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.

Cardiovascular disease (CVD) is the major 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 CVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing CVD in people with diabetes. Large benefits are seen when multiple risk factors are addressed globally (1,2). 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 (3).

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

- People with diabetes and hypertension should be treated to a systolic blood pressure (SBP) goal of <140 mmHg. **A**
- Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals, such as younger patients, if they can be achieved without undue treatment burden. **C**
- Individuals with diabetes should be treated to a diastolic blood pressure (DBP) <90 mmHg. **A**
- Lower diastolic targets, such as <80 mmHg, may be appropriate for certain individuals, such as younger patients, 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 higher than 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**
- 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 (ARB). **B** If one class is not tolerated, the other should be substituted. **C**
- Multiple-drug therapy (including a thiazide diuretic and ACE inhibitor/ARB, at maximal doses) is generally required to achieve blood pressure targets. **B**

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- If ACE inhibitors, ARBs, or diuretics are used, serum creatinine/estimated glomerular filtration rate (eGFR) 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. ACE inhibitors and ARBs are contraindicated during pregnancy. E

Hypertension is a common diabetes comorbidity that affects the majority of patients, with the prevalence depending on type of diabetes, age, obesity, and ethnicity. Hypertension is a major risk factor for both CVD and microvascular complications. In type 1 diabetes, hypertension is often the result of underlying nephropathy, 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 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.

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 CVD risk than office measurements (4,5). 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 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 (6). There is limited prespecified clinical trial evidence for the benefits of lower SBP or DBP targets (7). 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) to standard targets (upper limit of 140–160 mmHg systolic and 85–100 mmHg diastolic) found no significant reduction in mortality or nonfatal myocardial infarction (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 (8).

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), were conducted in the past decade to examine the benefit of tighter blood pressure control in patients with type 2 diabetes.

The ACCORD trial examined whether a lower SBP of <120 mmHg, in type 2 diabetic patients at high risk for CVD, provided greater cardiovascular protection than an SBP level of 130–140 mmHg (9). 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.

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), as well as significant reductions in the risk of death from any cause and of death from cardiovascular causes (10). 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-BP study 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 (11).

These results underscore the important clinical difference between patients who are able to easily achieve lower blood pressure levels (e.g., as seen in observational epidemiology studies) and patients who require intensive medical management to achieve these goals (e.g., the clinical trials).

Systolic Blood Pressure

The clear body of evidence that SBP >140 mmHg is harmful suggests that clinicians should promptly initiate and titrate therapy in an ongoing fashion to achieve and maintain SBP <140 mmHg in virtually all patients. Patients with long life expectancy may have renal benefits from long-term intensive blood pressure control. Additionally, individuals in whom stroke risk is a concern may, as part of shared decision making, have appropriately 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, the clearest 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 Hypertension Optimal Treatment (HOT) trial (12). This level may still be appropriate for patients with long life expectancy and those with chronic kidney disease and elevated urine albumin excretion (12). The 2015 American Diabetes Association (ADA) Standards of Care 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. This is 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 (7).

Treatment Strategies

Lifestyle Modifications

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 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 restricting sodium intake (<2,300 mg/day); reducing excess body weight; increasing consumption of fruits, 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) (13); and increasing activity levels (14). For individuals with diabetes and hypertension, setting a sodium intake goal of <1,500 mg/day should be considered on an individual basis.

These lifestyle (nonpharmacological) strategies may also positively affect glycemia and lipid control and should be encouraged in those with even mildly elevated blood pressure. The effects of lifestyle therapy on cardiovascular events have 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 (14). 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

Lowering of blood pressure with regimens based on a variety of antihypertensive agents, including ACE inhibitors, 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 (15–17). However, several studies have also shown no specific advantage to ACE inhibitors as initial treatment of hypertension in the general hypertensive population, while showing an advantage of initial therapy with low-dose thiazide diuretics on cardiovascular outcomes (14,18,19).

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 CVD, including a large subset with diabetes, an ACE inhibitor reduced CVD outcomes (20). In patients with congestive heart failure (CHF), including subgroups with diabetes, ARBs have been shown to reduce major CVD outcomes (21–24). In type 2 diabetic patients with significant diabetic kidney disease, ARBs were superior to calcium channel blockers for reducing heart failure (25). Although evidence for distinct advantages of RAS inhibitors on CVD outcomes in diabetes remains conflicting (10,19), the high CVD risks associated with diabetes, and the high prevalence of undiagnosed CVD, may still favor recommendations for their use as first-line hypertension therapy in people with diabetes (14).

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 (10). Another trial showed a decrease in morbidity and mortality in those receiving benazepril and amlodipine versus benazepril and hydrochlorothiazide (HCTZ). The compelling benefits of RAS inhibitors in diabetic patients with albuminuria or renal insufficiency provide additional rationale for 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 eGFR is <30 mL/min/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 timely fashion to overcome clinical inertia in achieving blood pressure targets.

Growing evidence suggests that there is an association between increase in sleep-time blood pressure and incidence of CVD 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 (26). Consider administering one or more antihypertensive medications at bedtime (27).

An important caveat is that most patients with hypertension require multiple-drug therapy to reach treatment goals (13). 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 classifications, one of which should be a diuretic, clinicians should consider an evaluation for secondary forms 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, since 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 has been associated with restricted maternal plasma volume, which may reduce uteroplacental perfusion (28).

DYSLIPIDEMIA/LIPID MANAGEMENT

Recommendations

Screening

- In adults, a screening lipid profile is reasonable at the time of first diagnosis, at the initial medical evaluation, and/or at age 40 years and periodically (e.g., every 1–2 years) thereafter. **E**

Treatment Recommendations and Goals

- Lifestyle modification focusing on the reduction of saturated fat, *trans* fat, and cholesterol intake; increase of omega-3 fatty acids, viscous fiber, and plant stanols/sterols; weight loss (if indicated); 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 and consider medical therapy to reduce risk of pancreatitis. **C**
- For patients of all ages with diabetes and overt CVD, high-intensity statin therapy should be added to lifestyle therapy. **A**
- For patients with diabetes aged <40 years with additional CVD risk factors, consider using moderate- or high-intensity statin and lifestyle therapy. **C**
- For patients with diabetes aged 40–75 years without additional CVD risk factors, consider using moderate-intensity statin and lifestyle therapy. **A**
- For patients with diabetes aged 40–75 years with additional CVD risk factors, consider using high-intensity statin and lifestyle therapy. **B**
- For patients with diabetes aged >75 years without additional CVD risk factors, consider using moderate-intensity statin therapy and lifestyle therapy. **B**
- For patients with diabetes aged >75 years with additional CVD risk factors, consider using moderate- 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**
- Cholesterol laboratory testing may be helpful in monitoring adherence to therapy, but may not be needed once the patient is stable on therapy. **E**
- Combination therapy (statin/fibrate and statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone and is not generally recommended. **A**
- Statin therapy is contraindicated in pregnancy. **B**

Lifestyle Intervention

Lifestyle intervention, including MNT, increased physical activity, weight loss, and smoking cessation, may allow some patients to reduce CVD risk factors, such as by lowering LDL cholesterol. 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* unsaturated fat intake and increasing 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.

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 CVD. Multiple clinical trials have demonstrated significant effects of pharmacological (primarily statin) therapy on CVD outcomes in individual subjects with CHD and for primary CVD prevention (29,30). Subgroup analyses of diabetic patients in larger trials (31–35) and trials in patients with diabetes (36,37) showed significant primary and secondary prevention of CVD events +/− CHD deaths 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 reduction in LDL cholesterol (38). As in those without diabetes, absolute reductions in objective CVD outcomes (CHD death and nonfatal MI) are greatest in people with high baseline CVD risk (known CVD and/or very high LDL cholesterol levels), but the overall benefits of statin therapy in people with diabetes at moderate or high risk for CVD are convincing (39,40). Statins are the drugs of choice for LDL cholesterol lowering and cardioprotection.

Most trials of statins and CVD outcomes tested specific doses of statins against placebo or other statins, rather than aiming for specific LDL cholesterol goals (41). In light of this fact, the 2015 ADA Standards of Care have been revised to recommend when to initiate and intensify statin therapy (high versus moderate) based on risk profile (**Table 8.1**).

The American College of Cardiology/American Heart Association new Pooled Cohort Equation, the "Risk Calculator," may be a useful tool to estimate 10-year atherosclerotic CVD (http://my.americanheart.org). Since diabetes itself confers increased risk for CVD, the Risk Calculator has limited use for assessing risk in individuals with diabetes. The following recommendations are

Table 8.1—Recommendations for statin treatment in people with diabetes

Age	Risk factors	Recommended statin dose*	Monitoring with lipid panel
<40 years	None	None	Annually or as needed to monitor for adherence
	CVD risk factor(s)**	Moderate or high	
	Overt CVD***	High	
40–75 years	None	Moderate	As needed to monitor adherence
	CVD risk factors	High	
	Overt CVD	High	
>75 years	None	Moderate	As needed to monitor adherence
	CVD risk factors	Moderate or high	
	Overt CVD	High	

*In addition to lifestyle therapy.
**CVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, and overweight and obesity.
***Overt CVD includes those with previous cardiovascular events or acute coronary syndromes.

supported by evidence from trials focusing specifically on patients with diabetes.

Age ≥40 Years

In all patients with diabetes aged ≥40 years, and if clinically indicated, moderate-intensity statin treatment should be considered, in addition to lifestyle therapy. Clinical trials in high-risk patients, such as those with acute coronary syndromes or previous cardiovascular events (42–44), have demonstrated that more aggressive therapy with high doses of statins led to a significant reduction in further events. Therefore, in patients with increased cardiovascular risk (e.g., LDL cholesterol ≥100 mg/dL [2.6 mmol/L], high blood pressure, smoking, and overweight/obesity) or with overt CVD, high-dose statins are recommended.

For adults with diabetes over 75 years of age, there are limited data regarding statin therapy. Statin therapy should be individualized based on risk profile. High-dose statins, if well tolerated, may still be appropriate and are recommended for older adults with overt CVD. 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 unique population.

Age <40 Years and/or Type 1 Diabetes

Very little clinical trial evidence exists for type 2 diabetic patients under the age of 40 years or for type 1 diabetic patients 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 similar, although not statistically significant, reduction in risk to patients with type 2 diabetes (32). Even though the data are not definitive, similar statin treatment approaches should be considered for both type 1 and type 2 diabetic patients, particularly in the presence of 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" (45) for additional discussion.

Treatment with a moderate dose of statin should be considered if the patient has increased cardiovascular risk (e.g., cardiovascular risk factors such as LDL cholesterol ≥100 mg/dL) and with a high dose of statin if the patient has overt CVD.

Ongoing Therapy and Monitoring With Lipid Panel

In adults with diabetes, a screening lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) is reasonable at the time of first diagnosis, at the initial medical evaluation, and/or at age 40 and periodically (e.g., every 1–2 years) thereafter. Once a patient is on a statin, testing for LDL cholesterol may be considered on an individual basis to, for example, monitor adherence and efficacy. In cases where patients are adherent, but 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 (46). Reduction of CVD events with statins correlates very closely with LDL cholesterol lowering (29). Clinicians should attempt to find a dose or alternative statin that is tolerable, if side effects occur. There is evidence for significant LDL cholesterol lowering from even extremely low, less than daily, statin doses (47).

When maximally tolerated doses of statins fail to significantly lower LDL cholesterol (<30% reduction from the patient's baseline), there is no strong evidence that combination therapy should be used to achieve additional LDL cholesterol lowering. Although niacin, fenofibrate, ezetimibe, and bile acid sequestrants all offer additional LDL cholesterol lowering to statins alone, there is insufficient evidence that such combination therapy provides a significant increment in CVD risk reduction over statin therapy alone.

Treatment of Other Lipoprotein Fractions or Targets

Hypertriglyceridemia should be addressed with dietary and lifestyle changes. Severe hypertriglyceridemia (>1,000 mg/dL) may warrant immediate pharmacological therapy (fibric acid derivatives or fish oil) to reduce the risk of acute pancreatitis. If severe hypertriglyceridemia is absent, then therapy targeting HDL cholesterol or triglycerides lacks the strong evidence base of statin therapy. If HDL cholesterol is <40 mg/dL and LDL cholesterol is between 100 and 129 mg/dL, a fibrate or niacin might be used, especially if a patient is intolerant to statins.

Low levels of HDL cholesterol, often associated with elevated triglyceride levels, are the most prevalent pattern of dyslipidemia in persons with type 2 diabetes. However, the evidence base for drugs that target these lipid fractions is significantly less robust than that for statin therapy (48). In a large trial specific to diabetic patients, fenofibrate failed to reduce overall cardiovascular outcomes (49).

Combination Therapy

Statin and Fibrate

Combination therapy (statin and fibrate) may be efficacious for treatment for LDL cholesterol, HDL cholesterol, and triglycerides, but this combination is associated with an increased risk for abnormal transaminase levels, myositis, or rhabdomyolysis. The risk of rhabdomyolysis is more common with higher doses of statins and with renal insufficiency and seems to be lower when statins are combined with fenofibrate than gemfibrozil (50).

In the ACCORD study, in patients with type 2 diabetes who were at high risk for CVD, 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 according to sex, with a benefit of combination therapy for men and possible harm for women, and a possible benefit for patients with both triglyceride level ≥204 mg/dL (2.3 mmol/L) and HDL cholesterol level ≤34 mg/dL (0.9 mmol/L) (51).

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 CVD, 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 matching placebo. The trial was halted early due to lack of efficacy on the primary CVD outcome (first event of the composite of death from CHD, nonfatal MI, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization) and a possible increase in ischemic stroke in those on combination therapy (52). Hence, combination therapy with niacin is not recommended given the lack of efficacy on major CVD outcomes, possible increase in risk of ischemic stroke, and side effects.

Diabetes With Statin Use

There is an increased risk of incident diabetes with statin use (53,54), which may be limited to those with diabetes risk factors. These patients may benefit from diabetes screening when on statin therapy. An analysis of one of the initial studies suggested that 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 (55). 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) (56). 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 (54). The RR-benefit ratio favoring statins is further supported by meta-analysis of individual data of over 170,000 persons from 27 randomized trials. This demonstrated that individuals at low risk of vascular disease, including those undergoing primary prevention, received benefits from statins that included reductions in major vascular events and vascular death without increase in incidence of cancer or deaths from other causes (30).

ANTIPLATELET AGENTS

Recommendations

- Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%). This includes most men aged >50 years or women aged >60 years who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). **C**
- Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk (10-year CVD risk <5%, such as in men aged <50 years and women aged <60 years with no major additional CVD risk factors), since the potential adverse effects from bleeding likely offset the potential benefits. **C**
- In patients in these age-groups 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 CVD. **A**
- For patients with CVD 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 and without a history of diabetes (57,58). Two randomized controlled trials of aspirin specifically in patients with diabetes failed to show a significant reduction in CVD end points, raising questions about the efficacy of aspirin for primary prevention in people with diabetes (59,60).

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 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 CVD events in men, but not in women. Conversely, aspirin had no effect on stroke in men but significantly reduced stroke in women. Sex differences in aspirin's effects have not been observed in studies of secondary prevention (57). 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 CVD 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 CVD risk greater than 1% per year, the number of CVD 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 (61).

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 CVD risk (10-year risk of CVD events over 10%) and who are not at increased risk for bleeding. This generally includes 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 CVD, and albuminuria (62).

However, aspirin is no longer recommended for those at low CVD risk (women under age 60 years and men under age 50 years with no major CVD risk factors; 10-year CVD risk under 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 CVD risk of 5–10%) until further research is available. Aspirin use in patients under the age of 21 years is contraindicated due to the associated risk of Reye syndrome.

Average daily dosages used in most clinical trials involving patients with diabetes ranged from 50 to 650 mg but were mostly in the range of 100 to 325 mg/day. There is little evidence to support any specific dose, but using the lowest possible dose may help reduce side effects (63). 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, impact 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 (64). Therefore, while "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), these observations alone are insufficient to empirically recommend that higher doses of aspirin be used in this group at this time.

A P2Y12 receptor antagonist in combination with aspirin should be used for at least 1 year in patients following an acute coronary syndrome. Evidence supports use of either ticagrelor or clopidogrel if no percutaneous coronary intervention (PCI) was performed and the use of clopidogrel, ticagrelor, or prasugrel if PCI was performed (65).

CORONARY HEART DISEASE

Recommendations

Screening

- In asymptomatic patients, routine screening for coronary artery disease (CAD) is not recommended because it does not improve outcomes as long as CVD risk factors are treated. **A**

Treatment

- In patients with known CVD, 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 a prior MI, 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 stable CHF, metformin may be used if renal function is normal but should be avoided in unstable or hospitalized patients with CHF. **B**

In all patients with diabetes, cardiovascular risk factors should be 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.

Screening

Candidates for advanced or invasive cardiac testing include those with *1*) typical or atypical cardiac symptoms and *2*) an abnormal resting ECG. The screening of asymptomatic patients with high CVD risk is not recommended (39), in part because these high-risk patients should already be receiving intensive medical therapy, an approach that provides similar benefit as invasive revascularization (66,67). There is also some evidence that silent MI may reverse over time, adding to the controversy concerning aggressive screening strategies (68). A randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic patients with type 2 diabetes and normal ECGs (69). 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 CAD fails to identify which patients with type 2 diabetes will have silent ischemia on screening tests (70,71). Any benefit of newer noninvasive CAD screening methods, such as computed tomography and computed tomography angiography, to identify patient subgroups for different treatment strategies, remain unproven. Although asymptomatic diabetic patients with higher coronary disease burden have more future cardiac events (72–74), 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 CVD 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 CVD risk factors. Patients at increased CVD risk should receive aspirin and a statin, and ACE inhibitor or ARB therapy if hypertensive, 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 CVD in the absence of these conditions are less clear, especially when LDL cholesterol is concomitantly controlled (75,76). In patients with a prior MI, β-blockers should be continued for at least 2 years after the event (77). A systematic review of 34,000 patients showed that metformin is as safe as other glucose-lowering treatments in patients with diabetes and CHF, even in those with reduced left ventricular ejection fraction or concomitant chronic kidney disease; however, metformin should be avoided in hospitalized patients (78).

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