10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2025

*American Diabetes Association Professional Practice Committee**

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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, an interprofessional 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) broadly refers to a history of acute coronary syndrome, myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease (PAD) including aortic aneurysm and is the leading cause of morbidity and mortality in people with diabetes (1). Diabetes itself confers independent ASCVD risk, and among people with diabetes, all major cardiovascular risk factors, including hypertension, hyperlipidemia, and obesity, are clustered and common (2). Numerous studies have shown the efficacy of managing individual cardiovascular risk factors in preventing or slowing ASCVD in people with diabetes. Furthermore, large benefits are seen when multiple cardiovascular risk factors (glycemic, blood pressure, and lipid management) are addressed simultaneously, with evidence for long-lasting benefits (3–5). Notably, most of the 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.

Under the current paradigm of comprehensive risk factor modification, cardiovascular morbidity and mortality have notably decreased in people with both type 1 and type 2 diabetes (1). In addition to the evidence from prospective intervention studies to support comprehensive ASCVD risk factor reduction, a large cohort study confirmed no or only marginally increased mortality, MI, and stroke risk compared with the general population when all major cardiovascular risk factors are managed to goal levels in people with type 2 diabetes (6). Despite these encouraging opportunities to reduce morbidity and mortality, cardiovascular risk factors are predicted to

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increase and only a minority of people with type 2 diabetes achieve recommended risk factor goals and are treated with guideline-recommended therapy (7–9). Therefore, continued focus on delivering high-quality comprehensive cardiovascular care and on addressing barriers to risk factor management are required to implement the treatment recommendations (1,10) outlined in this section.

Diabetes is also an important risk factor for incident heart failure, which is at least twofold more prevalent in people with diabetes compared with those without diabetes and is a major cause of morbidity and mortality (11). People with diabetes may present with a wide spectrum of heart failure, including heart failure with preserved ejection fraction (HFpEF), heart failure with mildly reduced ejection fraction (HFmEF), or heart failure with reduced ejection fraction (HFrEF) (12). Comorbid conditions including excess body weight and hypertension often precede the development of HFpEF and have been implicated in the pathophysiology of HFpEF (13). Coronary artery disease and prior MI are major risk factors and a cause of myocardial injury in ischemic heart disease leading to HFrEF. In addition, people with diabetes are at risk for developing structural heart disease and HFrEF in the absence of obstructive coronary artery disease (14). The pathophysiology of heart failure in people with diabetes and further details of screening, diagnosis, and treatment of people with heart failure and diabetes are also outlined in a previous consensus statement by the American Diabetes Association (ADA) (15).

There is an increasing appreciation of the common pathophysiology and interrelationship of cardiometabolic risk factors leading to both adverse cardiovascular and adverse kidney outcomes in people with diabetes, including ASCVD, heart failure, and chronic kidney disease (CKD) (16). These three comorbidities are frequently caused by metabolic risk, which is frequently driven by obesity and its associated risk factors, and the incidence of all three conditions rises with increasing A1C levels (17). Collectively, this combination of comorbidities has been termed cardiorenal metabolic disease or cardiovascular-kidney-metabolic health (18,19). Reasons to concurrently consider cardiovascular and kidney comorbidities in the management of people with diabetes include not only the common metabolic risk but also the major benefit observed across the spectrum of cardiovascular disease, heart failure, and renal outcomes in people with type 2 diabetes treated with sodium–glucose cotransporter 2 (SGLT2) inhibitors or glucagon-like peptide 1 receptor agonists (GLP-1 RAs). Therefore, in addition to the management of hyperglycemia, hypertension, and hyperlipidemia, treatment with SGLT2 inhibitors and/or GLP-1 RAs that have demonstrated benefit is considered a fundamental element of risk reduction and the pharmacological strategy to improve cardiovascular and kidney outcomes in people with type 2 diabetes (**Fig. 10.1**). In addition to the standards of care for the prevention and treatment of cardiovascular disease outlined below, the reader is referred to Section 9, "Pharmacologic Approaches to

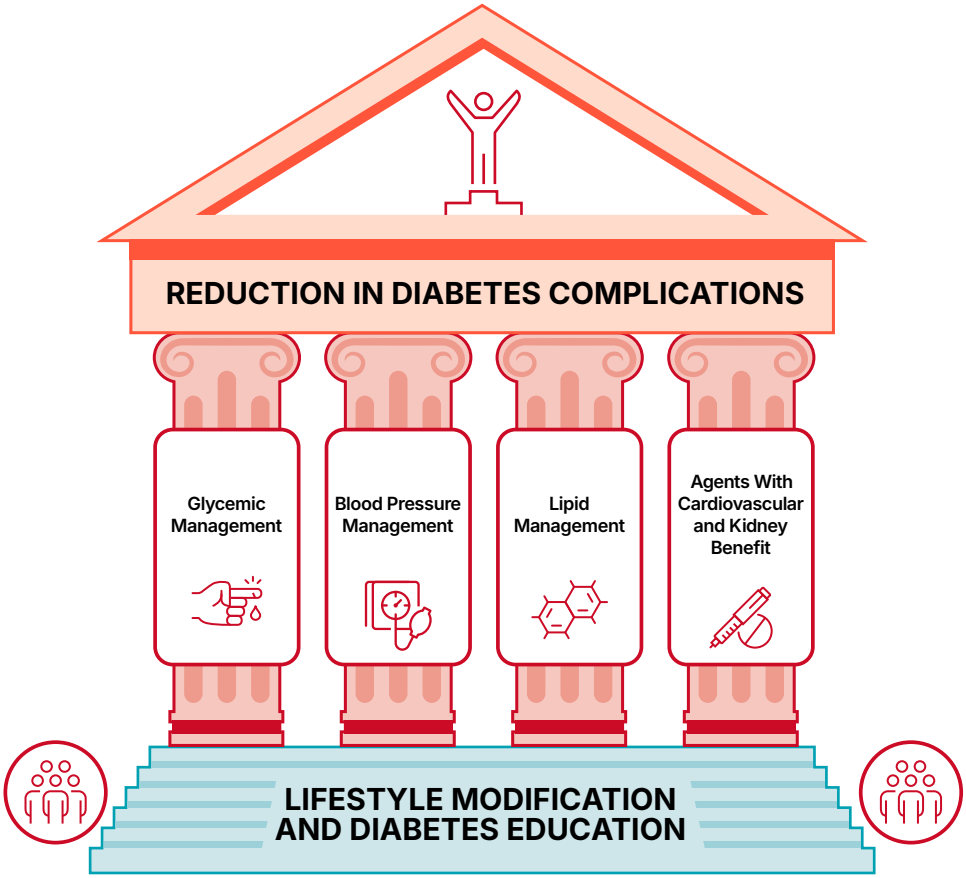


Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications.

Glycemic Treatment," and Section 11, "Chronic Kidney Disease and Risk Management," for a comprehensive review of pharmacological management of hyperglycemia and kidney benefit from SGLT2 inhibitors and GLP-1 RAs.

HYPERTENSION AND BLOOD PRESSURE MANAGEMENT

An elevated blood pressure is defined as a systolic blood pressure 120–129 mmHg and a diastolic blood pressure <80 mmHg (20). Hypertension is defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥80 mmHg (20). This is in agreement with the definition of hypertension by the American College of Cardiology and American Heart Association (20). Hypertension is common among people with either type 1 or type 2 diabetes. Hypertension is a major risk factor for ASCVD, heart failure, and microvascular complications. Moreover, numerous studies have shown that antihypertensive therapy reduces ASCVD events, heart failure, and microvascular complications. Please refer to the ADA position statement "Diabetes and Hypertension" for a detailed review of the epidemiology, diagnosis, and treatment of hypertension (21) and hypertension guideline recommendations (22–25).

Screening and Diagnosis

Recommendations

10.1 Blood pressure should be measured at every routine clinical visit, or at least every 6 months. Individuals found to have elevated blood pressure without a diagnosis of hypertension (systolic blood pressure 120–129 mmHg and diastolic blood pressure <80 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. **A** Hypertension is defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥80 mmHg based on an average of two or more measurements obtained on two or more occasions. **A** Individuals with blood pressure ≥180/110 mmHg and cardiovascular disease could be diagnosed with hypertension at a single visit. **E**

10.2 Counsel all people with hypertension and diabetes to monitor their blood pressure at home after appropriate education. **A**

Blood pressure should be measured at every routine clinical visit by a trained individual who 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 (26). Individuals identified to have elevated blood pressure or hypertension should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. However, in individuals with cardiovascular disease and blood pressure ≥180/110 mmHg, it is reasonable to diagnose hypertension at a single visit (22). Postural changes in blood pressure and pulse may be evidence of autonomic neuropathy and therefore require adjustment of blood pressure goals. 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 (27,28). In addition to confirming or refuting a diagnosis of hypertension, home blood pressure assessment may be useful to monitor antihypertensive treatment. A systematic review and meta-analysis of prospective studies concluded that blood pressure measurements from either 24-h ambulatory or home blood pressure measurements can predict cardiovascular risk (27–29). Moreover, home blood pressure monitoring may improve medication-taking behavior and thus help reduce cardiovascular risk (30).

Treatment Goals

Recommendations

10.3 For people with diabetes and hypertension, blood pressure goals should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and individual preferences. **B**

10.4 The on-treatment blood pressure goal is <130/80 mmHg, if it can be safely attained. **A**

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 deintensified for blood pressure <90/60 mmHg. **E** A blood pressure goal 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 (31–37). 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 achieving 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 (21), the International Society of Hypertension, and Europe European Society of Cardiology/European Society of Hypertension Blood Pressure/Hypertension Guidelines (24). The committee's recommendation for the blood pressure goal 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 goal systolic blood pressure of <120 mmHg decreases cardiovascular event rates by 25% in high-risk individuals, although people with diabetes were excluded from this trial (38). The 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 systolic blood pressure goal of <130 mmHg (39). While the ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial

(ACCORD BP) did not confirm that aiming for a systolic blood pressure <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 (40). The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial revealed that treatment with perindopril and 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 (41). Therefore, it is recommended that people with diabetes who have hypertension should be treated to blood pressure goals of <130/80 mmHg. Notably, there is an absence of high-quality data available to guide blood pressure goals in people with type 1 diabetes, but a similar blood pressure goal of <130/80 mmHg is recommended in people with type 1 diabetes. As discussed below, treatment should be individualized, and treatment goals should not be set to achieve <120/80 mmHg, as a mean achieved blood pressure <120/80 mmHg is associated with adverse events. For more information on individualized blood pressure goals in older individuals, please see Section 13, "Older Adults."

Randomized Controlled Trials of Intensive Versus Standard Blood Pressure Management

SPRINT provides the strongest evidence to support lower blood pressure goals in individuals at increased cardiovascular risk, although this trial excluded people with diabetes (38). The trial enrolled 9,361 individuals with a systolic blood pressure of ≥130 mmHg and increased cardiovascular risk and treated to a systolic blood pressure goal of <120 mmHg (intensive treatment) versus a goal of <140 mmHg (standard treatment). The primary composite outcome of 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 (AKI), 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 management in people with type 2 diabetes (40). In the study, a total of 4,733 individuals with type 2 diabetes were assigned to intensive therapy (aiming for a systolic blood pressure <120 mmHg) or standard therapy (aiming for a systolic blood pressure <140 mmHg). The mean achieved systolic blood pressures were 119 mmHg and 133 mmHg in the intensive and standard groups, 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.

Of note, the ACCORD BP and SPRINT trials aimed for 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 the two trials, but ACCORD BP was viewed as underpowered due to the composite primary end point being less sensitive to blood pressure regulation (38,40).

The more recent STEP trial assigned 8,511 individuals aged 60–80 years with hypertension to a systolic blood pressure goal of 110 to <130 mmHg (intensive treatment) or a goal of 130 to <150 mmHg (37). 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 occurred in 3.5% of individuals in the intensive treatment group versus 4.6% in the standard treatment group (hazard ratio [HR] 0.74 [95% CI 0.60–0.92]; $P = 0.007$). In this trial, 18.9% of individuals 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. For more information on hypotensive events in older adults, please see Section 13, "Older Adults."

In ADVANCE, 11,140 people with type 2 diabetes were randomized to receive either treatment with a fixed combination of perindopril and indapamide or matching placebo (41). The primary end point, a composite of cardiovascular death, nonfatal stroke or MI, or new or worsening renal or 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 individuals and aimed for a diastolic blood pressure <90 mmHg, <85 mmHg, or <80 mmHg (42). 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 goals (≤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 goal diastolic blood pressure of <80 mmHg compared with a goal diastolic blood pressure of <90 mmHg.

Meta-analyses of Trials

To clarify optimal blood pressure goals 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 intensive blood pressure management, allocation to a tighter blood pressure management significantly reduced the risk of stroke by 31% but did not reduce the risk of MI (43). Another meta-analysis of 19 trials that included 44,989 individuals 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 (37). 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 (35). 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 (20,31,32,34–36). 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. A recent systematic review and meta-analysis of nine trials enrolling 11,005 participants with type 2 diabetes reported that intensive blood pressure lowering resulted in a reduction in risk of stroke (risk ratio 0.64 [95% CI 0.52–0.79]) and macroalbuminuria (0.77 [0.63–0.93) with a posttreatment blood pressure of 125/73 mmHg, suggesting that blood pressure goals could be lowered from the current recommendations of 130/80 mmHg if tolerated (44).

Individualization of Treatment Goals

People with diabetes and clinicians should engage in a shared decision-making process to determine individual blood pressure goals (20). This approach acknowledges that the benefits and risks of intensive blood pressure goals are uncertain and may vary across individuals and is consistent with a person-focused approach to care that values individual priorities and health care professional judgment (45). Secondary analyses of ACCORD BP and SPRINT suggest that clinical factors can help identify individuals more likely to benefit from and less likely to be harmed by intensive blood pressure management (46,47).

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 (47,48). Extrapolation of these studies suggests that people with diabetes may also be more likely to benefit from intensive blood pressure management 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 goal of <130/80 mmHg for all people, with or without diabetes (21).

Potential adverse effects of antihypertensive therapy (e.g., hypotension, syncope, falls, AKI, and electrolyte abnormalities) should also be taken into account (38,40,49,50). Older individuals and those with CKD and frailty have been shown to be at higher risk of adverse effects of intensive blood pressure management (49). In addition, individuals with orthostatic hypotension, substantial comorbidity, functional limitations, or polypharmacy may be at high risk of adverse effects, and some individuals may prefer higher blood pressure goals to enhance quality of life. However, ACCORD BP demonstrated that intensive blood pressure lowering decreased the risk of cardiovascular events irrespective of baseline diastolic blood pressure in individuals who also received standard glycemic management (51). 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 2018 Cochrane systematic review of antihypertensive therapy for mild to moderate chronic hypertension included 63 trials and over 5,909 women and suggested that antihypertensive therapy probably reduces the risk of developing severe hypertension but may not affect the risk of fetal or neonatal death, small-for-gestational-age babies, or preterm birth (52). The Control of Hypertension in Pregnancy Study (CHIPS) (53) enrolled mostly women with chronic hypertension. In CHIPS, aiming for 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 aiming for 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 (54).

The more recent Chronic Hypertension and Pregnancy (CHAP) trial assigned pregnant individuals with mild chronic hypertension to antihypertensive medications to achieve 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) (55). The primary outcome, a composite of preeclampsia with severe features, medically indicated preterm birth at <35 weeks of gestation, placental abruption, or fetal or neonatal death, occurred in 30.2% of female participants in the active treatment group versus 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. There are subtle difference in recommendations by different guidelines; however, internationally, the majority of hypertension societies endorse a more aggressive approach, recommending therapy when blood pressure is ≥140/90 mmHg and attaining a therapeutic goal of 130/80 mmHg (56).

Current evidence supports managing blood pressure to 110–135/85 mmHg to reduce the risk of accelerated maternal hypertension and to minimize impairment of fetal growth. During pregnancy, treatment with ACE inhibitors, angiotensin receptor blockers (ARBs), direct renin inhibitors, mineralocorticoid receptor antagonists (MRAs), and neprilysin inhibitors 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 or ARB, renin inhibitor, MRA, or neprilysin inhibitor 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 hydralazine may be considered in the acute management of hypertension in pregnancy or severe preeclampsia (56). Diuretics are not recommended for blood pressure management in pregnancy but may be used during late-stage pregnancy if needed for volume management (56). 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 7–10 days postpartum. Long-term follow-up is recommended for these individuals, as they have increased lifetime cardiovascular risk (57). 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, smoking cessation, 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 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) (58), and increasing activity levels (59) (see Section 5, "Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes"). A systematic review of 10 randomized controlled trials reported that compared with control diet, the modified Dietary Approaches to Stop Hypertension (DASH) eating pattern could reduce mean systolic (−3.26 mmHg [95% CI −5.58 to −0.94 mmHg]; P = 0.006) and diastolic (−2.07 mmHg [95% CI −3.68 to −0.46 mmHg]; P = 0.01) blood pressure (60).

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**) (59). A lifestyle therapy plan should be developed in collaboration with the person with diabetes 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 (61,62).

Pharmacologic Interventions

Recommendations

10.7 In individuals with confirmed office-based blood pressure ≥130/80 mmHg, pharmacologic therapy should be initiated and titrated to achieve the recommended blood pressure goal of <130/80 mmHg. **A**

10.8 Individuals with confirmed office-based blood pressure ≥150/90 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 (ARBs) 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 goals. Avoid combinations of ACE inhibitors and ARBs and combinations of ACE inhibitors or ARBs (including ARBs and neprilysin inhibitors) with direct renin inhibitors. **A**

10.11 An ACE inhibitor or ARB, 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 Monitor for increased serum creatinine and for increased serum potassium levels when ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists (MRAs) are used, for hypokalemia when diuretics are used at routine visits, and 7–14 days after initiation or after a dose change. **B**

10.13 ACE inhibitors, angiotensin receptor blockers, MRAs, direct renin inhibitors, and neprilysin inhibitors should be avoided in sexually active individuals of childbearing potential who are not using reliable contraception and are contraindicated in pregnancy. **A**

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 150/90 mmHg may begin with a single drug. For individuals with blood pressure ≥150/90 mmHg, initial pharmacologic treatment with two antihypertensive medications is recommended to more effectively achieve blood pressure goals (63–65). Single-pill antihypertensive combinations may improve medication taking in some individuals (66).

Classes of Antihypertensive Medications. Initial treatment for hypertension should include any of the drug classes demonstrated to reduce cardiovascular events in people with diabetes (25): ACE inhibitors (67,68), ARBs (67,68), thiazide-like diuretics (69), or dihydropyridine calcium channel blockers (70). In people with diabetes and established coronary artery disease, ACE inhibitors or ARBs are recommended first-line therapy for hypertension (71–73). For individuals 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 (21) (**Fig. 10.2**). In individuals

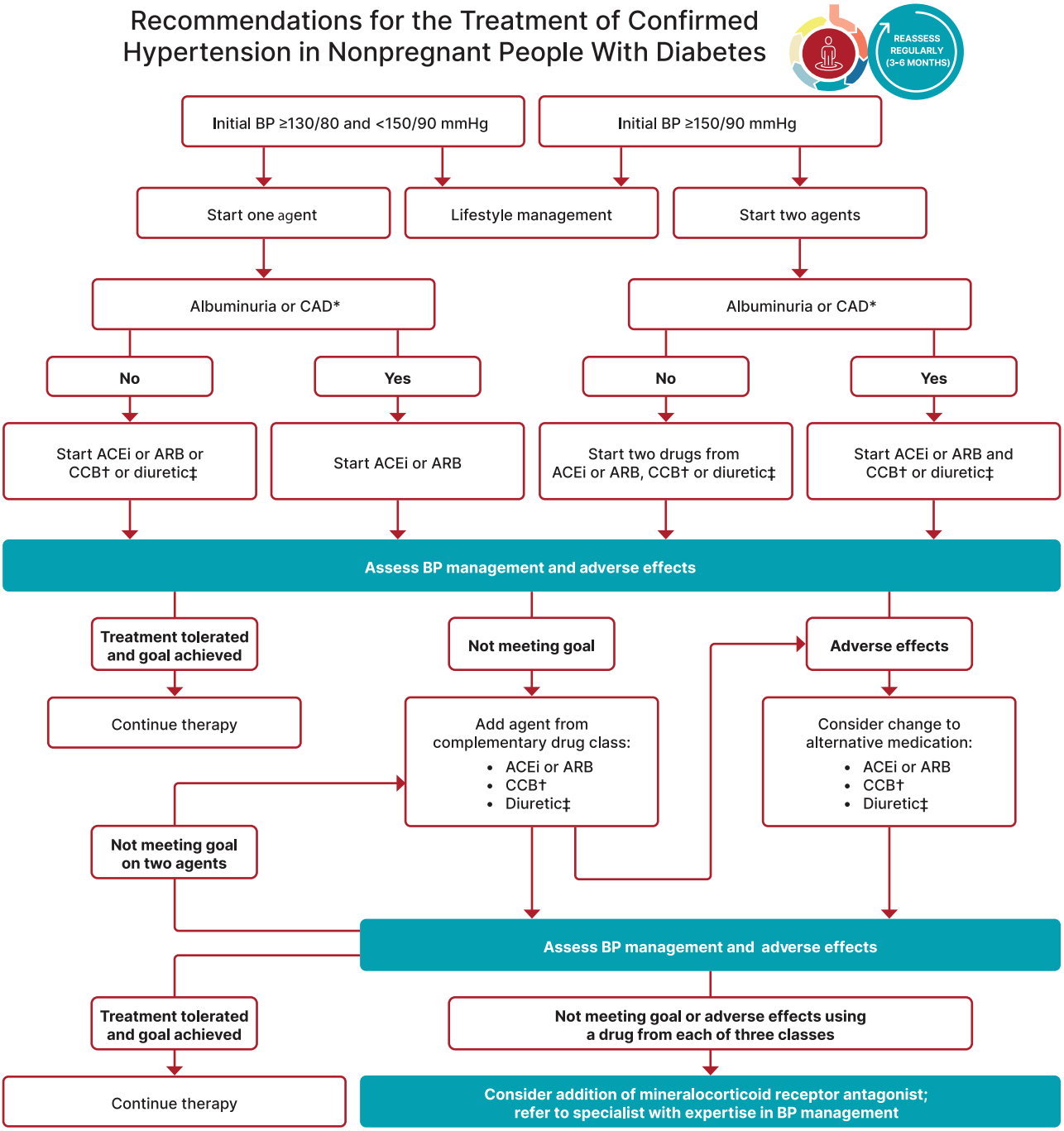


Figure 10.2—Recommendations for the treatment of confirmed hypertension in nonpregnant people with diabetes. *An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested for the treatment of hypertension in people with coronary artery disease (CAD) or urine albumin-to-creatinine ratio 30–299 mg/g creatinine and is strongly recommended for individuals with urine albumin-to-creatinine ratio ≥300 mg/g creatinine. †Dihydropyridine calcium channel blocker (CCB). ‡Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. BP, blood pressure. Adapted from de Boer et al. (21).

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 (74). 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 compared with thiazide-like diuretics or dihydropyridine calcium channel blockers (75). 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 (33,76,77).

Multiple-Drug Therapy. Multiple-drug therapy is often required to achieve blood pressure goals (**Fig. 10.2**), particularly in the setting of CKD in people with diabetes. 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 AKI (78–80). 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 goals.

Bedtime Dosing. Although prior analyses of randomized clinical trials found a benefit to evening versus morning dosing of antihypertensive medications (81,82), these results have not been reproduced in subsequent trials. Therefore, preferential use of antihypertensives at bedtime is not recommended (83).

Hyperkalemia and Acute Kidney Injury. Treatment with ACE inhibitors and ARBs or MRAs can cause AKI and hyperkalemia, while diuretics can cause AKI and either hypokalemia or hyperkalemia (depending on mechanism of action) (84,85). Detection and management of these abnormalities is important because AKI and hyperkalemia each increase the risks of cardiovascular events and death (86). Therefore, serum creatinine and potassium should be monitored after initiation of treatment with an ACE inhibitor or ARB, MRA, or diuretic and monitored during treatment and following uptitration of these medications, particularly among individuals with reduced glomerular filtration who are at increased risk of hyperkalemia and AKI (84,85,87).

Resistant Hypertension

Recommendation

10.14 Individuals with hypertension who are not meeting blood pressure goals on three classes of antihypertensive medications (including a diuretic) should be considered for MRA 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 primary and secondary hypertension. Difficulty following the care plan may also be a reason for resistant hypertension. International Society of Hypertension guidelines put a strong emphasis on screening for care plan difficulties in management of hypertension and recommend using objective measures such as review of pharmacy records, pill counting, and the chemical analysis of blood or urine rather than subjective methods of detecting inconsistencies in care plan engagement in routine clinical practice. However, this may not be feasible in all practice settings (22).

People with diabetes and confirmed resistant hypertension should be evaluated for secondary causes of hypertension, including primary hyperaldosteronism, renal artery stenosis, CKD, and obstructive sleep apnea. In general, barriers to medication taking (such as cost and side effects) should be identified and addressed (**Fig. 10.2**). MRAs, 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 (88). In addition, MRAs reduce albuminuria in people with diabetic nephropathy (89–91). However, adding an MRA to a treatment plan that includes an ACE inhibitor or ARB may increase the risk for hyperkalemia, emphasizing the importance of regular monitoring for serum creatinine and potassium in these individuals, and long-term outcome studies are needed to better evaluate the role of MRAs in blood pressure management.

LIPID MANAGEMENT

Lifestyle Intervention

Recommendations

10.15 Lifestyle modification focusing on weight loss (if indicated); application of a Mediterranean or DASH eating pattern; reduction of saturated fat and *trans* fat; increase of dietary n-3 fatty acids, viscous fiber, and plant stanol and sterol intake; and increased physical activity should be recommended to improve the lipid profile and reduce the risk of developing atherosclerotic cardiovascular disease (ASCVD) in people with diabetes. **A**

10.16 Intensify lifestyle therapy and optimize glycemic management for people with diabetes 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 and <50 mg/dL [<1.3 mmol/L] for women). **C**

Lifestyle intervention, including weight loss in people with overweight or obesity (when appropriate) (19,92), increased physical activity, and medical nutrition therapy, allows some individuals to reduce ASCVD risk factors. Nutrition intervention should be tailored according to each person's age, pharmacologic treatment, lipid levels, and medical conditions.

Recommendations should focus on application of a Mediterranean (93) or DASH eating pattern, reducing saturated and *trans* fat intake, and increasing plant stanol and sterol, n-3 fatty acid, and viscous fiber (such as in oats, legumes, and citrus) intake (19,92). Glycemic management may also beneficially modify plasma lipid levels, particularly in people with very high triglycerides and poor glycemic management. 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

10.17 In adults with prediabetes or diabetes not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diagnosis, at an initial medical evaluation, annually thereafter, or more frequently if indicated. **E**

10.18 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 facilitates monitoring the response to therapy and informs medication-taking behavior. **A**

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 individuals <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 an individual is taking a statin, LDL cholesterol levels should be assessed 4–12 weeks after initiation of statin therapy, after any change in dose, and annually (e.g., to monitor for medication taking and efficacy). Monitoring lipid profiles after initiation of statin therapy and during therapy increases the likelihood of dose titration and following the statin treatment plan (94–96). If LDL cholesterol levels are not responding despite medication taking, clinical judgment is recommended to determine the need for and timing of lipid panels. In individuals, the highly variable LDL cholesterol-lowering response seen with statins is poorly understood (97). 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 (98).

STATIN TREATMENT

Primary Prevention

Recommendations

10.19 For people with diabetes aged 40–75 years without ASCVD, use moderate-intensity statin therapy in addition to lifestyle therapy. **A**

10.20 For people with diabetes aged 20–39 years with additional ASCVD risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy. **C**

10.21 For people with diabetes aged 40–75 years at higher cardiovascular risk, including those with one or more additional ASCVD risk factors, high-intensity statin therapy is recommended to reduce LDL cholesterol by ≥50% of baseline and to obtain an LDL cholesterol goal of <70 mg/dL (<1.8 mmol/L). **A**

10.22 For people with diabetes aged 40–75 years at higher cardiovascular risk, especially those with multiple additional ASCVD risk factors and an LDL cholesterol ≥70 mg/dL (≥1.8 mmol/L), it may be reasonable to add ezetimibe or a PCSK9 inhibitor to maximum tolerated statin therapy. **B**

10.23 In adults with diabetes aged >75 years already on statin therapy, it is reasonable to continue statin treatment. **B**

10.24 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**

10.25 In people with diabetes intolerant to statin therapy, treatment with bempedoic acid is recommended to reduce cardiovascular event rates as an alternative cholesterol-lowering plan. **A**

10.26 In most circumstances, lipid-lowering agents should be stopped prior to conception and avoided in sexually active individuals of childbearing potential who are not using reliable contraception. **B** In some circumstances (e.g., for individuals with familial hypercholesterolemia or prior ASCVD event), statin therapy may be continued when the benefits outweigh risks. **E**

Secondary Prevention

Recommendations

10.27 For people of all ages with diabetes and ASCVD, high-intensity statin therapy should be added to lifestyle therapy. **A**

10.28 For people with diabetes and ASCVD, treatment with high-intensity statin therapy is recommended to obtain an LDL cholesterol reduction of ≥50% from baseline and an LDL cholesterol goal of <55 mg/dL (<1.4 mmol/L). 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**

10.29a For individuals who do not tolerate the intended statin intensity, the maximum tolerated statin dose should be used. **E**

10.29b For people with diabetes and ASCVD intolerant to statin therapy, PCSK9 inhibitor therapy with monoclonal antibody treatment, **A** bempedoic acid therapy, **A** or PCSK9 inhibitor therapy with inclisiran siRNA **E** should be considered as an alternative cholesterol-lowering therapy.

Initiating Statin Therapy

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 coronary heart disease (CHD) (99,100). Subgroup analyses of people with diabetes in larger trials (101–105) and trials in people with diabetes (106,107) showed significant primary and secondary prevention of ASCVD events and CHD death in people with diabetes. Meta-analyses including data from >18,000 people with diabetes from 14 randomized trials of statin therapy (mean follow-up 4.3 years) demonstrated 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 (108). 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 (108). It is important to note that the effects of statin therapy do not differ based on sex (109).

Accordingly, statins are the drugs of choice for LDL cholesterol lowering and cardioprotection. **Table 10.1** shows the two statin dosing intensities that are

Table 10.1—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	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 1–4 mg

Once-daily dosing. XL, extended release.

recommended for use in clinical practice. High-intensity statin therapy will achieve an approximately ≥50% reduction in LDL cholesterol, and moderate-intensity statin plans 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 an individual can tolerate. For individuals 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 (110,111). The relative benefit of lipid-lowering therapy has been uniform across most subgroups tested (100,108), 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 (19,112,113), although high-intensity therapy should be considered in the context of additional ASCVD risk factors (**Fig. 10.3**). 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, individuals 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 obtain an LDL cholesterol of <70 mg/dL (<1.8 mmol/L) (114–116). 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 goal of <70 mg/dL (<1.8 mmol/L) rather than 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 goal of <70 mg/dL (<1.8 mmol/L) (117). While there are no randomized controlled trials specifically assessing cardiovascular outcomes of adding ezetimibe or PCSK9 inhibitors to statin therapy in primary prevention, a portion of the participants without established cardiovascular disease were included in some studies, which also included participants with established cardiovascular disease. A meta-analysis suggests that there is a cardiovascular benefit of adding ezetimibe or PCSK9 inhibitors to treatment for people at high risk (118). There is less evidence for individuals 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 (100,107,108), and because older age confers higher risk, the absolute benefits are actually greater (100,119). 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.

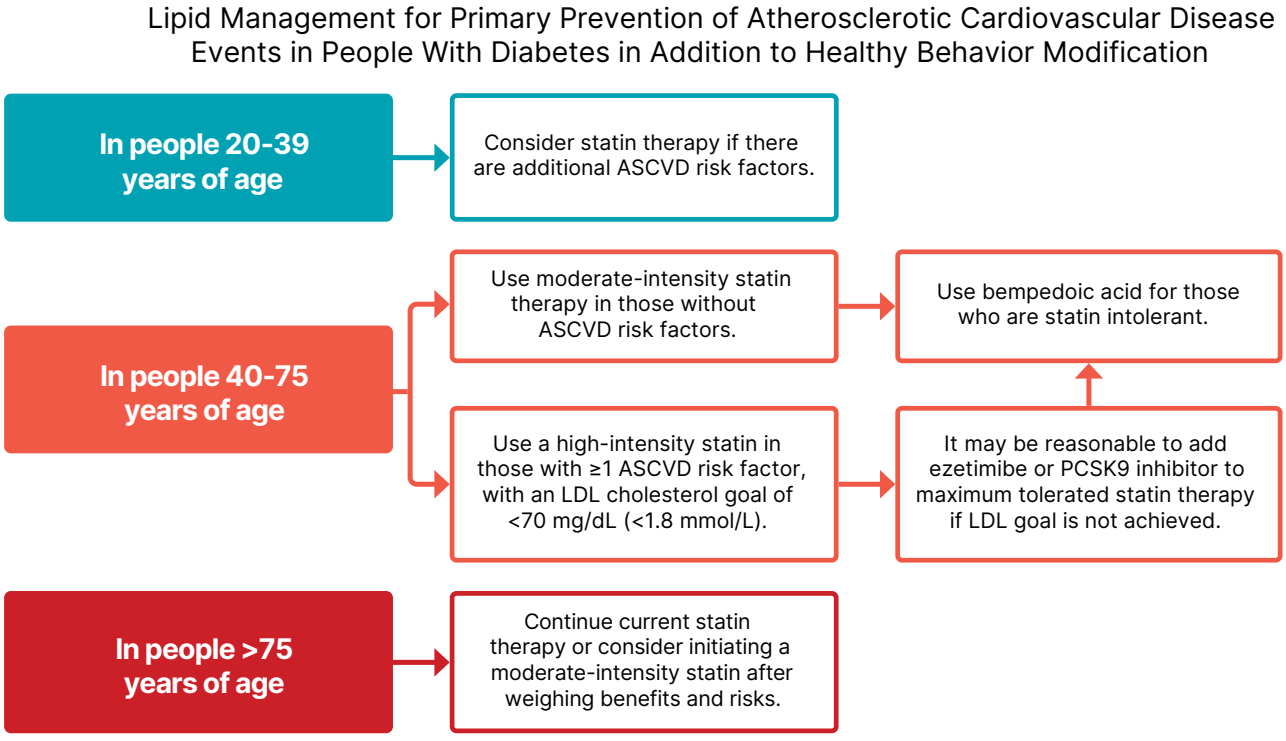


Figure 10.3—Recommendations for primary prevention of atherosclerotic cardiovascular disease (ASCVD) in people with diabetes using cholesterol-lowering therapy. Adapted from *"Standards of Care in Diabetes—2024* Abridged for Primary Care Professionals" (325).

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 reduction in risk proportionately similar, although not statistically significant, to that in people with type 2 diabetes (102). 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. Individuals <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 experiencing 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 individual 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" (120) for additional discussion.

Secondary Prevention (People With ASCVD)

Intensive therapy is indicated because cardiovascular event rates are increased in people with diabetes and established ASCVD, and it has been shown to be of benefit in multiple large meta-analyses and randomized cardiovascular outcomes trials (99,100,108,119,121). High-intensity statin therapy is recommended for all people with diabetes and ASCVD to obtain an LDL cholesterol reduction of ≥50% from baseline and an LDL cholesterol goal of <55 mg/dL (<1.4 mmol/L) (**Fig. 10.4**). The 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 (99). The Cholesterol Treatment Trialists' Collaboration, involving 26 statin trials, of which 5 compared high-intensity versus moderate-intensity statins, showed a 21% reduction in major cardiovascular events in people with diabetes for every 39 mg/dL (1 mmol/L) of LDL cholesterol lowering, irrespective of baseline LDL cholesterol or individual characteristics (108). The evidence to support lower LDL cholesterol goals in people with diabetes and established cardiovascular disease derives from multiple large, randomized trials investigating the benefits of adding nonstatin agents to statin therapy, including combination treatment with statins and ezetimibe (119,122) or PCSK9 inhibitors (121,123–125). Each trial found a large benefit in reducing ASCVD events that was directly related to the degree of further LDL cholesterol lowering. A large number of participants with diabetes were included in these trials, and prespecified analyses were completed to evaluate cardiovascular outcomes in people with and without diabetes (122,124,125). The decision to add a nonstatin agent should be made following a discussion between a clinician and a person with diabetes about the net benefit, safety, and cost of combination therapy.

Combination Therapy for LDL Cholesterol Lowering

Statins and Ezetimibe

The best evidence for combination therapy of statins and ezetimibe comes from the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). The trial showed the addition of ezetimibe to a moderate-intensity statin 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 (119). A subanalysis of participants with diabetes (27% of the 18,144 participants) showed a significant reduction of major adverse cardiovascular events with the combination treatment over moderate-intensity statin alone (122).

Statins and PCSK9 Inhibitors

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% (126,127). No cardiovascular outcome trials have been performed to assess whether PCSK9 inhibitor therapy reduces ASCVD event rates in individuals at low or moderate risk for ASCVD (primary prevention). The evidence on the effect of PSCK9 inhibition on ASCVD outcomes is from studies of treatment with the monoclonal antibodies alirocumab and evolocumab. When added to a maximally tolerated statin, these agents reduced LDL cholesterol by ~60% (121) and significantly reduced the risk of major adverse cardiovascular events by 15–20% in the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) (evolocumab) and ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trials (121,123,128). In the subanalyses of the participants with diabetes (40% in FOURIER and 28.8% in ODYSSEY OUTCOMES), similar benefits were seen compared with those for individuals without diabetes in FOURIER (125), whereas a greater absolute

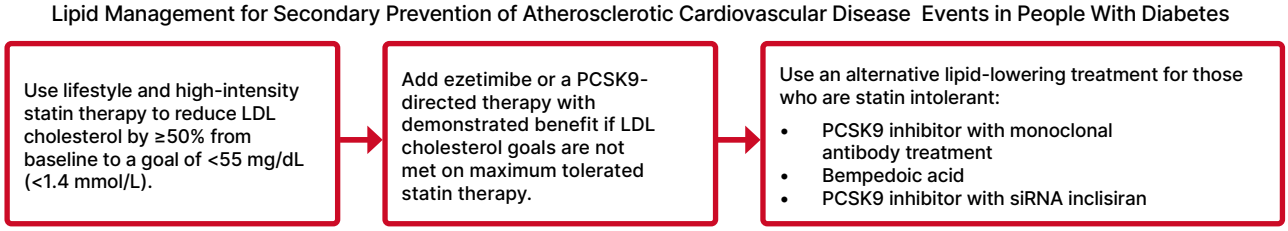


Figure 10.4—Recommendations for secondary prevention of atherosclerotic cardiovascular disease (ASCVD) in people with diabetes using cholesterol-lowering therapy. Adapted from *"Standards of Care in Diabetes—2024* Abridged for Primary Care Professionals" (325).

reduction was seen for participants with diabetes (2.3% [95% CI 0.4–4.2]) than for those with prediabetes (1.2% [0.0–2.4]) or normoglycemia (1.2% [−0.3 to 2.7]) in the ODYSSEY OUTCOMES trial (124).

In addition to the monoclonal antibodies, an siRNA, inclisiran, which also targets PSCK9, has demonstrated the ability to reduce LDL cholesterol by 49–52% in trials evaluating individuals with established cardiovascular disease or ASCVD risk equivalent (129). 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 an exploratory analysis, the prespecified cardiovascular end point of nonadjudicated cardiovascular events, including cardiac death, signs or symptoms of cardiac arrest, nonfatal MI, or stroke, occurred less frequently with inclisiran than placebo (7.4% vs. 10.2% in one trial and 7.8% vs. 10.3% in another trial). Cardiovascular outcome trials using inclisiran in people with established cardiovascular disease (130,131) and for primary prevention in those at high risk for cardiovascular disease (132) are currently ongoing.

Intolerance to Statin Therapy

Statin therapy is a hallmark approach to cardiovascular prevention and treatment; however, a subset of individuals experience partial (inability to tolerate sufficient dosage necessary to achieve therapeutic objectives due to adverse effects) or complete (inability to tolerate any dose) intolerance to statin therapy (133). Although the definition of statin intolerance differs between organizations and across clinical study methods, these individuals will require an alternative treatment approach. Initial steps in people intolerant to statins may include switching to a different high-intensity statin if a high-intensity statin is indicated, switching to moderate-intensity or low-intensity statin, lowering the statin dose, or using nondaily dosing with statins. While considering these alternative treatment plans, the addition of nonstatin treatment plans to maximum tolerated statin therapy should be considered, as these are frequently associated with improved medication-taking behavior and achievement of LDL cholesterol goals (133).

PCSK9-Directed Therapies

The PCSK9 monoclonal antibodies alirocumab and evolocumab both have been shown to be effective for LDL cholesterol reduction and fewer skeletal muscle–related adverse effects when studied in populations considered statin intolerant. The Study of Alirocumab in Patients With Primary Hypercholesterolemia and Moderate, High, or Very High Cardiovascular Risk, Who Are Intolerant to Statins (ODYSSEY ALTERNATIVE) trial studied the reduction in LDL cholesterol with alirocumab compared with ezetimibe or 20 mg atorvastatin in individuals at moderate to very high cardiovascular risk for 24 weeks. The proportion of the study population with type 2 diabetes was ∼24%. After the 24 weeks, alirocumab lowered LDL cholesterol levels by 54.8% versus 20.1% with ezetimibe. There were similar rates of any adverse event for all treatments; however, fewer events that led to treatment discontinuation and few skeletal muscle–related adverse events occurred with alirocumab (134).

The Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 1, 2, and 3 (GAUSS 1, 2, and 3) trials, as well as the Open-Label Study of Long-term Evaluation Against LDL Cholesterol (OSLER) open-label extension of the GAUSS 1 and 2 trials, evaluated the safety and LDL cholesterol reduction of evolocumab plus ezetimibe compared with ezetimibe alone in individuals with statin intolerance.

Reductions in LDL cholesterol ranged from 55% and 56% for evolocumab biweekly and monthly plus daily oral placebo, respectively, to 19% and 16% for ezetimibe daily plus biweekly or monthly subcutaneous placebo, respectively. Fewer musculoskeletal adverse effects occurred in those treated with evolocumab or ezetimibe than in those treated with ezetimibe plus placebo, although rates of discontinuation due to these effects were similar. Use of low-dose statins was allowed in these studies and was associated with an increase in the incidence of musculoskeletal adverse effects (135,136). Similar LDL cholesterol reductions were demonstrated in the GAUSS 3 trial after 24 weeks (54.5% with evolocumab compared with 16.7% with ezetimibe), with slightly higher rates of musculoskeletal adverse events (20.7% with evolocumab and 28.8% with ezetimibe). The higher rates of these adverse events may be due in part to the first phase of this trial, which randomized individuals to a statin rechallenge with either atorvastatin or placebo (137).

Inclisiran has also been proposed as an option for individuals with statin intolerance. Although most of the individuals in studies of inclisarin were on statin therapy, one short-term study (Trial to Evaluate the Effect of ALN-PCSSC Treatment on Low-density Lipoprotein Cholesterol [ORION-1]) included individuals with documented statin intolerance (138) and could continue into an open-label extension trial (Extension Trial of Inclisiran in Participants With Cardiovascular Disease and High Cholesterol [ORION-3]), where an LDL cholesterol reduction of ∼45% was maintained through the end of year 4 (139). It is important to note that of the ORION-3 participants, only 23% had diabetes and 33% were not taking statin therapy. Although it may be expected that those with statin intolerance experienced a response similar to the response of those on statin therapy, evaluation of response based on background lipid-lowering therapy was not described.

Bempedoic Acid

Bempedoic acid, a novel LDL cholesterol–lowering agent acting in the same pathway as statin but without activity in skeletal muscle, which limits the muscle-related adverse effects, lowers LDL cholesterol levels by 15% for those on statins and 24% for those not taking statins (140). Use of this agent with ezetimibe results in an additional 19% reduction in LDL cholesterol (140). The Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid or Placebo (CLEAR Outcomes) trial found a reduction in four-point major adverse cardiovascular events by 13% compared with placebo for individuals with established ASCVD (70% of population) or at high risk for ASCVD (30% of population) and considered to be intolerant to statin therapy. It is important to note that ∼19% of individuals were on very-low-dose statin therapy at baseline (141). Prespecified subanalyses evaluated the impact for individuals with diabetes and showed a 17% reduction in four-point major adverse cardiovascular events when treated with bempedoic acid (142). For individuals requiring primary prevention, the use of bempedoic acid resulted in a 30% reduction in primary composite outcome compared with placebo (143).

Lipid-Lowering Care Considerations for Individuals of Childbearing Potential

Individuals of childbearing potential are less likely to be treated with statins or achieve their LDL cholesterol goals based on their cardiovascular risk (144–146). This is likely related to concerns and lack of knowledge related to use of lipid-lowering agents during pregnancy. The trials evaluating the efficacy and safety of lipid-lowering medications exclude individuals who are pregnant and require individuals of childbearing potential to use contraception (some requiring two forms). Therefore, for many pregnant individuals, it is recommended that they discontinue lipid-lowering therapies during gestation. However, some individuals are at higher risk for cardiovascular events (e.g., those with familial hypercholesterolemia or preexisting ASCVD), and the risk of discontinuing all lipid-lowering therapy during preconception and pregnancy periods may be associated with an increased risk for cardiovascular events. Consideration of initiating or continuing statin therapy during pregnancy should occur with these high-risk individuals. Although the evidence is limited, statins did not increase teratogenic effects for individuals with familial hypercholesterolemia (147,148), and a meta-analysis of pravastatin in pregnant individuals showed a reduction in preeclampsia, premature birth, and neonatal intensive care unit admissions (149). There is limited information regarding the use of lipid-lowering therapies (other than bile acid sequestrants) during pregnancy. Thus, it is recommended that individuals of childbearing potential use a form of contraception when also using lipid-lowering medications with unknown risks, limited evidence on safety, or known risks during pregnancy regardless of intention to become pregnant, as many pregnancies are unplanned, and preconception counseling should be part of the routine care of individuals with diabetes who have childbearing potential. Counseling should include the known benefits and risks of lipid-lowering medications versus the risks and benefits of not treating the conditions for which they are prescribed, as well as other medications (e.g., noninsulin glucose-lowering therapies and antihypertensive agents), during pregnancy and recommendations for when changes in medications should occur prior to pregnancy (144) (see Section 15, "Management of Diabetes in Pregnancy," for more information on preconception counseling and lipid-lowering treatment during pregnancy).

Treatment of Other Lipoprotein Fractions or Goals

Recommendations

10.30 For individuals with fasting triglyceride levels ≥500 mg/dL (≥5.7 mmol/L), evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. **C**

10.31 In adults with hypertriglyceridemia (fasting triglycerides >150 mg/dL [>1.7 mmol/L] or nonfasting triglycerides >175 mg/dL [>2.0 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, and hypothyroidism), and medications that raise triglycerides. **C**

10.32 In individuals with ASCVD or other cardiovascular risk factors on a statin with managed LDL cholesterol but elevated triglycerides (150–499 mg/dL [1.7–5.6 mmol/L]), the addition of icosapent ethyl can be considered to reduce cardiovascular risk. **B**

Hypertriglyceridemia should be addressed with nutritional and lifestyle changes, including weight loss and abstinence from alcohol (150). Severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.7 mmol/L] and especially >1,000 mg/dL [>11.3 mmol/L]) may warrant pharmacologic therapy (fibric acid derivatives and/or fish oil) and reduction in dietary fat to reduce the risk of acute pancreatitis (151). Moderate- or high-intensity statin therapy should also be used as indicated to reduce risk of cardiovascular events (see STATIN TREATMENT, above) (150,152). In people with hypertriglyceridemia (fasting triglycerides >150 mg/dL [>1.7 mmol/L] or nonfasting triglycerides >175 mg/dL [>2.0 mmol/L]), lifestyle interventions, treatment of secondary factors, and avoidance of medications that might raise triglycerides are recommended.

For individuals with established cardiovascular disease or with risk factors for cardiovascular disease with elevated triglycerides (150–499 mg/dL [1.7–5.6 mmol/L]) after maximizing statin therapy, icosapent ethyl may be added to reduce cardiovascular risk. The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) showed that the addition of icosapent ethyl to statin therapy in this population resulted in 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 compared with placebo. This risk reduction was seen in individuals 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 individuals experiencing adverse events and serious adverse events were similar between the active and placebo treatment groups. It should be noted that data are lacking for other n-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products (153). 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 individuals 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 (154).

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 (155). In a large trial in people with diabetes, fenofibrate improved cardiovascular outcomes in subgroups with both elevated triglycerides (>200 mg/dL [2.3 mmol/L]) and low HDL cholesterol (<40 mg/dL [1.0 mmol/L]) (156); however, another fibrate, pemafibrate, failed to reduce overall cardiovascular outcomes in a similar population (157).

Other Combination Therapy

Recommendations

10.33 Statin plus fibrate combination therapy has not been shown to improve ASCVD outcomes and is generally not recommended. **A**

10.34 Statin plus niacin combination therapy has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. **A**

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) (158).

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) (159).

Statin and Niacin Combination Therapy

Large clinical trials, including the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) and Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trials, failed to demonstrate a benefit of adding niacin to individuals on appropriate statin therapy. In fact, there was a possible increased risk of ischemic stroke in the AIM-HIGH trial (160) and 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 the HPS2-THRIVE trial in those on combination therapy (161). 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 type 2 diabetes with statin use (162,163), 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 individuals at highest risk for diabetes (164). 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) (164). 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 individuals with statins for 4 years resulted in one additional case of diabetes while simultaneously preventing 5.4 vascular events among those 255 individuals (163).

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 argue against this association, as detailed in a 2018 European Atherosclerosis Society Consensus Panel statement (165). 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 (166–169). In addition, no change in cognitive function has been reported in studies with the addition of ezetimibe (119) or PCSK9 inhibitors (121,170) to statin therapy, including among individuals treated to very low LDL cholesterol levels. In addition, systematic reviews of randomized controlled trials and prospective cohort studies evaluating cognition in individuals receiving statins found that published data do not reveal an adverse effect of statins on cognition (171,172). 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 (173).

ANTIPLATELET AGENTS

Recommendations

10.35 Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of ASCVD. **A**

10.36a For individuals with ASCVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**

10.36b The length of treatment with dual antiplatelet therapy using low-dose aspirin and a P2Y12 inhibitor in individuals with diabetes after an acute coronary syndrome, acute ischemic stroke, or transient ischemic attack should be determined by an interprofessional team approach that includes a cardiovascular or neurological specialist, respectively. **E**

10.37 Combination therapy with aspirin plus low-dose rivaroxaban should be considered for individuals with stable coronary and/or peripheral artery disease (PAD) 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 individual 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 individuals with previous MI or stroke (secondary prevention) and is strongly recommended. In primary prevention, however, among individuals with no previous cardiovascular events, its net benefit is more controversial (162,174).

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 (175–177).

The Antithrombotic Trialists' Collaboration published an individual participant–level meta-analysis (178) of 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 (179). The primary efficacy end point was vascular death, MI, 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]) (180) and in the elderly (ASPREE [Aspirin in Reducing Events in the Elderly]) (181), in which 11% of participants had diabetes, found no benefit of aspirin on the primary efficacy end point and an increased risk of bleeding. In ARRIVE, with 12,546 individuals over a period of 60 months of follow-up, the primary end point occurred in 4.29% vs. 4.48% of individuals 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 individuals 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, which included 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 versus 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 (182).

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 or albuminuria) who are not at increased risk of bleeding (e.g., older age, anemia, or renal disease) (183–186). Noninvasive imaging techniques such as coronary calcium scoring may help further tailor aspirin therapy, particularly in those at low risk (187,188). For people >70 years of age (with or without diabetes), the balance appears to have greater risk than benefit (179,181). Thus, for primary prevention, the use of aspirin needs to be carefully considered and generally may 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 (174).

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 risk of bleeding. Clinical judgment should be used for those at intermediate risk (younger individuals with one or more risk factors or older individuals with no risk factors) until further research is available. Individuals' willingness to undergo long-term aspirin therapy should also be considered in shared decision-making (189). Aspirin use in individuals 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 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 (190). 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 individuals assigned to 81 mg and those assigned to 325 mg of aspirin daily (191). 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 (192). "Aspirin resistance" has been described in people with diabetes when measured by a variety of ex vivo and in vitro methods (platelet aggregometry and measurement of thromboxane B_2) (193), but other studies suggest no impairment in aspirin response among people with diabetes (194). A trial suggested that more frequent dosing of aspirin may reduce platelet reactivity in individuals with diabetes (195); 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 (196); however, the ASCEND trial found benefit of low-dose aspirin in those in this weight range, which would not validate this suggested hypothesis (179). It appears that 75–162 mg/day is optimal.

Indications for P2Y12 Receptor Antagonist Use

Combination dual antiplatelet therapy with aspirin and a P2Y12 receptor antagonist is indicated after acute coronary syndromes and coronary revascularization with stenting (197). In addition, current guidelines recommend short-term dual antiplatelet therapy after high-risk transient ischemic attack and minor stroke (198). The

indications for dual antiplatelet therapy and length of treatment are rapidly evolving and should be determined by an interprofessional team approach that includes a cardiovascular or neurological specialist, as appropriate. 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 (199). 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 (200). 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 (201,202). 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 individuals with history of percutaneous coronary intervention, while no net benefit was seen in individuals without prior percutaneous coronary intervention (202). 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 meta-analysis (203,204).

Combination Antiplatelet and Anticoagulation Therapy

Combination therapy with aspirin plus low-dose rivaroxaban may be considered for people with stable coronary and/or PAD 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 PAD, 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 (205,206). 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 (207), in which 6,564 individuals with PAD 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 individuals 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 individuals, 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 individuals with differing types and circumstances of cardiovascular complications.

CARDIOVASCULAR DISEASE

Screening

Recommendations

10.39a In asymptomatic individuals, routine screening for coronary artery disease is not recommended, as it does not improve outcomes as long as ASCVD risk factors are treated. **A**

10.39b Consider investigations for coronary artery disease in the presence of any of the following: signs or symptoms of cardiac or associated vascular disease, including carotid bruits, transient ischemic attack, stroke, claudication, or PAD; or electrocardiogram abnormalities (e.g., Q waves). **E**

10.40a Adults with diabetes are at increased risk for the development of asymptomatic cardiac structural or functional abnormalities (stage B heart failure) or symptomatic (stage C) heart failure. Consider screening adults with diabetes by measuring a natriuretic peptide (B-type natriuretic peptide [BNP] or N-terminal pro-BNP [NT-proBNP]) to facilitate prevention of stage C heart failure. **B**

10.40b In asymptomatic individuals with diabetes and abnormal natriuretic peptide levels, echocardiography is recommended to identify stage B heart failure. **A**

10.41 In asymptomatic individuals with diabetes and age ≥65 years, microvascular disease in any location, or foot complications or any end-organ damage from diabetes, screening for PAD with ankle-brachial index testing is recommended if a PAD diagnosis would change management. **B** In individuals with diabetes duration ≥10 years and high cardiovascular risk, screening for PAD should be considered. **E**

Treatment

Recommendations

10.42 Among people with type 2 diabetes who have established ASCVD or established kidney disease, a sodium–glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 receptor agonist (GLP-1 RA) with demonstrated cardiovascular disease benefit is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering treatment plans. **A**

10.42a In people with type 2 diabetes and established ASCVD, multiple ASCVD risk factors, or chronic kidney disease (CKD), an SGLT2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. **A**

10.42b In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, a GLP-1 RA with demonstrated car-diovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. **A**

10.42c In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, combined therapy with an SGLT2 inhibitor with demonstrated cardiovascular benefit and a GLP-1 RA with demonstrated cardiovascular benefit may be considered for additive reduction of the risk of adverse cardiovascular and kidney events. **A**

10.43a In people with type 2 diabetes and established heart failure with

either preserved or reduced ejection fraction, an SGLT2 inhibitor (including SGLT1/2 inhibitor) with proven benefit in this population is recommended to reduce the risk of worsening heart failure and cardiovascular death. **A**

10.43b In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, an SGLT2 inhibitor with proven benefit in this population is recommended to improve symptoms, physical limitations, and quality of life. **A**

10.44 For individuals with type 2 diabetes and CKD with albuminuria treated with maximum tolerated doses of ACE inhibitor or ARB, recommend treatment with a nonsteroidal MRA with demonstrated benefit to improve cardiovascular outcomes and reduce the risk of CKD progression. **A**

10.45 In individuals with diabetes with established ASCVD or aged ≥55 years with additional cardiovascular risk factors, ACE inhibitor or ARB therapy is recommended to reduce the risk of cardiovascular events and mortality. **A**

10.46a In individuals with diabetes and asymptomatic stage B heart failure, an interprofessional approach to optimize guideline-directed medical therapy, which should include a cardiovascular disease specialist, is recommended to reduce the risk for progression to symptomatic (stage C) heart failure. **A**

10.46b In individuals with diabetes and asymptomatic stage B heart failure, ACE inhibitors or ARBs and β-blockers are recommended to reduce the risk for progression to symptomatic (stage C) heart failure. **A**

10.46c In individuals with type 2 diabetes and asymptomatic stage B heart failure or with high risk of or established cardiovascular disease, treatment with an SGLT inhibitor with proven heart failure prevention benefit is recommended to reduce the risk of hospitalization for heart failure. **A**

10.46d In individuals with type 2 diabetes, obesity, and symptomatic heart failure with preserved ejection fraction, therapy with a GLP-1 RA with demonstrated benefit for reduction of heart failure–related symptoms, physical limitations, and exercise function is recommended. **A**

10.46e In individuals with type 2 diabetes and CKD, recommend treatment with a nonsteroidal MRA with demonstrated benefit to reduce the risk of hospitalization for heart failure. **A**

10.46f In individuals with diabetes, guideline-directed medical therapy for myocardial infarction and symptomatic stage C heart failure is recommended with ACE inhibitors or ARBs, MRAs, angiotensin receptor or neprilysin inhibitor, β-blockers, and SGLT2 inhibitors, similar to guideline-directed medical therapy for people without diabetes. **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**

10.48 Individuals with type 1 diabetes and those with type 2 diabetes who are ketosis prone and/or follow a ketogenic eating pattern who are treated with SGLT inhibition should be educated on the risks and signs of ketoacidosis and methods of risk management and provided with appropriate tools for accurate ketone measurement (i.e., serum β-hydroxybutyrate). **E**

Cardiac Testing

Candidates for advanced or invasive cardiac testing include those with *1*) symptoms or signs of cardiac or vascular disease 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 Individuals for Atherosclerotic Cardiovascular Disease

The screening of asymptomatic individuals with high ASCVD risk is not recommended (**Fig. 10.5**), in part because these high-risk people should already be receiving intensive medical therapy—an approach that provides benefits similar to those of invasive revascularization (208,209). A randomized observational trial demonstrated no clinical benefit of routine screening with adenosine-stress radionuclide myocardial perfusion imaging in asymptomatic people with type 2 diabetes and normal ECGs (210). Another randomized study showed that routine screening with coronary computed tomography angiography did not reduce the composite rate of all-cause mortality, nonfatal MI, or unstable angina in asymptomatic people with type 1 or type 2 diabetes (211). Studies have also 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 (212,213).

Any benefit of noninvasive coronary artery disease screening methods, such as computed tomography calcium scoring, to identify subgroups for different treatment strategies remains unproven in asymptomatic people with diabetes, though research is ongoing. Coronary calcium scoring in asymptomatic people with diabetes may help in risk stratification (214,215) and provide reasoning for treatment intensification and/or guiding informed individual decision-making and willingness for medication initiation and participation. However, 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 risk of such an approach in asymptomatic individuals remains controversial, particularly in the modern setting of aggressive ASCVD risk factor management.

Screening for Asymptomatic Heart Failure in People With Diabetes

People with diabetes are at an increased risk for developing heart failure, as shown in multiple longitudinal, observational studies (216,217). This association is not only observed in people with type 2 diabetes but also evident in people with type 1 diabetes (216,217). In a large multinational cohort of 750,000 people with diabetes without established cardiovascular disease, heart failure and CKD were the most frequent first manifestations of cardiovascular or kidney disease (218). For a detailed

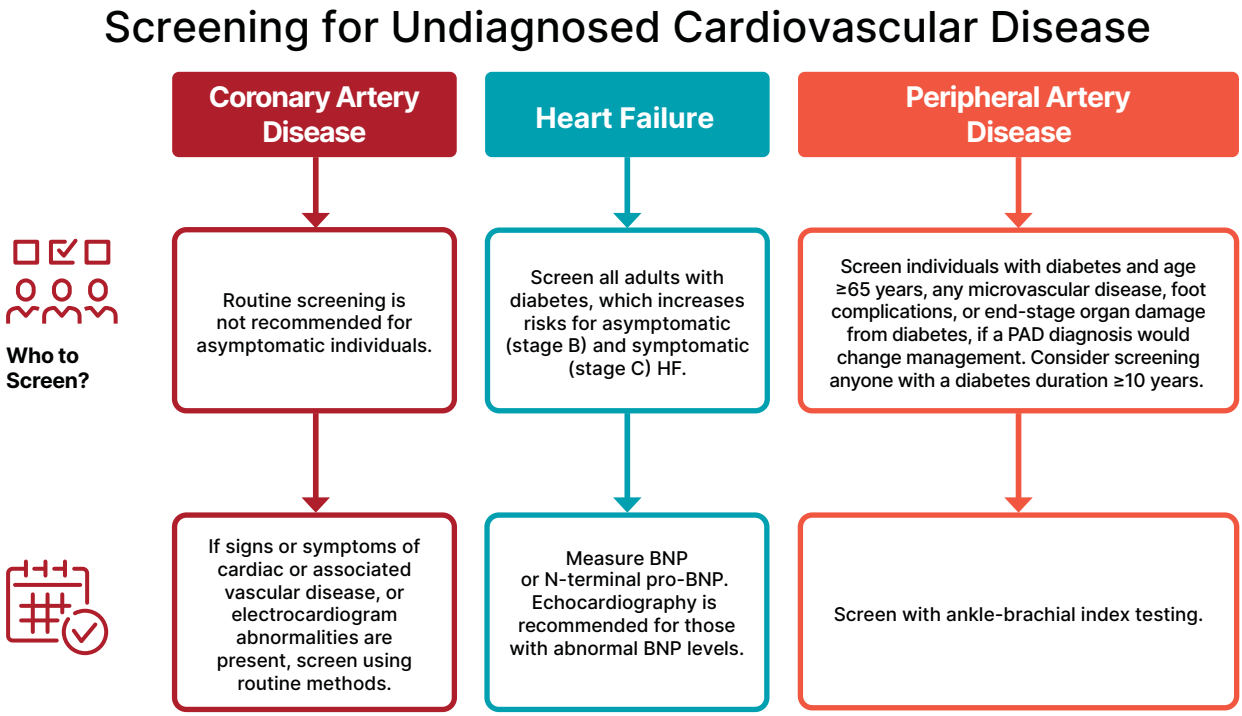


Figure 10.5—Recommendations for screening of asymptomatic and undiagnosed cardiovascular disease. BNP, B-type natriuretic peptide; HF, heart failure; PAD, peripheral artery disease. Adapted from *"Standards of Care in Diabetes—2024* Abridged for Primary Care Professionals" (325).

review of screening, diagnosis, and treatment recommendations of heart failure in people with diabetes, the reader is further referred to the ADA consensus report "Heart Failure: An Underappreciated Complication of Diabetes. A Consensus Report of the American Diabetes Association" (15).

People with diabetes are at particularly high risk for progression from asymptomatic stage A and B to symptomatic stage C and D heart failure (219,220). Identification, risk stratification, and early treatment of risk factors in people with diabetes and asymptomatic stages of heart failure reduce the risk for progression to symptomatic heart failure (221,222). In people with type 2 diabetes, measurement of natriuretic peptides, including B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP), identifies people at risk for heart failure development, progression of symptoms, and heart failure–related mortality (223–225). A similar association and prognostic values of increased NT-proBNP with increased cardiovascular and all-cause mortality has been reported in people with type 1 diabetes (226). Results from several randomized controlled trials revealed that more intensive treatment of risk factors in people with increased levels of natriuretic peptides reduces the risk for symptomatic heart failure, heart failure hospitalization, and newly diagnosed left ventricular dysfunction (222,227,228).

Based on collective evidence, consider screening asymptomatic adults with diabetes for the development of cardiac structural or functional abnormalities (stage B heart failure) by measurement of natriuretic peptides, including BNP or NT-proBNP levels. The biomarker threshold for abnormal values is BNP level ≥50 pg/mL and NT-proBNP level ≥125 pg/mL. Abnormal levels of natriuretic peptide will need to be evaluated in the context of each person, using clinical judgment, in the absence of any possible competing diagnoses, particularly recognizing conditions that may lead to increased levels of natriuretic peptide, including renal insufficiency, pulmonary disease including pulmonary hypertension and chronic obstructive lung disease, obstructive sleep apnea, ischemic and hemorrhagic stroke, and anemia. Conversely, natriuretic peptide levels may be decreased in the population with obesity, which impairs sensitivity of testing.

In people with diabetes and an abnormal natriuretic peptide level, echocardiography is recommended as the next step to screen for structural heart disease and echocardiographic Doppler indices for evidence of diastolic dysfunction and increased filling pressures (229). At this stage, an interprofessional approach, which should include a cardiovascular disease specialist, is recommended to implement a guideline-directed medical treatment strategy, which may reduce the risk of progression to symptomatic stages of heart failure (221). The recommendations for screening and treatment of heart failure in people with diabetes discussed in this section are consistent with the ADA consensus report on heart failure (15) and with current American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines for the management of heart failure (12).

Screening for Asymptomatic Peripheral Artery Disease in People With Diabetes

The risk for PAD in people with diabetes is higher than that in people without diabetes (230–232). In the PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program, 30% of people aged 50–69 years with a history of cigarette smoking or diabetes, or aged ≥70 years regardless of risk factors, had PAD (233). Similarly, in other screening studies, 26% of people with diabetes have been shown to have PAD (234), and diabetes increased

the odds of having PAD by 85% (235). Notably, classical symptoms of claudication are uncommon, and almost half of people with newly diagnosed PAD were asymptomatic (233). Conversely, up to two-thirds of people with asymptomatic PAD have been shown to have comorbid diabetes (236). Risk factors associated with an increased risk for PAD in people with diabetes include age, smoking, hypertension, dyslipidemia, worse glycemic management, longer duration of diabetes, neuropathy, and retinopathy as well as a prior history of cardiovascular disease (237,238). In addition, the presence of microvascular disease is associated with adverse outcomes in people with PAD, including an increased risk for future limb amputation (239,240). While a positive screening test for PAD in an asymptomatic population has been associated with increased cardiovascular event rates (241,242), prospective, randomized studies addressing whether screening for PAD in people with diabetes improves long-term limb outcomes and cardiovascular event rates are limited. In the randomized controlled Viborg Vascular (VIVA) trial, 50,156 participants, some with and some without diabetes, were randomized to combined vascular screening for abdominal aortic aneurysm, PAD, and hypertension or to no screening. Vascular screening was associated with increased pharmacologic therapy (antiplatelet, lipid-lowering, and antihypertensive therapy), reduced in-hospital time for PAD and coronary artery disease, and reduced mortality (243). Therefore, the committee recommends screening for asymptomatic PAD using ankle-brachial index in people with diabetes in whom a diagnosis of PAD may help further intensify pharmacologic therapies. These people include those with age ≥65 years, diabetes with duration ≥10 years, microvascular disease, clinical evidence of foot complications, or any end-organ damage from diabetes.

Lifestyle and Pharmacologic Interventions

Intensive lifestyle intervention focusing on weight loss through decreased caloric intake and increased physical activity, as performed in the Look AHEAD (Action for Health in Diabetes) trial, may be considered for improving glucose management, fitness, and some ASCVD risk factors (244). Individuals at increased ASCVD risk should receive statin, ACE inhibitor, or ARB therapy if the individual has hypertension, and possibly aspirin, unless there are contraindications to a particular drug class.

Clear cardiovascular benefit exists for ACE inhibitor or ARB therapy in people with diabetes. The Heart Outcomes Prevention Evaluation (HOPE) study randomized 9,297 individuals aged ≥55 years with a history of vascular disease or diabetes plus one other cardiovascular risk factor to either ramipril or placebo. Ramipril significantly reduced cardiovascular and all-cause mortality, MI, and stroke (245). ACE inhibitors or ARB therapy also have well-established long-term benefit in people with diabetes and CKD or hypertension, and these agents are recommended for hypertension management in people with known ASCVD (particularly coronary artery disease) (72,73,246). People with type 2 diabetes and CKD should be considered for treatment with finerenone to reduce cardiovascular outcomes and the risk of CKD progression (247–250). 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 (251,252).

Glucose-Lowering Therapies and Cardiovascular Outcomes

In 2008, the U.S. Food and Drug Administration (FDA) issued guidance for industry to perform cardiovascular outcomes trials for all new medications for the treatment of type 2 diabetes amid concerns of increased cardiovascular risk (253). 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.

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 (254). The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) showed that treatment with empagliflozin 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]; $P < 0.001$) (255). Similarly, 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 person-years; HR 0.86 [95% CI 0.75–0.97]). Of note, there was an increased risk of lower-limb amputation with canagliflozin (6.3 vs. 3.4 participants per 1,000 person-years; HR 1.97 [95% CI 1.41–2.75]) (256). However, no significant increase in lower-limb amputations, fractures, AKI, or hyperkalemia was noted for canagliflozin relative to placebo in other trials of canagliflozin (257).

The Dapagliflozin Effect on Cardiovascular Events-Thrombosis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial 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 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]; $P = 0.17$) (258). 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. Further studies have shown renoprotective effects of dapagliflozin (259).

The Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) (260) 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]; $P < 0.001$). However, 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.

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 GLP-1 RA, versus placebo on cardiovascular outcomes in 9,340 people with type 2 diabetes at high risk for cardiovascular disease or with cardiovascular disease (261). 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%) than in 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]; $P = 0.007$) (261).

Results of trials with semaglutide, albiglutide, and dulaglutide, once-weekly GLP-1 RAs, were consistent with the LEADER trial (262–264). However, lixisenatide and extended-release exenatide were not superior to placebo with respect to the primary end point of cardiovascular outcomes (265). 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, and dapagliflozin, with lesser benefits seen with ertugliflozin) and four FDA-approved GLP-1 RAs (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 RAs and SGLT2 inhibitors reduce risk of atherosclerotic major adverse cardiovascular events to a comparable degree in people with type 2 diabetes and established ASCVD (266,267). 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 (268,269). In people with type 2 diabetes and established ASCVD, multiple ASCVD risk factors, or CKD, 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 GLP-1 RA with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. For many individuals, use of either an SGLT2 inhibitor or a GLP-1 RA 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 RA may be considered to provide the complementary outcomes benefits associated with these classes of medication (270).

Prevention and Treatment of Heart Failure

Prevention of Symptomatic Heart Failure

ACE Inhibitors or ARBs and β-Blockers. Early primary prevention strategies and treatment of associated risk factors reduce incident, symptomatic heart failure and should include lifestyle intervention with nutrition, physical activity, weight management, and smoking cessation (271–274) (**Fig. 10.6**). The vast majority of incident heart failure is preceded by hypertension; up to 91% of all new heart failure development in the Framingham cohort occurred in people with a previous diagnosis of hypertension (275). Therefore, management of hypertension constitutes a key goal in people with diabetes and stage A or B heart failure. For example, in the UK Prospective Diabetes Study (UKPDS) trial, intensive blood pressure management in people with type 2 diabetes reduced the risk for heart failure by 56% (276). Similarly, in the SPRINT trial, intensive treatment of hypertension decreased the risk for development of incident heart failure by 36% (277). As discussed in the HYPERTENSION AND BLOOD PRESSURE MANAGEMENT section above, use of ACE inhibitors or ARBs is the preferred treatment strategy for management of hypertension in people with diabetes, particularly in the presence of albuminuria or coronary artery disease. People with diabetes and stage B heart failure who remain asymptomatic but have evidence of structural heart disease, including history of MI, acute coronary syndrome, or left ventricular ejection fraction (LVEF) ≤40%, should be treated with ACE inhibitors or ARBs plus β-blockers according to current treatment guidelines (12). In the landmark Studies of Left Ventricular Dysfunction (SOLVD) study, in which 15% of people had diabetes, treatment with enalapril reduced incident heart failure in people with asymptomatic left ventricular dysfunction by 20% (278). In the Survival and Ventricular Enlargement (SAVE) study,

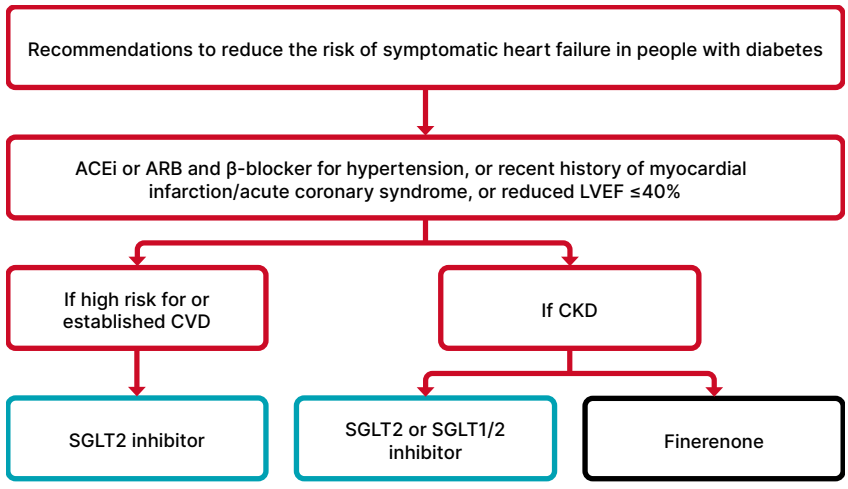


Figure 10.6—Overview of recommendations for the prevention of the development of symptomatic heart failure in people with diabetes. ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; LVEF, left ventricle ejection fraction; SGLT2, sodium–glucose cotransporter 2. Adapted from *"Standards of Care in Diabetes—2024* Abridged for Primary Care Professionals" (325).

which enrolled asymptomatic people with reduced LVEF after MI, including 23% people with diabetes, treatment with captopril reduced the development of heart failure by 37% (279). Subsequent retrospective analyses from both trials revealed that concomitant use of β-blockers was associated with decreased risk of progression to symptomatic heart failure (280,281). The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) study randomized people with a history of MI and reduced LVEF to treatment with carvedilol (282). Approximately half of the study participants were asymptomatic, and 23% of study participants had a history of diabetes. Treatment with carvedilol reduced mortality by 23%, and there was a 14% risk reduction for heart failure hospitalization. Finally, in the Reversal of Ventricular Remodeling With Toprol-XL (REVERT) trial, in which 45% of the people enrolled had diabetes, metoprolol improved adverse cardiac remodeling in asymptomatic individuals with an LVEF <40% and mild left ventricular dilatation (283).

SGLT Inhibitors. SGLT2 inhibitors constitute a key treatment approach to reduce cardiovascular disease and heart failure outcomes in people with diabetes. People with type 2 diabetes and increased cardiovascular risk or established cardiovascular disease should be treated with an SGLT2 inhibitor to prevent the development of incident heart failure. This includes people with type 2 diabetes and asymptomatic stage B heart failure. In the EMPA-REG OUTCOME trial, only 10% of study participants had a prior history of heart failure, and treatment with empagliflozin reduced the relative risk for hospitalization from heart failure by 35% (255). In the CANVAS Program, hospitalization from heart failure was reduced by 33% in people allocated to canagliflozin, and only 14% of individuals enrolled had a prior history of heart failure (256). In the DECLARE-TIMI 58 study, only 10% of study participants had a prior history of heart failure, and dapagliflozin reduced cardiovascular mortality and hospitalization for heart failure by 17%, which was consistent across multiple study subgroups regardless of a prior history of heart failure (258). Finally, in the Effect of Sotagliflozin on Cardiovascular and Renal Events in Participants With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial, randomization to the SGLT1/2 inhibitor sotagliflozin reduced the primary outcome of death from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure in people with type 2 diabetes, CKD, and risk for cardiovascular disease (284). Therefore, SGLT inhibitor treatment is recommended in asymptomatic people with type 2 diabetes at risk or with established cardiovascular disease to prevent incident heart failure and hospitalization from heart failure.

Finerenone. Finerenone is a nonsteroidal MRA and has recently been studied in people with diabetes and CKD, including the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and the Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease (FIGARO-DKD) studies. In FIDELIO-DKD, finerenone was compared with placebo for the primary outcome of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes in people with type 2 diabetes and CKD (285). A prespecified secondary outcome was death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for heart failure, which was reduced by 13% in the finerenone group. The incidence of heart failure hospitalization occurred less in the finerenone-treated group, and only 7.7% of study participants had a prior history of heart failure. In the FIGARO-DKD trial, finerenone reduced the primary outcome of death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for heart failure (HR 0.87 [95% CI 0.76–0.98]; P = 0.03) in people with type 2 diabetes and CKD (248). Only 7.8% of all participants had a prior history of heart failure, and the incidence of hospitalization for heart failure was reduced in the finerenone-allocated treatment arm (HR 0.71 [95% CI 0.56–0.90]). Owing to these observations, treatment with finerenone is recommended in people with type 2 diabetes and CKD to reduce the risk of progression from stage A heart failure to symptomatic incident heart failure.

Treatment of Symptomatic Heart Failure

In general, current guideline-directed medical therapy for a history of MI and symptomatic stage C and D heart failure in people with diabetes is similar to that for people without diabetes. At these advanced stages of heart failure, a collaborative approach with a cardiovascular specialist is recommended. The treatment recommendations are detailed in current 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines for the management of heart failure (12).

Glucose-Lowering Medications and Heart Failure: Discussion of Heart Failure Outcomes

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 (286–288). 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 (289). 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 (290); 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 (291).

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 individuals 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) (292). However, three other cardiovascular outcomes trials—Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) (293), Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (294), and the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) (295)—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 RAs lixisenatide, liraglutide, semaglutide, exenatide once weekly, albiglutide, or dulaglutide compared with placebo (261,264, 265,296,297).

SGLT2 inhibitors reduce the incidence of heart failure and improve heart failure–related outcomes, including hospitalization for heart failure and heart failure–related symptoms, in people with diabetes with preserved or reduced ejection fraction (250,255–257,298–306). The results of these clinical trials have been extensively outlined in the 2024 American Diabetes Association "Standards of Care in Diabetes" (307). Briefly, in the EMPA-REG OUTCOME trial, the addition of empagliflozin to standard care led to a significant 35% reduction in hospitalization for heart failure compared with placebo (255). Similarly, in CANVAS and DECLARE-TIMI 58, there were 33% and 27% reductions, respectively, in hospitalization for heart failure with SGLT2 inhibitor use versus placebo (256,258). Additional data from the CREDENCE trial with canagliflozin showed a 39% reduction in hospitalization for heart failure and a 31% reduction in the composite of cardiovascular death or hospitalization for heart failure, in a population with CKD and albuminuria (UACR >300–5,000 mg/g) (257).

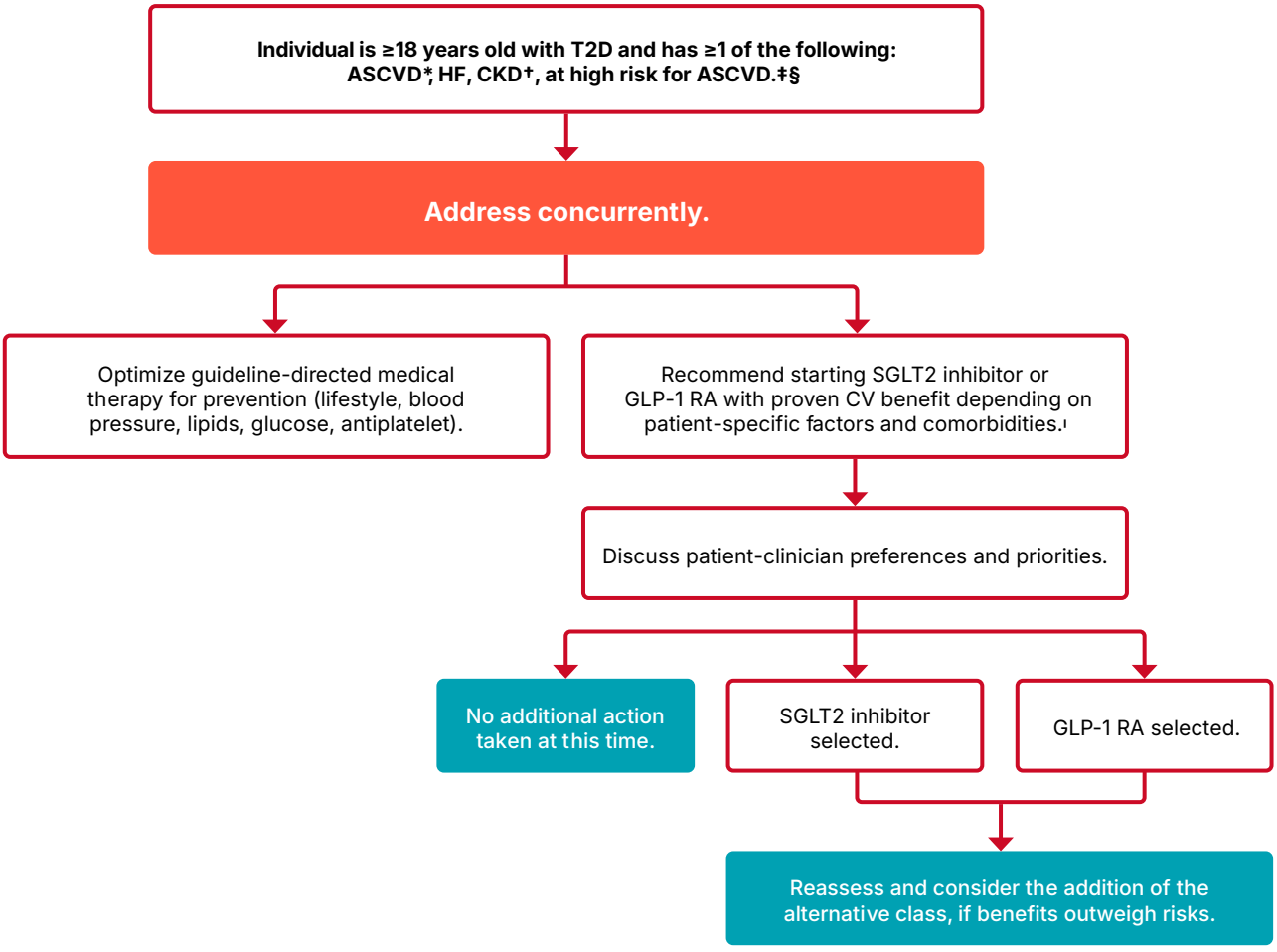
The DAPA-HF trial specifically evaluated the effects of dapagliflozin on the primary outcome of a composite of worsening heart failure or cardiovascular death in individuals with New York Heart Association (NYHA) class II, III, or IV heart failure and an ejection fraction of 40% or less (299,307). Dapagliflozin 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 (299). Similar results were obtained in clinical trials with empagliflozin (303). In Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved), the primary outcome of cardiovascular death or hospitalization for heart failure was reduced in adults with NYHA functional class I–IV and chronic HFpEF (LVEF >40%), extending the previously seen benefit in people with heart failure to those with preserved ejection fraction irrespective of the presence of type 2 diabetes (250). A similar benefit for heart failure outcomes was seen in the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial for dapagliflozin in people with mildly reduced or preserved ejection fraction (302). In addition, a large meta-analysis (308) including the EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, DELIVER, and the Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trials included 21,947 individuals 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. In addition to the hospitalization and mortality benefit in people with heart failure, SGLT2 inhibitors improve clinical stability and functional status in individuals with heart failure (301,304–306). 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. Therefore, in people with type 2 diabetes and established HFpEF or HFrEF, an SGLT2 inhibitor with proven benefit in this population is recommended to reduce the risk of worsening heart failure and cardiovascular death. In addition, an SGLT2 inhibitor is recommended in this population to improve symptoms, physical limitations, and quality of life.

Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, was recently approved by the FDA to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure in people with heart failure or type 2 diabetes, CKD, and other cardiovascular risk factors. This drug is distinct from other SGLT inhibitors, as it lowers glucose via delayed glucose absorption in the gut via inhibition of the cotransporter SGLT1 in addition to increasing urinary glucose excretion; however, it is not currently approved by the FDA for glycemic management of type 1 or type 2 diabetes. Sotagliflozin was evaluated in the SCORED trial (284), which was ended early due to lack of funding, and examined the safety and efficacy of sotagliflozin in people with type 2 diabetes and CKD and risks for cardiovascular disease. 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 deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure was reduced with sotagliflozin. In the SOLOIST trial, sotagliflozin initiated during or shortly after hospitalization in people with diabetes also reduced the risk for the primary end point of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure (309). 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 individuals 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 (309).

One concern with expanded use of SGLT inhibition is the infrequent but serious risk of diabetic ketoacidosis, including the atypical presentation of euglycemic ketoacidosis. There are multiple proposed pathways through which SGLT inhibition results in ketosis (increased β-hydroxybutyrate and acetoacetate), such as increased production due to reduction in insulin doses, increases in glucagon levels leading to increased lipolysis and ketone production, and decreased renal clearance of ketones (310,311). Thus, the use of SGLT inhibitors (whether for glycemic management or another indication) increases the susceptibility to diabetic ketoacidosis, particularly when other risk factors or situations occur (including, but not limited to, insulin pump malfunctions, significant reduction in insulin doses, and nutritional intake plans with prolonged periods of fasting or carbohydrate restriction). Although there were low rates of ketoacidosis in the cardiovascular and heart failure outcomes trials evaluating SGLT inhibition, these studies excluded individuals with type 1 diabetes and/or recent history of diabetic ketoacidosis (309,312). To decrease the risk of ketoacidosis when using SGLT inhibition in people with type 1 diabetes, it is recommended

that clinicians assess the underlying susceptibility; provide education regarding the risks, symptoms, and prevention strategies; and prescribe home monitoring supplies for β-hydroxybutyrate (311,313). Use of these processes may have contributed to the lower rates of ketoacidosis seen in some of the studies of these agents for adjunctive glycemic management in people with type 1 diabetes (314–316) compared with those that did not include preventative strategies (310,317). Reassessment of susceptibility, education, and provision of monitoring supplies should reoccur throughout the duration of SGLT inhibitor treatment, particularly as preventative strategies and monitoring can minimize, but not eliminate, the risk of ketoacidosis in those who are susceptible (318,319).

The selective nonsteroidal MRA finerenone has been shown in the FIGARO-DKD trial, which included people with type 2 diabetes and CKD, to reduce the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure (248). A prespecified subgroup analysis from FIGARO-DKD further revealed that in individuals 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 (247). Furthermore, the incidence of heart failure hospitalization was reduced in finerenone-treated people with type 2 diabetes. Finally, in a pooled analysis from both FIDELIO-DKD and FIGARO-DKD, treatment with finerenone reduced the composite of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure was reduced (249). These collective studies indicate that finerenone improves cardiovascular and renal outcomes in people with type 2 diabetes. Therefore, in people



* ASCVD is defined as a history of an acute coronary syndrome or myocardial infarction, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

† CKD is a clinical diagnosis marked by reduced eGFR, the presence of albuminuria, or both.

‡ Consider an SGLT2 inhibitor when the individual has established ASCVD, HF, or CKD or is at high risk for ASCVD. Consider a GLP-1 RA when the individual has established ASCVD or is at high risk for ASCVD.

§ Individuals at high risk for ASCVD include those with end-organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, and obesity).

ˈ Most individuals enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

Figure 10.7—Approach to risk reduction with sodium–glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 receptor agonist (GLP-1 RA) therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; T2D, type 2 diabetes. Adapted with permission from Das et al. (324).

with type 2 diabetes and CKD with albuminuria treated with maximum tolerated doses of ACE inhibitor or ARB, addition of finerenone should be considered to improve cardiovascular outcomes, including the risk for heart failure hospitalization, and to reduce the risk of CKD progression.

Approximately 45% of people admitted for HFpEF have diabetes, and most people with HFpEF have obesity (320,321). Conversely, weight loss improves symptoms of HFpEF (322). Therefore, the Semaglutide Treatment Effect in People with Obesity and HFpEF (STEP-HFpEF) trial evaluated whether the GLP-1 RA semaglutide improves symptoms related to heart failure (323). In the study, 616 people with type 2 diabetes and a BMI of 30 or greater with HFpEF were assigned to receive once-weekly semaglutide at a dose of 2.4 mg or placebo. The primary end point was the change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (range from 0 to 100) and the change in weight. After 1 year of treatment, the mean change in the score was 13.7 points with semaglutide and 6.4 points with placebo, and the mean body weight was reduced by 9.8% in the group assigned to semaglutide compared with 3.4% with placebo. In addition, in the confirmatory secondary end point, semaglutide treatment improved 6-min walk distance. In a hierarchical analysis, semaglutide favored the composite end point of death, heart failure events, change in the Kansas City Cardiomyopathy Questionnaire clinical summary score, and C-reactive protein levels. Therefore, the committee recommends treatment with a GLP-1 RA with demonstrated benefit in individuals with type 2 diabetes, obesity, and symptomatic HFpEF for the reduction of HF-related symptoms, physical limitations, and exercise function in this population.

Clinical Approach

As has been carefully outlined in **Fig. 9.3** in 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 RA as part of the comprehensive approach to cardiovascular and kidney risk reduction. Importantly, these agents should be included in the plan of care irrespective of the need for additional glucose lowering and irrespective of metformin use. Such an approach has also been described in the ADA-endorsed American College of Cardiology "2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes" (324). **Figure 10.7**, reproduced from that decision pathway, outlines the approach to risk reduction with SGLT2 inhibitor or GLP-1 RA 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 type 2 diabetes and established cardiovascular or kidney disease. Incorporation of SGLT2 inhibitor or GLP-1 RA therapy in the care of individuals with diabetes 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 facilitate these transitions in clinical care and, in turn, improve outcomes for people with type 2 diabetes who are at high risk for ASCVD, heart failure, or CKD.

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