo-controlled trial of 5,988 adults with NYHA functional class I–IV chronic HFpEF (left ventricular ejection fraction >40%), evaluated the efficacy of empagliflozin 10 mg daily versus placebo on top of standard of care on the primary outcome of composite cardiovascular death or hospitalization for heart failure (189). Approximately 50% of subjects had type 2 diabetes at baseline. Over a median of 26.2 months, there was a 21% reduction (HR 0.79 [95% CI 0.69–0.90]; P < 0.001) of the primary outcome. The effects of empagliflozin were consistent in people with or without diabetes (189).

In the DELIVER trial, 6,263 individuals with heart failure and an ejection fraction >40% were randomized to receive either dapagliflozin or placebo (199). The primary outcome of a composite of worsening heart failure, defined as hospitalization or urgent visit for heart failure, or cardiovascular death was reduced by 18% in patients treated with dapagliflozin compared with placebo (HR 0.82 [95% CI 0.73–0.92]; P < 0.001). Approximately 44% of patients randomized to either dapagliflozin or placebo had type 2 diabetes, and results were consistent regardless of the presence of type 2 diabetes.

A large recent meta-analysis (227) including data from EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, DELIVER, and Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes

Post Worsening Heart Failure (SOLOIST-WHF) included 21,947 patients and demonstrated reduced risk for the composite of cardiovascular death or hospitalization for heart failure, cardiovascular death, first hospitalization for heart failure, and all-cause mortality. The findings on the studied end points were consistent in both trials of heart failure with mildly reduced or preserved ejection fraction and in all five trials combined. Collectively, these studies indicate that SGLT2 inhibitors reduce the risk for heart failure hospitalization and cardiovascular death in a wide range of people with heart failure.

Additional data are accumulating regarding the effects of SGLT inhibition in people hospitalized for acute decompensated heart failure and in people with heart failure and HFpEF. As an example, the investigational SGLT1 and SGLT2 inhibitor sotagliflozin has also been studied in the SOLOIST-WHF trial (228). In SOLOIST-WHF, 1,222 people with type 2 diabetes who were recently hospitalized for worsening heart failure were randomized to sotagliflozin 200 mg once daily (with uptitration to 400 mg once daily if tolerated) or placebo either before or within 3 days after hospital discharge. Patients were eligible if hospitalized for signs and symptoms of heart failure (including elevated natriuretic peptide levels) requiring treatment with intravenous diuretic therapy. Exclusion criteria included end-stage heart failure or recent acute coronary syndrome or intervention, or an eGFR <30 mL/min/1.73 m^2). Patients were required to be clinically stable prior to randomization, defined as no use of supplemental oxygen, a systolic blood pressure ≥ 100 mmHg, and no need for intravenous inotropic or vasodilator therapy other than nitrates. Similar to SCORED, SOLOIST-WHF ended early due to a lack of funding, resulting in a change to the prespecified primary end point prior to unblinding to accommodate a lower than anticipated number of end point events. At a median follow-up of 9 months, the rate of primary end point events (the total number of cardiovascular deaths and hospitalizations and urgent visits for heart failure) was lower in the sotagliflozin group than in the placebo group (51.0 vs. 76.3; HR 0.67 [95% CI 0.52–0.85]; $P < 0.001$). No significant between-group differences were found in the rates of cardiovascular death or all-cause mortality. Both diarrhea (6.1%

vs. 3.4%) and severe hypoglycemia (1.5% vs. 0.3%) were more common with sotagliflozin than with placebo. The trial was originally also intended to evaluate the effects of SGLT inhibition in people with HFpEF, and ultimately no evidence of heterogeneity of treatment effect by ejection fraction was noted. However, the relatively small percentage of such patients enrolled (only 21% of participants had ejection fraction >50%) and the early termination of the trial limited the ability to determine the effects of sotagliflozin in HFpEF specifically.

In addition to the hospitalization and mortality benefit in people with heart failure, several recent analyses have addressed whether SGLT2 inhibitor treatment improves clinical stability and functional status in individuals with heart failure. In 3,730 patients with NYHA class II–IV heart failure with an ejection fraction of ≤ 40%, treatment with empagliflozin reduced the combined risk of death, hospitalization for heart failure, or an emergent/urgent heart failure visit requiring intravenous treatment and reduced the total number of hospitalizations for heart failure requiring intensive care, a vasopressor or positive inotropic drug, or mechanical or surgical intervention (229). In addition, patients treated with empagliflozin were more likely to experience an improvement in NYHA functional class (229). In people hospitalized for acute de novo or decompensated chronic heart failure, initiation of empagliflozin treatment during hospitalization reduced the primary outcome of a composite of death from any cause, number of heart failure events and time to first heart failure event, or a 5-point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score (230). Furthermore, PRESERVED-HF, a multicenter study (26 sites in the U.S.) showed that dapagliflozin treatment leads to significant improvement in both symptoms and physical limitation, as well as objective measures of exercise function in people with chronic HFpEF, regardless of diabetes status (198). Finally, canagliflozin improved heart failure symptoms assessed using the Kansas City Cardiomyopathy Questionnaire Total Symptom Score, irrespective of left ventricular ejection fraction or the presence of diabetes (231). Therefore, in people with type 2 diabetes and established HFpEF or HFrEF, an SGLT2 inhibitor with proven benefit in this patient population is recommended to reduce the risk

of worsening heart failure and cardiovascular death. In addition, an SGLT2 inhibitor is recommended in this patient population to improve symptoms, physical limitations, and quality of life. The benefits seen in this patient population likely represent a class effect, and they appear unrelated to glucose lowering given comparable outcomes in people with heart failure with and without diabetes.

Finerenone in People With Type 2 Diabetes and Chronic Kidney Disease

As discussed in detail in Section 11, "Chronic Kidney Disease and Risk Management," people with diabetes are at an increased risk for CKD, which increases cardiovascular risk (232). Finerenone, a selective nonsteroidal mineralocorticoid antagonist, has been shown in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial to improve CKD outcomes in people with type 2 diabetes with stage 3 or 4 CKD and severe albuminuria (233). In the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial, 7,437 patients with UACR 30–300 mg/g and eGFR 25–90 mL/min/1.73 m^2 or UACR 300–5,000 and eGFR ≥ 60 mL/min/1.73 m^2 on maximum dose of renin-angiotensin system blockade were randomized to receive finerenone or placebo (186). The HR of the primary outcome of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization from heart failure was reduced by 13% in patients treated with finerenone. A prespecified subgroup analysis from FIGARO-DKD further revealed that in patients without symptomatic HFrEF, finerenone reduces the risk for new-onset heart failure and improves heart failure outcomes in people with type 2 diabetes and CKD (187). Finally, in the pooled analysis of 13,026 people with type 2 diabetes and CKD from both FIDELIO-DKD and FIGARO-DKD, the HRs for the composite of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure as well as a composite of kidney failure, a sustained ≥ 57% decrease in eGFR from baseline over ≥ 4 weeks, or renal death were 0.86 and 0.77, respectively (188). These collective studies indicate that finerenone improves cardiovascular and renal outcomes in people with type 2 diabetes. Therefore, in people with type 2 diabetes and CKD with albuminuria treated with maximum tolerated doses of ACE
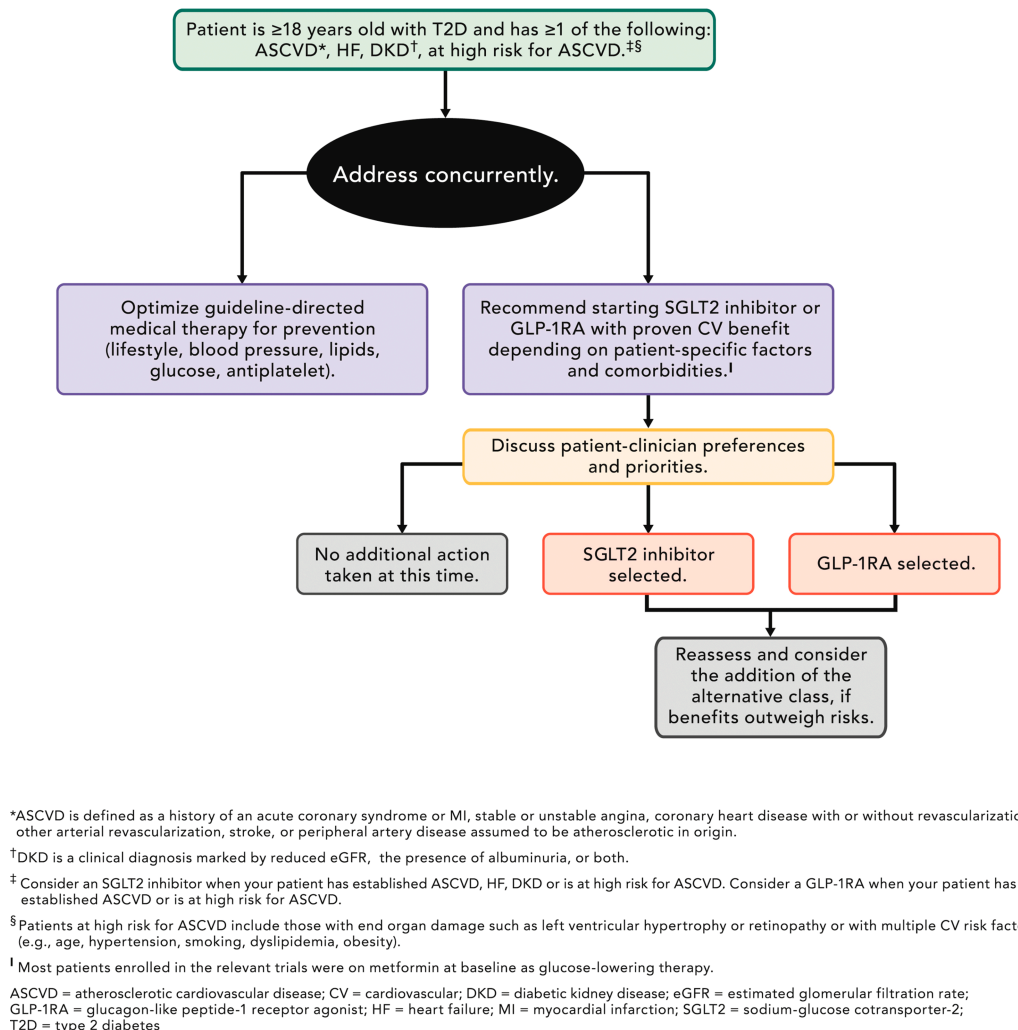
Figure 10.3—Approach to risk reduction with SGLT2 inhibitor or GLP-1 receptor agonist therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy. Reprinted with permission from Das et al. (234).

inhibitor or ARB, addition of finernone should be considered to improve cardiovascular outcomes and reduce the risk of CKD progression.

Clinical Approach

As has been carefully outlined in **Fig. 9.3** in the preceding Section 9, "Pharmacologic Approaches to Glycemic Treatment," people with type 2 diabetes with or at high risk for ASCVD, heart failure, or CKD should be treated with a cardioprotective SGLT2 inhibitor and/or GLP-1 receptor agonist as part of the comprehensive approach to cardiovascular and kidney risk reduction. Importantly, these agents should be included in the regimen of care irrespective of the need for additional glucose lowering, and irrespective of metformin use. Such an approach has also been described in the American Diabetes Association–endorsed American

College of Cardiology "2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes" (234). **Figure 10.3**, reproduced from that decision pathway, outlines the 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.

Adoption of these agents should be reasonably straightforward in people with established cardiovascular or kidney disease who are later diagnosed with diabetes, as the cardioprotective agents can be used from the outset of diabetes management. On the other hand, incorporation of SGLT2 inhibitor or GLP-1 receptor agonist therapy in the care of

individuals with more long-standing diabetes may be more challenging, particularly if patients are using an already complex glucose-lowering regimen. In such patients, SGLT2 inhibitor or GLP-1 receptor agonist therapy may need to replace some or all of their existing medications to minimize risks of hypoglycemia and adverse side effects, and potentially to minimize medication costs. Close collaboration between primary and specialty care professionals can help to facilitate these transitions in clinical care and, in turn, improve outcomes for highrisk people with type 2 diabetes.

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