9. 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 12 "Children and Adolescents."

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).

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

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

- Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg and a diastolic blood pressure goal of <90 mmHg. **A**
- Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. **C**
- In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120–160/80–105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. **E**

Treatment

- Patients with confirmed office-based blood pressure >140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. **A**
- Patients with confirmed office-based blood pressure >160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. **A**

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- Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). Multiple-drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). **A**
- An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine (**A**) or 30–299 mg/g creatinine (**B**). If one class is not tolerated, the other should be substituted. **B**
- For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored. **B**
- For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. **B**

Hypertension, defined as a sustained blood pressure ≥140/90 mmHg, is a common comorbidity of type 1 and type 2 diabetes. The prevalence of hypertension depends on type of diabetes, age, sex, BMI, and race/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. Please refer to the American Diabetes Association (ADA) position statement "Diabetes and Hypertension" for a detailed review (5).

Screening and Diagnosis

Blood pressure should be measured 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 (6,7). 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 (8). 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 (9,10). There is limited prespecified clinical trial evidence for the benefits of lower systolic blood pressure (SBP) or diastolic blood pressure (DBP) targets (11). 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 (12).

Randomized Controlled Trials of Intensive Versus Standard Blood Pressure Control

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. Additional studies, such as the Systolic Blood Pressure Intervention Trial (SPRINT) and the Hypertension Optimal Treatment (HOT) trial, also examined the potential benefits of intensive versus standard control, though the relevance of their results to people with diabetes is less clear.

ACCORD. The ACCORD trial examined whether an 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 (13). The study did not find a benefit in the primary end point (nonfatal MI, nonfatal stroke, and cardiovascular death) comparing intensive blood pressure treatment (intensive BP; goal <120 mmHg, average blood pressure achieved 119/64 mmHg on 3.4 medications) with standard treatment (standard BP; average blood pressure achieved 143/70 mmHg on 2.1 medications). However, a follow-up analysis found a strong interaction between glycemic control and blood pressure control. Compared with the standard glycemia/standard BP control group in the blood pressure trial, the intensive BP/intensive glycemia, intensive BP/standard glycemia, and standard BP/intensive glycemia groups all showed benefit for reducing the risk of major cardiovascular disease (14). Stroke was significantly reduced in the intensive BP treatment groups, but the intensive BP/intensive glycemia group showed no evidence of incremental benefit compared with either single intensive intervention (14). Thus, more intensive blood pressure control may be reasonable in certain motivated, ACCORD-like patients (40–79 years of age with prior evidence of cardiovascular disease or multiple cardiovascular risk factors) who have been educated about the added treatment burden, side effects, and costs of more intensive blood pressure control and for patients who prefer to lower their risk of stroke beyond what can be achieved through standard care.

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 (15). 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. The recently published 6-year follow-up of the ADVANCE trial, 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 (16).

HOT. The Hypertension Optimal Treatment (HOT) trial included patients with and without diabetes and compared DBP targets of ≤90, ≤85, and ≤80 mmHg. Post hoc analyses found cardiovascular benefit with more intensive targets in the subpopulation with diabetes (17). The HOT trial results, taken together with the higher quality data from ACCORD and ADVANCE, support the current recommendation to achieve blood pressure levels <140/90 mmHg, with lower targets in selected patients.

SPRINT. The 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. Patients assigned to the intensive SBP target of <120 mmHg, compared with a target SBP of 140 mmHg, had reduced RR of cardiovascular events by almost a third and of death by almost a quarter, though risks of electrolyte abnormalities and acute kidney injury were increased (18). *Of note, patients with diabetes were excluded from participating in this trial, so the results have no direct implications for blood pressure management in patients with diabetes.*

Systolic Blood Pressure

The evidence that SBP >140 mmHg is harmful is irrefutable, suggesting that clinicians promptly initiate and titrate therapy to achieve and maintain SBP <140 mmHg in most patients. For some patients, lower SBP targets closer to 130 mmHg are appropriate. 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 (9). Therefore, individuals in whom cardiovascular disease risk, particularly stroke, is a concern may, as part of shared decision making, have lower systolic targets than 140 mmHg. This is especially true if lower blood pressure can be achieved with few drugs and without side effects of therapy. For older adults, treating to an SBP of <130 mmHg has not been shown to improve cardiovascular outcomes (19).

Diastolic Blood Pressure

Similarly, strong evidence from randomized clinical trials supports DBP targets of <90 mmHg. These targets are in harmony with the Eighth Joint National Committee (JNC 8) recommendation of a DBP threshold of <90 mmHg for individuals over 18 years of age with diabetes (11). A DBP of <80 mmHg may still be appropriate for patients with long life expectancy, chronic kidney disease, elevated urinary albumin excretion, evidence of cardiovascular disease, or additional risk factors such as dyslipidemia, smoking, or obesity (17). In older adults, treating to a DBP of <70 mmHg has been associated with a greater risk of mortality (20).

Treatment Strategies

Lifestyle Intervention

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 pharmacologic monotherapy.

Lifestyle therapy consists of reducing excess body weight through caloric restriction, 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) (21), and increasing activity levels (11).

These lifestyle (nonpharmacologic) 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. Nonpharmacologic 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, pharmacologic therapy should be initiated along with nonpharmacologic therapy (11). A lifestyle therapy plan should be developed in collaboration with the patient and discussed as part of diabetes management.

Pharmacologic Interventions

Lowering of blood pressure with regimens based on a variety of antihypertensive agents, including ACE inhibitors, angiotensin receptor blockers (ARBs), diuretics, and calcium channel blockers has been shown to be effective in reducing cardiovascular events (9,22).

In people with diabetes and albuminuria, ACE inhibitors or ARBs 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 and the development of albuminuria when compared with placebo, even after adjustment for differences in blood pressure, an effect that has been termed a "blood pressure independent effect" (23). In patients with congestive heart failure, including subgroups with diabetes, ARBs have been shown to reduce major ASCVD outcomes (24–26). Among patients with type 2 diabetes, urine albumin–to–creatinine ratio (UACR)

≥300 mg/g creatinine, and elevated serum creatinine concentration, an ARB significantly reduced progression of kidney disease compared with placebo (27). A meta-analysis confirmed that treatment of patients with diabetic kidney disease with an ACE inhibitor or ARB reduces the risk of progressing to end-stage renal disease, though strong evidence of benefit was limited to participants with baseline UACR ≥300 mg/g creatinine (28). Smaller trials also suggest reduction in composite cardiovascular events and reduced progression of advanced nephropathy (29–31).

However, the superiority of ACE inhibitors or ARBs over other antihypertensive agents for prevention of cardiovascular outcomes has not been consistently shown for all patients with diabetes (22,28,32,33). In particular, a recent meta-analysis suggests that thiazide-type diuretics or dihydropyridine calcium channel blockers have cardiovascular benefit similar to that of ACE inhibitors or ARBs (22). Therefore, among patients without albuminuria for whom cardiovascular disease prevention is the primary goal of blood pressure control, a thiazide-like diuretic or dihydropyridine calcium channel blocker may be considered instead of or in addition to an ACE inhibitor or ARB.

There are no adequate head-to-head comparisons of ACE inhibitors and ARBs, but there is clinical trial support for each of the following statements: In patients with type 1 diabetes with hypertension and any degree of albuminuria, ACE inhibitors have been shown to reduce loss of glomerular filtration rate and delay the progression of nephropathy. In patients with type 2 diabetes, hypertension, and UACR 30–299 mg/g creatinine, ACE inhibitors and ARBs have been shown to delay the progression to UACR ≥300 mg/g creatinine. 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 acute kidney injury (34,35).

Combination Drug Therapy

The blood pressure arm of the ADVANCE trial demonstrated that routine administration of a fixed-dose combination of the ACE inhibitor perindopril and the thiazide-like 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 (15). Another trial showed a decrease in morbidity and mortality in those receiving ACE inhibitor benazepril and calcium channel blocker amlodipine versus benazepril and thiazide-like diuretic hydrochlorothiazide (36,37). If needed to achieve blood pressure targets, amlodipine and indapamide or hydrochlorothiazide or thiazide-like diuretic chlorthalidone can be added. If estimated glomerular filtration rate is <30 mL/min/1.73 m^2, a loop diuretic 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 absence of nocturnal blood pressure dipping and the incidence of ASCVD. 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 (38). Consider administering one or more antihypertensive medications at bedtime (39).

Other Considerations

An important caveat is that most patients with diabetes and hypertension require multiple-drug therapy to reach blood pressure treatment goals (21). 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

Since there is a lack of randomized controlled trials of antihypertensive therapy in pregnant women with diabetes, recommendations for the management of hypertension in pregnant women with diabetes should be similar to those for all pregnant women. The American College of Obstetricians and Gynecologists (ACOG) has recommended that women with mild gestational hypertension (SBP <160 mmHg or DBP <110 mmHg) do not need to be treated with antihypertensive medications as there is no benefit identified that clearly outweighs potential risks of therapy (40). A 2014 Cochrane systematic review of antihypertensive therapy for mild to moderate chronic hypertension that included 49 trials and over 4,700 women did not find any conclusive evidence for or against blood pressure treatment to reduce the risk of preeclampsia for the mother or effects on perinatal outcomes such as preterm birth, small-for-gestational-age infants, or fetal death (41). For pregnant women who require antihypertensive therapy, SBP levels of 120–160 mmHg and DBP levels of 80–105 mmHg are suggested to optimize maternal health without risking fetal harm. Lower targets (SBP 110–119 mmHg and DBP 65–79 mmHg) may contribute to improved long-term maternal health; however, they may be associated with impaired fetal growth. Pregnant women with hypertension and evidence of end-organ damage from cardiovascular and/or renal disease may be considered for lower blood pressure targets to avoid progression of these conditions during pregnancy.

During pregnancy, treatment with ACE inhibitors, ARBs, and spironolactone are contraindicated as they may cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, hydralazine, carvedilol, clonidine, and long-acting nifedipine (40). Diuretics are not recommended for blood pressure control in pregnancy but may be used during late-stage pregnancy if needed for volume control (40,42). ACOG also recommends that postpartum patients with gestational hypertension, preeclampsia, and superimposed preeclampsia have their blood pressures observed for 72 h in hospital and for 7–10 days postpartum. Long-term follow-up is recommended for these women as they have increased lifetime cardiovascular risk (43).

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 dietary ω-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 for patients with recent acute coronary syndrome and LDL cholesterol ≥50 mg/dL (1.3 mmol/L) and should be considered for these patients **A** and also in patients with diabetes and history of ASCVD who cannot tolerate high-intensity statin therapy. **E**
- 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, pharmacologic treatment, lipid levels, and medical conditions. Recommendations should focus on reducing saturated fat, cholesterol, and *trans* fat intake and increasing plant stanols/sterols, ω-3 fatty acids, and viscous fiber (such as in oats, legumes, and citrus). Glycemic control may 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 ASCVD. Multiple clinical trials have demonstrated the beneficial effects of pharmacologic (statin) therapy on ASCVD outcomes in subjects with and without CHD (44,45). Subgroup analyses of patients with diabetes in larger trials (46–50) and trials in patients with diabetes (51,52) 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 (53).

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 (54,55). 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 (56), suggesting that the initiation and intensification of statin therapy be based on risk profile (**Table 9.1** and **Table 9.2**).

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

Table 9.1—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) or in patients with a history of ASCVD 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) or in patients with a history of ASCVD 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, chronic kidney disease, albuminuria, and family history of premature ASCVD.

use for assessing cardiovascular risk in individuals with diabetes.

Age 40–75 Years

In low-risk patients with diabetes aged 40–75 years, moderate-intensity statin treatment should be considered in addition to lifestyle therapy. Clinical trials in high-risk 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) and with ASCVD (57–59) have demonstrated that more aggressive therapy with high doses of statins led to a significant reduction in cardiovascular events. High-intensity statins are recommended in all such patients.

Age >75 Years

For adults with diabetes >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 11 "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 similar, although not statistically significant, reduction in risk as patients with type 2 diabetes (47). 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" (60) for additional discussion.

Table 9.2—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30% 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. XL, extended release.

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 (61). 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 (62).

Increased frequency of LDL cholesterol monitoring should be considered for patients with new-onset ACS. 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, had 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 (63). Therefore, for people meeting IMPROVE-IT eligibility criteria, ezetimibe should be added to moderate-intensity statin therapy. Though not explicitly studied, these results may also suggest that the addition of ezetimibe should be considered for any patient with diabetes and history of ASCVD who cannot tolerate high-intensity statin therapy.

Statins and PCSK9 Inhibitors

Placebo-controlled trials evaluating the addition of the 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 (64,65). 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 (66). Severe hypertriglyceridemia (>1,000 mg/dL) may warrant pharmacologic 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 (67). In a large trial in patients with diabetes, fenofibrate failed to reduce overall cardiovascular outcomes (68).

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 (compared with fenofibrate) (69).

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) (70).

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 (71). 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 (72,73), 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 (74). 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) (74). 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 (73).

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 deter their use in individuals with diabetes at high risk for ASCVD (75).

ANTIPLATELET AGENTS

Recommendations

- 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 and may have benefits beyond this period. **B**

- 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. This includes most men and women with diabetes aged ≥50 years who have at least one additional major risk factor (family history of premature atherosclerotic cardiovascular disease, hypertension, dyslipidemia, smoking, 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, such as in men or women with diabetes aged <50 years with no other major atherosclerotic cardiovascular disease risk factors, as the potential adverse effects from bleeding likely offset the potential benefits. **C**
- When considering aspirin therapy in patients with diabetes <50 years of age with multiple other atherosclerotic cardiovascular disease risk factors, clinical judgment is required. **E**

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 (76,77). 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 (78–80).

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 (76). 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 (81).

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 and who are not at increased risk for bleeding (82). This previous statement included sex-specific recommendations for use of aspirin therapy as primary prevention persons with diabetes. However, since that time, multiple recent well-conducted studies and meta-analyses have 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, current recommendations for using aspirin as primary prevention include both men and women aged ≥50 years with diabetes and at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or chronic kidney disease/albuminuria) who are not at increased risk of bleeding (83–86). While risk calculators such as those from the American College of Cardiology/American Heart Association (http://my.americanheart.org) may be a useful tool to estimate 10-year ASCVD risk, diabetes itself confers increased risk for ASCVD. As a result, such risk calculators have limited utility in helping to assess the potential benefits of aspirin therapy in individuals with diabetes. Noninvasive imaging techniques such as coronary computed tomography angiography may potentially help further tailor aspirin therapy, particularly in those at low risk (87), but are not generally recommended. Sex differences in the antiplatelet effect of aspirin have been suggested in the general population (88); 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) as the low benefit is likely to be outweighed by the risks of bleeding. Clinical judgment should be used for those at intermediate risk (younger patients with one or more risk factors or older patients with no risk factors) until further research is available. Patients' willingness to undergo long-term aspirin therapy should also be considered (89). Aspirin use in patients aged <21 years is generally contraindicated due to the associated risk of Reye syndrome.

Aspirin Dosing

Average daily dosages used in most clinical trials involving 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 (90). 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 (91). "Aspirin resistance" has been described in patients with diabetes when measured by a variety of ex vivo and in vitro methods (platelet aggregometry, measurement of thromboxane B_2) (88), but other studies suggest no impairment in aspirin response among patients with diabetes (92). A recent trial suggested that more frequent dosing regimens of aspirin may reduce platelet reactivity in individuals with diabetes (93); 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 and may have benefits beyond this period. Evidence supports use of either ticagrelor or clopidogrel if no percutaneous coronary intervention was performed and clopidogrel, ticagrelor, or prasugrel if a percutaneous coronary intervention was performed (94). In patients with diabetes and prior MI (1–3 years before), adding ticagrelor to aspirin significantly reduces the risk of recurrent ischemic events including cardiovascular and coronary heart disease death (95). More studies are needed to investigate the longer-term benefits of these therapies after ACS among patients with diabetes.

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 estimated glomerular filtration remains >30 mL/min 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. Pharmacologic stress echocardiography or nuclear imaging should be considered in individuals with diabetes in whom resting ECG abnormalities preclude exercise stress testing (e.g., left bundle branch block or ST-T abnormalities). In addition, individuals who require stress testing and are unable to exercise should undergo pharmacologic stress echocardiography or nuclear imaging.

Screening Asymptomatic Patients

The screening of asymptomatic patients with high ASCVD risk is not recommended (96), in part because these high-risk patients should already be receiving intensive medical therapy—an approach that provides similar benefit as invasive revascularization (97,98). There is also some evidence that silent MI may reverse over time, adding to the controversy concerning aggressive screening strategies (99). 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 (100–102). However, a randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic patients with type 2 diabetes and normal ECGs (103). 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 (104,105). 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 (100,106,107), 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 Pharmacologic Interventions

Intensive lifestyle intervention focusing on weight loss through decreased caloric intake and increased physical activity as performed in the Action for Health in Diabetes (Look AHEAD) trial may be considered for improving glucose control, fitness, and some ASCVD risk factors (108). 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 (109,110). In patients with prior MI, β-blockers should be continued for at least 2 years after the event (111).

Diabetes and Heart Failure

As many as 50% of patients with type 2 diabetes may develop heart failure (112). 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 (113–115). Therefore, thiazolidinedione use should be avoided in patients with symptomatic heart failure.

Recent studies have also examined the relationship between dipeptidyl peptidase 4 (DPP-4) inhibitors and heart failure and have had mixed results. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) study showed that patients treated with 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) (116). Two other recent multicenter, randomized, double-blind, noninferiority trials, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) and Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), did not show associations between DPP-4 inhibitor use and heart failure. 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]) (117). 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]) (117). 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) (118).

Antihyperglycemic Therapies and Cardiovascular Outcomes

Recently published cardiovascular outcome trials have provided additional data on cardiovascular outcomes in patients with type 2 diabetes with cardiovascular disease or at high risk for cardiovascular disease. The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was a randomized, double-blind trial that assessed the effect of empagliflozin, a sodium–glucose cotransporter 2 (SGLT2) inhibitor, versus placebo and standard care on cardiovascular outcomes in patients with type 2 diabetes and existing cardiovascular disease. Study participants had a mean age of 63 years, 57% had diabetes for more than 10 years, and 99% had established cardiovascular disease. EMPA-REG OUTCOME showed that over a median follow-up of 3.1 years, treatment reduced the composite outcome of MI, stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group) and cardiovascular death by 38% (absolute rate 3.7% vs. 5.9%) (119). The FDA recently added a new indication for empagliflozin, to reduce the risk of cardiovascular death in adults with type 2 diabetes and cardiovascular disease. Whether other SGLT2 inhibitors will have the same effect in high-risk patients and whether empagliflozin or other SGLT2 inhibitors will have a similar effect in lower-risk patients with diabetes remains unknown.

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER) trial was a randomized, double-blind trial that assessed the effect of liraglutide, a glucagon-like peptide 1 receptor agonist, versus placebo and standard care on cardiovascular outcomes in patients with type 2 diabetes at high risk for cardiovascular disease or with cardiovascular disease. Study participants had a mean age of 64 years and a mean duration of diabetes of nearly 13 years. Over 80% of study participants had established cardiovascular disease inclusive of a prior MI, prior stroke or transient ischemic attack, prior revascularization procedure, or ≥50% stenosis of coronary, carotid, or lower-extremity arteries. LEADER showed that the composite primary outcome (MI, stroke, or cardiovascular death) occurred in fewer participants in the treatment group (13.0%) when compared with the placebo group (14.9%) after a median follow-up of 3.8 years (120). Whether other glucagon-like peptide 1 receptor agonists will have the same effect in high-risk patients or if this drug class will have similar effects in lower-risk patients with diabetes remains unknown.

References

1. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999-2010. N Engl J Med 2013;368:1613–1624
2. Buse JB, Ginsberg HN, Bakris GL, et al.; American Heart Association; American Diabetes Association. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 2007;30:162–172
3. Gaede P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–591
4. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics, Division of Health Care Statistics. Crude and age-adjusted hospital discharge rates for major cardiovascular disease as first-listed diagnosis per 1,000 diabetic population, United States, 1988–2006 [Internet]. Available from http://www.cdc.gov/diabetes/statistics/cvdhosp/cvd/fig3.htm. Accessed 27 August 2015
5. de Boer I, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement of the American Diabetes Association. Diabetes Care. In press
6. Bobrie G, Genès N, Vaur L, et al. Is "isolated home" hypertension as opposed to "isolated office" hypertension a sign of greater cardiovascular risk? Arch Intern Med 2001;161:2205–2211
7. Sega R, Facchetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation 2005;111:1777–1783
8. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903–1913
9. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015;313:603–615
10. Arguedas JA, Leiva V, Wright JM. Blood pressure targets for hypertension in people with diabetes mellitus. Cochrane Database Syst Rev 2013;10:CD008277
11. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507–520

12. McBrien K, Rabi DM, Campbell N, et al. Intensive and standard blood pressure targets in patients with type 2 diabetes mellitus: systematic review and meta-analysis. Arch Intern Med 2012;172:1296–1303
13. ACCORD Study Group, Cushman WC, Evans GW, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–1585
14. Margolis KL, O'Connor PJ, Morgan TM, et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. Diabetes Care 2014;37:1721–1728
15. Patel A, ADVANCE Collaborative Group, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829–840
16. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392–1406
17. Hansson L, Zanchetti A, Carruthers SG, et al.; HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755–1762
18. Wright JT Jr, Williamson JD, Whelton PK, et al.; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–2116
19. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. Diabetes Care 2012;35:2650–2664
20. Anderson RJ, Bahn GD, Moritz TE, Kaufman D, Abraira C, Duckworth W; VADT Study Group. Blood pressure and cardiovascular disease risk in the Veterans Affairs Diabetes Trial. Diabetes Care 2011;34:34–38
21. Sacks FM, Svetkey LP, Vollmer WM, et al.; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med 2001;344:3–10
22. Bangalore S, Fakheri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials [published correction appears in BMJ 2016;352:i1525]. BMJ 2016;352:i438
23. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253–259
24. Granger CB, McMurray JJV, Yusuf S, et al.; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362:772–776
25. McMurray JJV, Ostergren J, Swedberg K, et al.; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362:767–771
26. Pfeffer MA, Swedberg K, Granger CB, et al.; CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362:759–766
27. Brenner BM, Cooper ME, de Zeeuw D, et al. RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–869
28. Palmer SC, Mavridis D, Navarese E, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet 2015;385:2047–2056
29. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. Diabetes Care 1998;21:597–603
30. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998;338:645–652
31. Schrier RW, Estacio RO, Mehler PS, Hiatt WR. Appropriate blood pressure control in hypertensive and normotensive type 2 diabetes mellitus: a summary of the ABCD trial. Nat Clin Pract Nephrol 2007;3:428–438
32. Whelton PK, Barzilay J, Cushman WC, et al.; ALLHAT Collaborative Research Group. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med 2005;165:1401–1409
33. Remonti LR, Dias S, Leitão CB, et al. Classes of antihypertensive agents and mortality in hypertensive patients with type 2 diabetes-Network meta-analysis of randomized trials. J Diabetes Complications 2016;30:1192–1200
34. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–1559
35. Fried LF, Emanuele N, Zhang JH, et al.; VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med 2013;369:1892–1903
36. Jamerson K, Weber MA, Bakris GL, et al.; ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008;359:2417–2428
37. Weber MA, Bakris GL, Jamerson K, et al.; ACCOMPLISH Investigators. Cardiovascular events during differing hypertension therapies in patients with diabetes. J Am Coll Cardiol 2010;56:77–85
38. Hermida RC, Ayala DE, Mojón A, Fernández JR. Influence of time of day of blood pressure-lowering treatment on cardiovascular risk in hypertensive patients with type 2 diabetes. Diabetes Care 2011;34:1270–1276
39. Zhao P, Xu P, Wan C, Wang Z. Evening versus morning dosing regimen drug therapy for hypertension. Cochrane Database Syst Rev 2011;10:CD004184
40. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122–1131
41. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev2014;2:CD002252
42. Al-Balas M, Bozzo P, Einarson A. Use of diuretics during pregnancy. Can Fam Physician 2009;55:44–45
43. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. BMJ 2001;323:1213–1217
44. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581–590
45. Baigent C, Keech A, Kearney PM, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–1278
46. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). Diabetes Care 1997;20:614–620
47. Collins R, Armitage J, Parish S, Sleigh P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361:2005–2016
48. Goldberg RB, Mellies MJ, Sacks FM, et al.; The Care Investigators. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol And Recurrent Events (CARE) trial. Circulation 1998;98:2513–2519
49. Shepherd J, Barter P, Carmena R, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. Diabetes Care 2006;29:1220–1226
50. Sever PS, Poulter NR, Dahlöf B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA). Diabetes Care 2005;28:1151–1157
51. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease

Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN). Diabetes Care 2006;29:1478–1485
52. Colhoun HM, Betteridge DJ, Durrington PN, et al.; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–696
53. Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371:117–125
54. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013 (1):CD004816
55. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study [published correction appears in BMJ 2013;347:f4356]. BMJ 2013;346:f2610
56. Hayward RA, Hofer TP, Vijan S. Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem. Ann Intern Med 2006;145:520–530
57. Cannon CP, Braunwald E, McCabe CH, et al.; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–1504
58. de Lemos JA, Blazing MA, Wiviott SD, et al.; Investigators. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA 2004;292:1307–1316
59. Nissen SE, Tuzcu EM, Schoenhagen P, et al.; REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004;291:1071–1080
60. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation 2014;130:1110–1130
61. Chasman DI, Posada D, Subrahmanyan L, Cook NR, Stanton VP Jr, Ridker PM. Pharmacogenetic study of statin therapy and cholesterol reduction. JAMA 2004;291:2821–2827
62. Meek C, Wierzbicki AS, Jewkes C, et al. Daily and intermittent rosuvastatin 5 mg therapy in statin intolerant patients: an observational study. Curr Med Res Opin 2012;28:371–378
63. Cannon CP, Blazing MA, Giugliano RP, et al.; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387–2397
64. Moriarty PM, Jacobson TA, Bruckert E, et al. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. J Clin Lipidol 2014;8:554–561
65. Zhang X-L, Zhu Q-Q, Zhu L, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. BMC Med 2015;13:123
66. Berglund L, Brunzell JD, Goldberg AC, et al.; Endocrine Society. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012;97:2969–2989
67. Singh IM, Shishehbor MH, Ansell BJ. High-density lipoprotein as a therapeutic target: a systematic review. JAMA 2007;298:786–798
68. Keech A, Simes RJ, Barter P, et al.; FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849–1861
69. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. Am J Cardiol 2005;95:120–122
70. ACCORD Study Group, Ginsberg HN, Elam MB, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563–1574
71. AIM-HIGH Investigators, Boden WE, Probstfield JL, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011;365:2255–2267
72. Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. Diabetes Care 2009;32:1924–1929
73. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010;375:735–742
74. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet 2012;380:565–571
75. Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. Ann Intern Med 2013;159:688–697
76. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849–1860
77. Perk J, De Backer G, Gohlke H, et al.; European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012;33:1635–1701
78. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008;337:a1840
79. Zhang C, Sun A, Zhang P, et al. Aspirin for primary prevention of cardiovascular events in patients with diabetes: a meta-analysis. Diabetes Res Clin Pract 2010;87:211–218
80. De Berardis G, Sacco M, Strippoli GFM, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ 2009;339:b4531
81. Pignone M, Earnshaw S, Tice JA, Pletcher MJ. Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. Ann Intern Med 2006;144:326–336
82. Pignone M, Alberts MJ, Colwell JA, et al.; American Diabetes Association; American Heart Association; American College of Cardiology Foundation. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. Diabetes Care 2010;33:1395–1402
83. Huxley RR, Peters SAE, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2015;3:198–206
84. Peters SAE, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. Diabetologia 2014;57:1542–1551
85. Kalyani RR, Lazo M, Ouyang P, et al. Sex differences in diabetes and risk of incident coronary artery disease in healthy young and middle-aged adults. Diabetes Care 2014;37:830–838
86. Peters SAE, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. Lancet 2014;383:1973–1980
87. Dimitriu-Leen AC, Scholte AJHA, van Rosendael AR, et al. Value of coronary computed tomography angiography in tailoring aspirin therapy for primary prevention of atherosclerotic events in patients at high risk with diabetes mellitus. Am J Cardiol 2016;117:887–893
88. Larsen SB, Grove EL, Neergaard-Petersen S, Würtz M, Hvas A-M, Kristensen SD. Determinants of reduced antiplatelet effect of aspirin in patients with stable coronary artery disease. PLoS One 2015;10:e0126767
89. Mora S, Ames JM, Manson JE. Low-dose aspirin in the primary prevention of cardiovascular disease: shared decision making in clinical practice. JAMA 2016;316:709–710
90. Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. JAMA 2007;297:2018–2024
91. Davì G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med 2007;357:2482–2494
92. Zaccardi F, Rizzi A, Petrucci G, et al. In vivo platelet activation and aspirin responsiveness in type 1 diabetes. Diabetes 2016;65:503–509
93. Bethel MA, Harrison P, Sourij H, et al. Randomized controlled trial comparing impact on platelet reactivity of twice-daily with once-daily

aspirin in people with type 2 diabetes. Diabet Med 2016;33:224–230
94. Vandvik PO, Lincoff AM, Gore JM, et al.; American College of Chest Physicians. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [published correction appears in Chest 2012;141:1129]. Chest 2012;141 (Suppl.):e637S–e668S
95. Bhatt DL, Bonaca MP, Bansilal S, et al. Reduction in ischemic events with ticagrelor in diabetic patients with prior myocardial infarction in PEGASUS-TIMI 54. J Am Coll Cardiol 2016;67: 2732–2740
96. Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO, Barrett EJ; ADA. Screening for coronary artery disease in patients with diabetes. Diabetes Care 2007;30:2729–2736
97. Boden WE, O'Rourke RA, Teo KK, et al.; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–1516
98. BARI 2D Study Group, Frye RL, August P, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009;360:2503–2015
99. Wackers FJT, Chyun DA, Young LH, et al.; Detection of Ischemia in Asymptomatic Diabetics (DIAD) Investigators. Resolution of asymptomatic myocardial ischemia in patients with type 2 diabetes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. Diabetes Care 2007;30:2892–2898
100. Elkeles RS, Godsland IF, Feher MD, et al.; PREDICT Study Group. Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with type 2 diabetes: the PREDICT study. Eur Heart J 2008;29: 2244–2251
101. Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. J Am Coll Cardiol 2004;43:1663–1669
102. Anand DV, Lim E, Hopkins D, et al. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. Eur Heart J 2006;27:713–721
103. Young LH, Wackers FJT, Chyun DA, et al.; DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. JAMA 2009;301:1547–1555
104. Wackers FJT, Young LH, Inzucchi SE, et al.; Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care 2004; 27:1954–1961
105. Scognamiglio R, Negut C, Ramondo A, Tiengo A, Avogaro A. Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. J Am Coll Cardiol 2006;47:65–71
106. Hadamitzky M, Hein F, Meyer T, et al. Prognostic value of coronary computed tomographic angiography in diabetic patients without known coronary artery disease. Diabetes Care 2010;33:1358–1363
107. Choi E-K, Chun EJ, Choi S-I, et al. Assessment of subclinical coronary atherosclerosis in asymptomatic patients with type 2 diabetes mellitus with single photon emission computed tomography and coronary computed tomography angiography. Am J Cardiol 2009;104: 890–896
108. Look AHEAD Research Group, Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145–154
109. Braunwald E, Domanski MJ, Fowler SE, et al.; PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med 2004;351:2058–2068
110. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators, Yusuf S, Teo K, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet 2008;372:1174–1183
111. Kezerashvili A, Marzo K, De Leon J. Beta blocker use after acute myocardial infarction in the patient with normal systolic function: when is it "ok" to discontinue? Curr Cardiol Rev 2012; 8:77–84
112. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974;34:29–34
113. Dormandy JA, Charbonnel B, Eckland DJA, et al.; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–1289
114. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA 2007;298:1189–1195
115. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007;298:1180–1188
116. Scirica BM, Bhatt DL, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317–1326
117. Zannad F, Cannon CP, Cushman WC, et al.; EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet 2015;385:2067–2076
118. Green JB, Bethel MA, Armstrong PW, et al.; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–242
119. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
120. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322