8. Cardiovascular Disease and Risk Management

American Diabetes Association

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For prevention and management of diabetes complications in children and adolescents, please refer to Section 11 "Children and Adolescents."

In all patients with diabetes, cardiovascular risk factors should be systematically assessed at least annually. These risk factors include dyslipidemia, hypertension, smoking, a family history of premature coronary disease, and the presence of albuminuria. Abnormal risk factors should be treated as described elsewhere in these guidelines.

Atherosclerotic cardiovascular disease (ASCVD)—defined as acute coronary syndromes (ACSs), a history of myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin—is the leading cause of morbidity and mortality for individuals with diabetes and is the largest contributor to the direct and indirect costs of diabetes. The common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for ASCVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing ASCVD in people with diabetes. Large benefits are seen when multiple risk factors are addressed simultaneously. There is evidence that measures of 10-year coronary heart disease (CHD) risk among U.S. adults with diabetes have improved significantly over the past decade (1) and that ASCVD morbidity and mortality have decreased (2–4).

HYPERTENSION/BLOOD PRESSURE CONTROL

Recommendations

Screening and Diagnosis

- Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. **B**

Goals

Systolic Targets

- People with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg. **A**
- Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals with diabetes, such as younger patients, those with albuminuria, and/or those with hypertension and one or more additional atherosclerotic cardiovascular disease risk factors, if they can be achieved without undue treatment burden. **C**

Diastolic Targets

- Individuals with diabetes should be treated to a diastolic blood pressure goal of <90 mmHg. **A**
- Lower diastolic targets, such as <80 mmHg, may be appropriate for certain individuals with diabetes, such as younger patients, those with albuminuria, and/or those with hypertension and one or more additional atherosclerotic cardiovascular disease risk factors, if they can be achieved without undue treatment burden. **B**

Treatment

- Patients with blood pressure >120/80 mmHg should be advised on lifestyle changes to reduce blood pressure. **B**
- Patients with confirmed office-based blood pressure >140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve blood pressure goals. **A**

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- In older adults, pharmacological therapy to achieve treatment goals of <130/70 mmHg is not recommended; treating to systolic blood pressure <130 mmHg has not been shown to improve cardiovascular outcomes and treating to diastolic blood pressure <70 mmHg has been associated with higher mortality. **C**
- Lifestyle therapy for elevated blood pressure consists of weight loss, if overweight or obese; a Dietary Approaches to Stop Hypertension (DASH)-style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. **B**
- Pharmacological therapy for patients with diabetes and hypertension should comprise a regimen that includes either an ACE inhibitor or an angiotensin receptor blocker but not both. **B** If one class is not tolerated, the other should be substituted. **C**
- Multiple-drug therapy (including a thiazide diuretic and ACE inhibitor/angiotensin receptor blocker, at maximal doses) is generally required to achieve blood pressure targets. **B**
- If ACE inhibitors, angiotensin receptor blockers, or diuretics are used, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored. **E**
- In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 110–129/65–79 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. **E**

Hypertension is a common diabetes comorbidity that affects many patients, with the prevalence depending on type of diabetes, age, BMI, and ethnicity. Hypertension is a major risk factor for both ASCVD and microvascular complications. In type 1 diabetes, hypertension is often the result of underlying diabetic kidney disease, while in type 2 diabetes, it usually coexists with other cardiometabolic risk factors.

Screening and Diagnosis

Blood pressure measurement should be done by a trained individual and should follow the guidelines established for the general population: measurement in the seated position, with feet on the floor and arm supported at heart level, after 5 min of rest. Cuff size should be appropriate for the upper-arm circumference. Elevated values should be confirmed on a separate day. Postural changes in blood pressure and pulse may be evidence of autonomic neuropathy and therefore require adjustment of blood pressure targets.

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. Studies in individuals without diabetes found that home measurements may better correlate with ASCVD risk than office measurements (5,6). However, most of the evidence of benefits of hypertension treatment in people with diabetes is based on office measurements.

Treatment Goals

Epidemiological analyses show that blood pressure >115/75 mmHg is associated with increased cardiovascular event rates and mortality in individuals with diabetes and that systolic blood pressure (SBP) >120 mmHg predicts long-term end-stage renal disease. Randomized clinical trials have demonstrated the benefit (reduction of CHD events, stroke, and diabetic kidney disease) of lowering blood pressure to <140 mmHg systolic and <90 mmHg diastolic in individuals with diabetes (7). There is limited prespecified clinical trial evidence for the benefits of lower SBP or diastolic blood pressure (DBP) targets (8). A meta-analysis of randomized trials of adults with type 2 diabetes comparing intensive blood pressure targets (upper limit of 130 mmHg systolic and 80 mmHg diastolic) with standard targets (upper limit of 140–160 mmHg systolic and 85–100 mmHg diastolic) found no significant reduction in mortality or nonfatal MI. There was a statistically significant 35% relative risk (RR) reduction in stroke with intensive targets, but the absolute risk reduction was only 1%, and intensive targets were associated with an increased risk for adverse events such as hypotension and syncope (9).

ACCORD, ADVANCE, SPRINT, AND HOT

Given the epidemiological relationship between lower blood pressure and better long-term clinical outcomes, two landmark trials, Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation–Blood Pressure (ADVANCE-BP), examined the benefit of tighter blood pressure control in patients with type 2 diabetes.

ACCORD. The ACCORD trial examined whether a lower SBP of <120 mmHg in patients with type 2 diabetes at high risk for ASCVD provided greater cardiovascular protection than an SBP of 130–140 mmHg (10). The study did not find a benefit in primary end point (nonfatal MI, nonfatal stroke, and cardiovascular death) comparing intensive blood pressure treatment (goal <120 mmHg, average blood pressure achieved = 119/64 mmHg on 3.4 medications) with standard treatment (average blood pressure achieved = 143/70 mmHg on 2.1 medications). In ACCORD, there was no benefit of aggressive blood pressure lowering, despite the extra cost and efforts.

ADVANCE. In ADVANCE, the active blood pressure intervention arm (a single-pill, fixed-dose combination of perindopril and indapamide) showed a significant reduction in the risk of the primary composite end point (major macrovascular or microvascular event) and significant reductions in the risk of death from any cause and of death from cardiovascular causes (11). The baseline blood pressure among the study subjects was 145/81 mmHg. Compared with the placebo group, the patients treated with a single-pill, fixed-dose combination of perindopril and indapamide experienced an average reduction of 5.6 mmHg in SBP and 2.2 mmHg in DBP. The final blood pressure in the treated group was 136/73 mmHg, not quite the intensive or tight control achieved in ACCORD. Recently published 6-year follow-up of the ADVANCE–Post-Trial Observational Study (ADVANCE-ON) reported that the reductions in the risk of death from any cause and of death from cardiovascular causes in the intervention group were attenuated, but remained significant (12).

SPRINT. Systolic Blood Pressure Intervention Trial (SPRINT) was a multicenter, randomized controlled trial that compared two strategies for treating SBP with either the standard target of <140 mmHg or an intensive target of <120 mmHg; primary outcomes were MI, ACS, stroke, heart failure, and death due to cardiovascular disease. *Of note, patients with diabetes*

were excluded from participating in this trial, so the results have no direct implications for blood pressure management in this population. The National Institutes of Health halted this study early because intensive therapy with a target SBP of 120 mmHg demonstrated a risk reduction of cardiovascular events by almost a third and the risk of death by almost a quarter compared with a target SBP of 140 mmHg (13).

HOT. The results from the ACCORD and Hypertension Optimal Treatment (HOT) (14) trials support the recommendation to achieve blood pressure levels <140/90 mmHg and underscore the important clinical difference between patients who are able to easily achieve lower blood pressure levels (e.g., as seen in observational epidemiological studies) and patients who require intensive medical management to achieve lower blood pressure goals (e.g., the clinical trials).

Systolic Blood Pressure

There is strong evidence that SBP >140 mmHg is harmful, suggesting that clinicians should promptly initiate and titrate therapy in an ongoing fashion to achieve and maintain SBP <140 mmHg in most patients (see Section 10 "Older Adults"). A recent systematic review and meta-analysis evaluating SBP lowering in adults with type 2 diabetes showed that each 10-mmHg reduction of SBP was associated with significantly lower risk of mortality, cardiovascular events, CHD, stroke, albuminuria, and retinopathy. However, when trials were stratified by mean baseline SBP ≥140 mmHg or <140 mmHg, blood pressure–lowering treatment was associated with lower risks of stroke and albuminuria, regardless of initial SBP (15). Therefore, individuals in whom stroke risk is a concern may, as part of shared decision making, have lower systolic targets such as <130 mmHg. This is especially true if lower blood pressure can be achieved with few drugs and without side effects of therapy.

Diastolic Blood Pressure

Similarly, strong evidence from randomized clinical trials supports DBP targets of <90 mmHg. Prior recommendations for lower DBP targets (<80 mmHg) were based primarily on a post hoc analysis of the HOT trial (14). A DBP of <80 mmHg may still be appropriate for patients with long life expectancy, those with chronic kidney disease, elevated urinary albumin excretion, and additional ASCVD risk factors such as dyslipidemia, smoking, or obesity (14). The 2016 American Diabetes Association (ADA) Standards of Care recommendations have been revised to reflect the higher-quality evidence that exists to support a goal of DBP <90 mmHg, although lower targets may be appropriate for certain individuals. These targets are in harmonization with a recent publication by the Eighth Joint National Committee that recommended for individuals over 18 years of age with diabetes a DBP threshold of <90 mmHg and SBP <140 mmHg (8).

Treatment Strategies

Lifestyle Modification

Although there are no well-controlled studies of diet and exercise in the treatment of elevated blood pressure or hypertension in individuals with diabetes, the Dietary Approaches to Stop Hypertension (DASH) study evaluated the impact of healthy dietary patterns in individuals without diabetes and has shown antihypertensive effects similar to those of pharmacological monotherapy.

Lifestyle therapy consists of reducing excess body weight, 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) (16), and increasing activity levels (17).

These lifestyle (nonpharmacological) strategies may also positively affect glycemia and lipid control and should be encouraged in those with even mildly elevated blood pressure, although the impact of lifestyle therapy on cardiovascular events has not been established. Nonpharmacological therapy is reasonable in individuals with diabetes and mildly elevated blood pressure (SBP >120 mmHg or DBP >80 mmHg). If the blood pressure is confirmed to be ≥140 mmHg systolic and/or ≥90 mmHg diastolic, pharmacological therapy should be initiated along with nonpharmacological therapy (17). To enable long-term adherence, lifestyle therapy should be adapted to suit the needs of the patient and discussed as part of diabetes management.

Pharmacological Interventions

ACE Inhibitors. Lowering of blood pressure with regimens based on a variety of antihypertensive agents, including ACE inhibitors, angiotensin receptor blockers (ARBs), β-blockers, diuretics, and calcium channel blockers, has been shown to be effective in reducing cardiovascular events. Several studies have suggested that ACE inhibitors may be superior to dihydropyridine calcium channel blockers in reducing cardiovascular events (18–20). However, several studies have also shown no specific advantage to ACE inhibitors as an initial treatment of hypertension in the general hypertensive population, while showing an advantage of initial therapy with low-dose thiazide diuretics on cardiovascular outcomes (17,21,22).

Angiotensin Receptor Blockers. In people with diabetes, inhibitors of the renin-angiotensin system (RAS) may have unique advantages for initial or early treatment of hypertension. In a trial of individuals at high risk for ASCVD, including a large subset with diabetes, an ACE inhibitor reduced ASCVD outcomes (23). In patients with congestive heart failure, including subgroups with diabetes, ARBs have been shown to reduce major ASCVD outcomes (24–27). In patients with type 2 diabetes with significant diabetic kidney disease, ARBs were superior to calcium channel blockers for reducing heart failure (28). Although evidence for distinct advantages of RAS inhibitors on ASCVD outcomes in diabetes remains conflicting (11,22), the high ASCVD risks associated with diabetes and the high prevalence of undiagnosed ASCVD may still favor recommendations for their use as first-line antihypertensive therapy in people with diabetes (17).

However, the use of both ACE inhibitors and ARBs in combination is not recommended given the lack of added ASCVD benefit and increased rate of adverse events—namely, hyperkalemia, syncope, and renal dysfunction (29).

Other Pharmacological Interventions

The blood pressure arm of the ADVANCE trial demonstrated that routine administration of a fixed combination of the ACE inhibitor perindopril and the diuretic indapamide significantly reduced combined microvascular and macrovascular outcomes, as well as death from cardiovascular causes and total mortality. The improved outcomes could also have been due to lower achieved blood pressure in the perindopril–indapamide arm (11). Another trial showed a decrease

in morbidity and mortality in those receiving benazepril and amlodipine versus benazepril and hydrochlorothiazide (HCTZ) (30). The compelling benefits of RAS inhibitors in patients with diabetes and albuminuria or renal insufficiency provide additional rationale for the use of these agents (see Section 9 "Microvascular Complications and Foot Care"). If needed to achieve blood pressure targets, amlodipine, HCTZ, or chlorthalidone can be added. If estimated glomerular filtration rate is <30 mL/min/1.73 m^2, a loop diuretic, rather than HCTZ or chlorthalidone, should be prescribed. Titration of and/or addition of further blood pressure medications should be made in a timely fashion to overcome clinical inertia in achieving blood pressure targets.

Bedtime Dosing

Growing evidence suggests that there is an association between increase in sleep-time blood pressure and incidence of ASCVD events. A randomized controlled trial of 448 participants with type 2 diabetes and hypertension demonstrated reduced cardiovascular events and mortality with median follow-up of 5.4 years if at least one antihypertensive medication was given at bedtime (31). Consider administering one or more antihypertensive medications at bedtime (32).

Other Considerations

An important caveat is that most patients with diabetes with hypertension require multiple-drug therapy to reach treatment goals (16). Identifying and addressing barriers to medication adherence (such as cost and side effects) should routinely be done. If blood pressure remains uncontrolled despite confirmed adherence to optimal doses of at least three antihypertensive agents of different classes, one of which should be a diuretic, clinicians should consider an evaluation for secondary causes of hypertension.

Pregnancy and Antihypertensive Medications

In a pregnancy complicated by diabetes and chronic hypertension, target blood pressure goals of SBP 110–129 mmHg and DBP 65–79 mmHg are reasonable, as they contribute to improved long-term maternal health. Lower blood pressure levels may be associated with impaired fetal growth. During pregnancy, treatment with ACE inhibitors and ARBs is contraindicated, as they may cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin. Chronic diuretic use during pregnancy is not recommended as it has been associated with restricted maternal plasma volume, which may reduce uteroplacental perfusion (33).

LIPID MANAGEMENT

Recommendations

- In adults not taking statins, it is reasonable to obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and every 5 years thereafter, or more frequently if indicated. **E**
- Obtain a lipid profile at initiation of statin therapy and periodically thereafter as it may help to monitor the response to therapy and inform adherence. **E**
- Lifestyle modification focusing on weight loss (if indicated); the reduction of saturated fat, *trans* fat, and cholesterol intake; increase of omega-3 fatty acids, viscous fiber, and plant stanols/sterols intake; and increased physical activity should be recommended to improve the lipid profile in patients with diabetes. **A**
- Intensify lifestyle therapy and optimize glycemic control for patients with elevated triglyceride levels (≥150 mg/dL [1.7 mmol/L]) and/or low HDL cholesterol (<40 mg/dL [1.0 mmol/L] for men, <50 mg/dL [1.3 mmol/L] for women). **C**
- For patients 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**
- For patients of all ages with diabetes and atherosclerotic cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy. **A**
- For patients with diabetes aged <40 years with additional atherosclerotic cardiovascular disease risk factors, consider using moderate-intensity or high-intensity statin and lifestyle therapy. **C**
- For patients with diabetes aged 40–75 years without additional atherosclerotic cardiovascular disease risk factors, consider using moderate-intensity statin and lifestyle therapy. **A**
- For patients with diabetes aged 40–75 years with additional atherosclerotic cardiovascular disease risk factors, consider using high-intensity statin and lifestyle therapy. **B**
- For patients with diabetes aged >75 years without additional atherosclerotic cardiovascular disease risk factors, consider using moderate-intensity statin therapy and lifestyle therapy. **B**
- For patients with diabetes aged >75 years with additional atherosclerotic cardiovascular disease risk factors, consider using moderate-intensity or high-intensity statin therapy and lifestyle therapy. **B**
- In clinical practice, providers may need to adjust intensity of statin therapy based on individual patient response to medication (e.g., side effects, tolerability, LDL cholesterol levels). **E**
- The addition of ezetimibe to moderate-intensity statin therapy has been shown to provide additional cardiovascular benefit compared with moderate-intensity statin therapy alone and may be considered for patients with a recent acute coronary syndrome with LDL cholesterol ≥50 mg/dL (1.3 mmol/L) or for those patients who cannot tolerate high-intensity statin therapy. **A**
- Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. **A** However, therapy with statin and fenofibrate may be considered for men with both triglyceride level ≥204 mg/dL (2.3 mmol/L) and HDL cholesterol level ≤34 mg/dL (0.9 mmol/L). **B**
- Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone and may increase the risk of stroke and is not generally recommended. **A**
- Statin therapy is contraindicated in pregnancy. **B**

Lifestyle Intervention

Lifestyle intervention, including weight loss, increased physical activity, and medical nutrition therapy, allows some patients to reduce ASCVD risk factors.

Nutrition intervention should be tailored according to each patient's age, diabetes type, pharmacological treatment, lipid levels, and medical conditions. Recommendations should focus on reducing saturated fat, cholesterol, and *trans* fat intake and increasing plant stanols/sterols, omega-3 fatty acids, and viscous fiber (such as in oats, legumes, and citrus). Glycemic control can also beneficially modify plasma lipid levels, particularly in patients with very high triglycerides and poor glycemic control.

Table 8.1—Recommendations for statin and combination treatment in people with diabetes

Age	Risk factors	Recommended statin intensity*
<40 years	None	None
	ASCVD risk factor(s)**	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ASCVD	High
	ACS and LDL cholesterol >50 mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins	Moderate plus ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS and LDL cholesterol >50 mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins	Moderate plus ezetimibe

*In addition to lifestyle therapy.
**ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, overweight and obesity, and family history of premature ASCVD.

Statin Treatment

Initiating Statin Therapy Based on Risk

Patients 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 pharmacological (statin) therapy on ASCVD outcomes in subjects with and without CHD (34,35). Subgroup analyses of patients with diabetes in larger trials (36–40) and trials in patients with diabetes (41,42) showed significant primary and secondary prevention of ASCVD events and CHD death in patients with diabetes. Meta-analyses, including data from over 18,000 patients with diabetes from 14 randomized trials of statin therapy (mean follow-up 4.3 years), demonstrate a 9% proportional reduction in all-cause mortality and 13% reduction in vascular mortality for each mmol/L (39 mg/dL) reduction in LDL cholesterol (43).

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 (44,45). Statins are the drugs of choice for LDL cholesterol lowering and cardioprotection.

Most trials of statins and ASCVD outcomes tested specific doses of statins against placebo or other statins rather than aiming for specific LDL cholesterol goals (46). In light of this fact, the 2016 ADA Standards of Care position statement was revised to recommend when to initiate and intensify statin therapy (high vs. moderate intensity) based on risk profile (**Table 8.1** and **Table 8.2**).

The Risk Calculator. The American College of Cardiology/American Heart Association ASCVD risk calculator may be a useful tool to estimate 10-year ASCVD (http://my.americanheart.org). As diabetes itself confers increased risk for ASCVD, the risk calculator has limited use for assessing cardiovascular risk in individuals with diabetes.

Age ≥40 Years

In all patients with diabetes aged ≥40 years, moderate-intensity statin treatment should be considered in addition to lifestyle therapy. Clinical trials in high-risk patients, such as those with ACS or previous cardiovascular events (47–49), have demonstrated that more aggressive therapy with high doses of statins led to a significant reduction in further events. Therefore, high-dose statins are recommended in patients with increased cardiovascular risk (e.g., LDL cholesterol ≥100 mg/dL [2.6 mmol/L], high blood pressure, smoking, albuminuria, and family history of premature ASCVD) or with ASCVD.

Age >75 Years

For adults with diabetes over 75 years of age, there are limited data regarding the benefits and risks of statin therapy. Statin therapy should be individualized based on risk profile. High-intensity statins, if well tolerated, are still appropriate and recommended for older adults with ASCVD. High-intensity statin therapy may also be appropriate in adults with diabetes >75 years of age with additional ASCVD risk factors. However, the risk–benefit profile should be routinely evaluated in this population, with downward titration (e.g., high to moderate intensity) performed as needed. See Section 10 "Older Adults" for more details on clinical considerations for this population.

Age <40 Years and/or Type 1 Diabetes

Very little clinical trial evidence exists for patients with type 2 diabetes under the age of 40 years or for patients with type 1 diabetes of any age. In the Heart Protection Study (lower age limit 40 years), the subgroup of ~600 patients with type 1 diabetes had a proportionately

Table 8.2—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy	Moderate-intensity statin therapy
Lowers LDL cholesterol by ≥50%	Lowers LDL cholesterol by 30% to <50%
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 2–4 mg

*Once-daily dosing.

similar, although not statistically significant, reduction in risk as patients with type 2 diabetes (37). Even though the data are not definitive, similar statin treatment approaches should be considered for patients with type 1 or type 2 diabetes, particularly in the presence of other cardiovascular risk factors. Please refer to "Type 1 Diabetes Mellitus and Cardiovascular Disease: A Scientific Statement From the American Heart Association and American Diabetes Association" (50) for additional discussion.

High-intensity statin therapy is recommended for all patients with diabetes and ASCVD. Treatment with a moderate dose of statin should be considered if the patient does not have ASCVD but has additional ASCVD risk factors.

Ongoing Therapy and Monitoring With Lipid Panel

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. A lipid panel should also be obtained immediately before initiating statin therapy. Once a patient is taking a statin, testing for LDL cholesterol may be considered on an individual basis (e.g., to monitor for adherence and efficacy). In cases where patients are adherent, but the LDL cholesterol level is not responding, clinical judgment is recommended to determine the need for and timing of lipid panels. In individual patients, the highly variable LDL cholesterol–lowering response seen with statins is poorly understood (51). When maximally tolerated doses of statins fail to substantially lower LDL cholesterol (<30% reduction from the patient's baseline), there is no strong evidence that combination therapy should be used. 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 (52).

Increased frequency of LDL cholesterol monitoring should be considered for patients with new-onset ACS. A recent randomized controlled trial evaluated the addition of ezetimibe to moderate-intensity statin therapy and demonstrated ASCVD risk benefit over statin monotherapy (53). Increased frequency of LDL cholesterol monitoring may also be considered in adults with heterozygous familial hypercholesterolemia who require additional lowering of LDL cholesterol.

Combination Therapy for LDL Cholesterol Lowering

Statins and Ezetimibe

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a randomized controlled trial comparing the addition of ezetimibe to simvastatin therapy versus simvastatin alone. Individuals were ≥50 years of age who experienced an ACS within the preceding 10 days and had an LDL cholesterol level ≥50 mg/dL (1.3 mmol/L). In those with diabetes (27%), the combination of moderate-intensity simvastatin (40 mg) and ezetimibe (10 mg) showed a significant reduction of major adverse cardiovascular events with an absolute risk reduction of 5% (40% vs. 45%) and RR reduction of 14% (RR 0.86 [95% CI 0.78–0.94]) over moderate-intensity simvastatin (40 mg) alone (53). Therefore, for people meeting IMPROVE-IT eligibility criteria who can only tolerate a moderate-dose statin, the addition of ezetimibe to statin therapy should be considered.

Statins and PCSK9 Inhibitors

Placebo-controlled trials evaluating the addition of the novel PCSK9 inhibitors, evolocumab and alirocumab, to maximally tolerated doses of statin therapy in participants who were at high risk for ASCVD demonstrated an average reduction in LDL cholesterol ranging from 36% to 59%. These agents may therefore be considered as adjunctive therapy for patients with diabetes at high risk for ASCVD events who require additional lowering of LDL cholesterol or who require but are intolerant to high-intensity statin therapy (54,55). It is important to note that the effects of this novel class of agents on ASCVD outcomes are unknown as phase 4 studies are currently under way.

Treatment of Other Lipoprotein Fractions or Targets

Hypertriglyceridemia should be addressed with dietary and lifestyle changes including abstinence from alcohol (56). Severe hypertriglyceridemia (>1,000 mg/dL) may warrant immediate pharmacological therapy (fibric acid derivatives and/or fish oil) to reduce the risk of acute pancreatitis.

Low levels of HDL cholesterol, often associated with elevated triglyceride levels, are the most prevalent pattern of dyslipidemia in individuals 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 (57). In a large trial in patients with diabetes, fenofibrate failed to reduce overall cardiovascular outcomes (58).

Combination Therapy

Statin and Fibrate

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 (59) (compared with fenofibrate).

In the ACCORD study, in patients 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 as 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) (60).

Statin and Niacin

The Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial randomized over 3,000 patients (about one-third with diabetes) with established ASCVD, low LDL cholesterol levels (<180 mg/dL [4.7 mmol/L]), low HDL cholesterol levels (men <40 mg/dL [1.0 mmol/L] and women <50 mg/dL [1.3 mmol/L]), and triglyceride levels of 150–400 mg/dL (1.7–4.5 mmol/L) to statin therapy plus extended-release niacin or placebo. The trial was halted early due to lack of efficacy on the primary ASCVD outcome (first event of the composite of death from CHD, nonfatal MI, ischemic stroke, hospitalization for an ACS, or symptom-driven coronary or cerebral revascularization) and a possible increase in ischemic stroke in those on combination therapy (61). Therefore, combination therapy with a statin and niacin is not recommended given the lack of efficacy on major ASCVD outcomes,

possible increase in risk of ischemic stroke, and side effects.

Diabetes With Statin Use

Several studies have reported an increased risk of incident diabetes with statin use (62,63), which may be limited to those with diabetes risk factors. An analysis of one of the initial studies suggested that although statins were linked to diabetes risk, the cardiovascular event rate reduction with statins far outweighed the risk of incident diabetes even for patients at highest risk for diabetes (64). 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) (64). A meta-analysis of 13 randomized statin trials with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of diabetes, so that (on average) treatment of 255 patients with statins for 4 years resulted in one additional case of diabetes, while simultaneously preventing 5.4 vascular events among those 255 patients (63).

Statins and Cognitive Function

A recent systematic review of the U.S. Food and Drug Administration's postmarketing surveillance databases, randomized controlled trials, and cohort, case-control, and cross-sectional studies evaluating cognition in patients receiving statins found that published data do not reveal an adverse effect of statins on cognition. Therefore, a concern that statins might cause cognitive dysfunction or dementia should not prohibit their use in individuals with diabetes at high risk for ASCVD (65).

ANTIPLATELET AGENTS

Recommendations

- Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes who are at increased cardiovascular risk (10-year risk >10%). This includes most men or women with diabetes aged ≥50 years who have at least one additional major risk factor (family history of premature atherosclerotic cardiovascular disease, hypertension, smoking, dyslipidemia, or albuminuria) and are not at increased risk of bleeding. **C**
- Aspirin should not be recommended for atherosclerotic cardiovascular disease prevention for adults with diabetes at low atherosclerotic cardiovascular disease risk (10-year atherosclerotic cardiovascular disease risk <5%), such as in men or women with diabetes aged <50 years with no major additional atherosclerotic cardiovascular disease risk factors, as the potential adverse effects from bleeding likely offset the potential benefits. **C**
- In patients with diabetes <50 years of age with multiple other risk factors (e.g., 10-year risk 5–10%), clinical judgment is required. **E**
- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease. **A**
- For patients with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**
- Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome. **B**

Risk Reduction

Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with previous MI or stroke (secondary prevention). Its net benefit in primary prevention among patients with no previous cardiovascular events is more controversial, both for patients with diabetes and for patients without diabetes (66,67). Previous randomized controlled trials of aspirin specifically in patients 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 (68–71).

The Antithrombotic Trialists' (ATT) collaborators published an individual patient-level meta-analysis of the six large trials of aspirin for primary prevention in the general population. These trials collectively enrolled over 95,000 participants, including almost 4,000 with diabetes. Overall, they found that aspirin reduced the risk of serious vascular events by 12% (RR 0.88 [95% CI 0.82–0.94]). The largest reduction was for nonfatal MI, with little effect on CHD death (RR 0.95 [95% CI 0.78–1.15]) or total stroke. There was some evidence of a difference in aspirin effect by sex: aspirin significantly reduced ASCVD events in men, but not in women. Conversely, aspirin had no effect on stroke in men but significantly reduced stroke in women. However, there was no heterogeneity of effect by sex in the risk of serious vascular events ($P = 0.9$). Sex differences in aspirin's effects have not been observed in studies of secondary prevention (66). In the six trials examined by the ATT collaborators, the effects of aspirin on major vascular events were similar for patients with or without diabetes: RR 0.88 (95% CI 0.67–1.15) and RR 0.87 (95% CI 0.79–0.96), respectively. The confidence interval was wider for those with diabetes because of smaller numbers.

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 effects appear to be an increased risk of gastrointestinal bleeding. The excess risk may be as high as 1–5 per 1,000 per year in real-world settings. In adults with ASCVD risk >1% per year, the number of ASCVD events prevented will be similar to or greater than the number of episodes of bleeding induced, although these complications do not have equal effects on long-term health (72).

Treatment Considerations

In 2010, a position statement of the ADA, the American Heart Association, and the American College of Cardiology Foundation recommended that low-dose (75–162 mg/day) aspirin for primary prevention is reasonable for adults with diabetes and no previous history of vascular disease who are at increased ASCVD risk (10-year risk of ASCVD events over 10%) and who are not at increased risk for bleeding. This previous recommendation included most men over age 50 years and women over age 60 years who also have one or more of the following major risk factors: smoking, hypertension, dyslipidemia, family history of premature ASCVD, and albuminuria (73).

Sex Considerations

Multiple recent well-conducted studies and meta-analyses reported a risk of heart disease and stroke that is equivalent if not higher in women compared with men with diabetes, including among nonelderly adults. Thus, the recommendations for using aspirin as primary

prevention are now revised to include both men and women aged ≥50 years with diabetes and one or more major risk factors to reflect these more recent findings (74–77). Sex differences in the antiplatelet effect of aspirin have been suggested in the general population (78); however, further studies are needed to investigate the presence of such differences in individuals with diabetes.

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; 10-year ASCVD risk <5%) as the low benefit is likely to be outweighed by the risks of significant bleeding. Clinical judgment should be used for those at intermediate risk (younger patients with one or more risk factors or older patients with no risk factors; those with 10-year ASCVD risk of 5–10%) until further research is available. Aspirin use in patients aged <21 years is contraindicated due to the associated risk of Reye syndrome.

Aspirin Dosing

Average daily dosages used in most clinical trials involving patients with diabetes ranged from 50 mg to 650 mg but were mostly in the range of 100–325 mg/day. There is little evidence to support any specific dose, but using the lowest possible dose may help to reduce side effects (79). In the U.S., the most common low-dose tablet is 81 mg. Although platelets from patients 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 the patient with diabetes. Many alternate pathways for platelet activation exist that are independent of thromboxane A_2 and thus not sensitive to the effects of aspirin (80). "Aspirin resistance" appears higher in patients with diabetes when measured by a variety of ex vivo and in vitro methods (platelet aggregometry, measurement of thromboxane B_2) (78). A recent trial suggested that more frequent dosing regimens of aspirin may reduce platelet reactivity in individuals with diabetes (81); however, these observations alone are insufficient to empirically recommend that higher doses of aspirin be used in this group at this time. It appears that 75–162 mg/day is optimal.

Indications for P2Y12 Use

A P2Y12 receptor antagonist in combination with aspirin should be used for at least 1 year in patients following an ACS. 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 (82).

CORONARY HEART DISEASE

Recommendations

Screening

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

Treatment

- In patients with known atherosclerotic cardiovascular disease, use aspirin and statin therapy (if not contraindicated) **A** and consider ACE inhibitor therapy **C** to reduce the risk of cardiovascular events.
- In patients with prior myocardial infarction, β-blockers should be continued for at least 2 years after the event. **B**
- In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. **A**
- In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if renal function is normal but should be avoided in unstable or hospitalized patients with congestive heart failure. **B**

Cardiac Testing

Candidates for advanced or invasive cardiac testing include those with *1*) typical or atypical cardiac symptoms and *2*) an abnormal resting electrocardiogram (ECG). Exercise ECG testing without or with echocardiography may be used as the initial test. In adults with diabetes ≥40 years of age, measurement of coronary artery calcium is also reasonable for cardiovascular risk assessment. Pharmacological 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 pharmacological stress echocardiography or nuclear imaging.

Screening Asymptomatic Patients

The screening of asymptomatic patients with high ASCVD risk is not recommended (44), in part because these high-risk patients should already be receiving intensive medical therapy—an approach that provides similar benefit as invasive revascularization (83,84). There is also some evidence that silent MI may reverse over time, adding to the controversy concerning aggressive screening strategies (85). In prospective trials, coronary artery calcium has been established as an independent predictor of future ASCVD events in patients with diabetes and is superior to both the UK Prospective Diabetes Study (UKPDS) risk engine and the Framingham Risk Score in predicting risk in this population (86–88). However, a randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic patients with type 2 diabetes and normal ECGs (89). Despite abnormal myocardial perfusion imaging in more than one in five patients, cardiac outcomes were essentially equal (and very low) in screened versus unscreened patients. Accordingly, indiscriminate screening is not considered cost-effective. Studies have found that a risk factor–based approach to the initial diagnostic evaluation and subsequent follow-up for coronary artery disease fails to identify which patients with type 2 diabetes will have silent ischemia on screening tests (90,91). Any benefit of newer noninvasive coronary artery disease screening methods, such as computed tomography and computed tomography angiography, to identify patient subgroups for different treatment strategies remains unproven. Although asymptomatic patients with diabetes with higher coronary disease burden have more future cardiac events

(86,92,93), the role of these tests beyond risk stratification is not clear. Their routine use leads to radiation exposure and may result in unnecessary invasive testing such as coronary angiography and revascularization procedures. The ultimate balance of benefit, cost, and risks of such an approach in asymptomatic patients remains controversial, particularly in the modern setting of aggressive ASCVD risk factor control.

Lifestyle and Pharmacological Interventions

Intensive lifestyle intervention focusing on weight loss through decreased caloric intake and increased physical activity as performed in the Action for Health in Diabetes (Look AHEAD) trial may be considered for improving glucose control, fitness, and some ASCVD risk factors. Patients at increased ASCVD risk should receive aspirin and a statin and ACE inhibitor or ARB therapy if the patient has hypertension, unless there are contraindications to a particular drug class. While clear benefit exists for ACE inhibitor and ARB therapy in patients with nephropathy or hypertension, the benefits in patients with ASCVD in the absence of these conditions are less clear, especially when LDL cholesterol is concomitantly controlled (94,95). In patients with prior MI, β-blockers should be continued for at least 2 years after the event (96).

Diabetes and Heart Failure

Almost 50% of patients with type 2 diabetes will develop heart failure (97). Data on the effects of glucose-lowering agents on heart failure outcomes have demonstrated that thiazolidinediones have a strong and consistent relationship with heart failure (98–100). Therefore, thiazolidinedione use should be avoided in patients with symptomatic heart failure.

Recent studies have now examined the relationship between dipeptidyl peptidase 4 (DPP-4) inhibitors and heart failure and have mixed results. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) study showed that patients treated with saxagliptin (a DPP-4 inhibitor) were more likely to be hospitalized for heart failure than were those given placebo (3.5% vs. 2.8%, respectively) (101). However, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) and Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), recent multicenter, randomized, double-blind, noninferiority trials, evaluated heart failure and mortality outcomes in patients with type 2 diabetes taking different DPP-4 inhibitors, alogliptin and sitagliptin, respectively, compared with placebo. EXAMINE reported that the hospital admission rate for heart failure was 3.1% for patients randomly assigned to alogliptin compared with 2.9% for those randomly assigned to placebo (hazard ratio 1.07 [95% CI 0.79–1.46]) (102). Alogliptin had no effect on the composite end point of cardiovascular death and hospital admission for heart failure in the post hoc analysis (hazard ratio 1.00 [95% CI 0.82–1.21]) (102). TECOS showed a nonsignificant difference in the rate of heart failure hospitalization for the sitagliptin group (3.1%; 1.07 per 100 person-years) compared with the placebo group (3.1%; 1.09 per 100 person-years) (103).

EMPA-REG OUTCOME Study

The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was a randomized, double-blind, placebo-controlled trial that assessed the effect of empagliflozin, a sodium–glucose cotransporter 2 inhibitor on cardiovascular outcomes (stroke, MI, amputation, or coronary, carotid, or peripheral artery obstruction) in patients with type 2 diabetes at high risk for cardiovascular disease. Study participants had a mean age of 63 years, 57% had diabetes for more than 10 years, and 70% had a history of either stroke or MI. EMPA-REG OUTCOME showed that the therapy reduced the aggregate outcome of MI, stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group), due to a 38% reduction in cardiovascular death (absolute rate 3.7% vs. 5.9%) (104). Empagliflozin is the first of the recently approved diabetes treatments associated with a lower risk of cardiovascular disease. Whether empagliflozin or other sodium–glucose cotransporter 2 inhibitors will have a similar effect in lower-risk patients with diabetes remains unknown.

Metformin

A systematic review of 34,000 patients showed that metformin is as safe as other glucose-lowering treatments in patients with diabetes and congestive heart failure, even in those with reduced left ventricular ejection fraction or concomitant chronic kidney disease; however, metformin should be avoided in hospitalized patients (105).

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