



## 9. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes—2018*

American Diabetes Association

*Diabetes Care* 2018;41(Suppl. 1):S86–S104 | <https://doi.org/10.2337/dc18-S009>

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

*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 coronary heart disease, cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin—is the leading cause of morbidity and mortality for individuals with diabetes and is the largest contributor to the direct and indirect costs of diabetes. Common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for ASCVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing ASCVD in people with diabetes. Furthermore, large benefits are seen when multiple cardiovascular risk factors are addressed simultaneously. Under the current paradigm of aggressive risk factor modification in patients with diabetes, 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).

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

### HYPERTENSION/BLOOD PRESSURE CONTROL

Hypertension, defined as a sustained blood pressure  $\geq 140/90$  mmHg, is common among patients with either type 1 or type 2 diabetes. Hypertension is a major risk factor for both ASCVD and microvascular complications. Moreover, numerous studies have shown that antihypertensive therapy reduces ASCVD events, heart failure, and microvascular complications. Please refer to the American Diabetes Association (ADA)

*Suggested citation:* American Diabetes Association. 9. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes—2018. *Diabetes Care* 2018;41(Suppl. 1):S86–S104

© 2017 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

position statement “Diabetes and Hypertension” for a detailed review of the epidemiology, diagnosis, and treatment of hypertension (5).

### Screening and Diagnosis

#### Recommendations

- Blood pressure should be measured at every routine clinical visit. Patients found to have elevated blood pressure ( $\geq 140/90$ ) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. **B**
- All hypertensive patients with diabetes should monitor their blood pressure at home. **B**

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. Orthostatic blood pressure measurements should be checked on initial visit and as indicated.

Home blood pressure self-monitoring and 24-h ambulatory blood pressure monitoring may provide evidence of white coat hypertension, masked hypertension, or other discrepancies between office and “true” blood pressure (5). In addition to confirming or refuting a diagnosis of hypertension, home blood pressure assessment may be useful to monitor antihypertensive treatment. Studies of individuals without diabetes found that home measurements may better correlate with ASCVD risk than office measurements (6,7). Moreover, home blood pressures may improve patient medication adherence and thus help reduce cardiovascular risk (8).

### Treatment Goals

#### Recommendations

- 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 preexisting hypertension who are treated with antihypertensive therapy, 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**

Randomized clinical trials have demonstrated unequivocally that treatment of hypertension to blood pressure  $<140/90$  mmHg reduces cardiovascular events as well as microvascular complications (9–15). Therefore, patients with type 1 or type 2 diabetes who have hypertension should, at a minimum, be treated to blood pressure targets of  $<140/90$  mmHg. Intensification of antihypertensive therapy to target blood pressures lower than  $<140/90$  mmHg (e.g.,  $<130/80$  or  $<120/80$  mmHg) may be beneficial for selected patients with diabetes such as those with a high risk of cardiovascular disease. Such intensive blood pressure control has been evaluated in large randomized clinical trials and meta-analyses of clinical trials.

#### Randomized Controlled Trials of Intensive Versus Standard Blood Pressure Control

The Action to Control Cardiovascular Risk in Diabetes blood pressure (ACCORD BP) trial provides the strongest direct assessment of the benefits and risks of intensive blood pressure control among people with type 2 diabetes (16). In ACCORD BP, compared with standard blood pressure control (target systolic blood pressure  $<140$  mmHg), intensive blood pressure control (target systolic blood pressure  $<120$  mmHg) did not reduce total major atherosclerotic cardiovascular events but did reduce the risk of stroke, at the expense of increased adverse events (Table 9.1). The ACCORD BP results suggest that blood pressure targets more intensive than  $<140/90$  mmHg are not likely to improve cardiovascular outcomes among most people with type 2 diabetes but may be reasonable in selected

patients who have been educated about added treatment burden, side effects, and costs, as discussed below.

Additional studies, such as the Systolic Blood Pressure Intervention Trial (SPRINT) and the Hypertension Optimal Treatment (HOT) trial, also examined effects of intensive versus standard control (Table 9.1), though the relevance of their results to people with diabetes is less clear. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation—Blood Pressure (ADVANCE BP) trial did not explicitly test blood pressure targets (17); the achieved blood pressure in the intervention group was higher than that achieved in the ACCORD BP intensive arm and would be consistent with a target blood pressure of  $<140/90$  mmHg. Notably, ACCORD BP and SPRINT measured blood pressure using automated office blood pressure measurements, which yields values that are generally lower than typical office blood pressure readings by approximately 5–10 mmHg (18), suggesting that implementing the ACCORD BP or SPRINT protocols in an outpatient clinic might require a systolic blood pressure target higher than  $<120$  mmHg.

#### Meta-analyses of Trials

To clarify optimal blood pressure targets in patients with diabetes, meta-analyses have stratified clinical trials by mean baseline blood pressure or mean blood pressure attained in the intervention (or intensive treatment) arm. Based on these analyses, antihypertensive treatment appears to be beneficial when mean baseline blood pressure is  $\geq 140/90$  mmHg or mean attained intensive blood pressure is  $\geq 130/80$  mmHg (5,9,12–14). Among trials with lower baseline or attained blood pressure, antihypertensive treatment reduced the risk of stroke, retinopathy, and albuminuria, but effects on other ASCVD outcomes and heart failure were not evident. Taken together, these meta-analyses consistently show that treating patients with baseline blood pressure  $\geq 140$  mmHg to targets  $<140$  mmHg is beneficial, while more intensive targets may offer additional, though probably less robust, benefits.

#### Individualization of Treatment Targets

Patients and clinicians should engage in a shared decision-making process to determine individual blood pressure targets,

**Table 9.1—Randomized controlled trials of intensive versus standard hypertension treatment strategies**

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP (16)	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	Systolic blood pressure target: <120 mmHg Achieved (mean) systolic/diastolic: 119.3/64.4 mmHg	Systolic blood pressure target: 130–140 mmHg Achieved (mean) systolic/diastolic: 133.5/70.5 mmHg	<ul style="list-style-type: none"> <li>No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death</li> <li>Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment</li> <li>Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities</li> </ul>
ADVANCE BP (17)	11,140 participants with T2D aged 55 years and older with prior evidence of CVD or multiple cardiovascular risk factors	Intervention: a single-pill, fixed-dose combination of perindopril and indapamide Achieved (mean) systolic/diastolic: 136/73 mmHg	Control: placebo Achieved (mean) systolic/diastolic: 141.6/75.2 mmHg	<ul style="list-style-type: none"> <li>Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%)</li> <li>6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (142)</li> </ul>
HOT (143)	18,790 participants, including 1,501 with diabetes	Diastolic blood pressure target: ≤80 mmHg	Diastolic blood pressure target: ≤90 mmHg	<ul style="list-style-type: none"> <li>In the overall trial, there was no cardiovascular benefit with more intensive targets</li> <li>In the subpopulation with diabetes, an intensive diastolic target was associated with a significantly reduced risk (51%) of CVD events</li> </ul>
SPRINT (144)	9,361 participants without diabetes	Systolic blood pressure target: <120 mmHg Achieved (mean): 121.4 mmHg	Systolic blood pressure target: <140 mmHg Achieved (mean): 136.2 mmHg	<ul style="list-style-type: none"> <li>Intensive systolic blood pressure target lowered risk of the primary composite outcome 25% (MI, ACS, stroke, heart failure, and death due to CVD)</li> <li>Intensive target reduced risk of death 27%</li> <li>Intensive therapy increased risks of electrolyte abnormalities and AKI</li> </ul>

CVD, cardiovascular disease; T2D, type 2 diabetes. Data from this table can also be found in the ADA position statement “Diabetes and Hypertension” (5).

with the acknowledgment that the benefits and risks of intensive blood pressure targets are uncertain and may vary across patients (5). Similar to the factors that influence management of hyperglycemia, factors that influence blood pressure treatment targets may include risks of treatment (e.g., hypotension, drug adverse effects), life expectancy, comorbidities including vascular complications, patient attitude and expected treatment efforts, and resources and support system (19). Specific factors to consider are the absolute risk of cardiovascular events (15,20), risk of progressive kidney disease as reflected by albuminuria, adverse effects, age, and overall treatment burden. Patients who have higher risk of cardiovascular events (particularly stroke) or albuminuria and who are able to attain intensive blood pressure control relatively easily and without substantial adverse effects may be best suited for intensive blood pressure targets. In contrast, patients with conditions more common in older

adults, such as functional limitations, polypharmacy, and multimorbidity, may be best suited for less intensive blood pressure targets. Notably, there is an absence of high-quality data available to guide blood pressure targets in type 1 diabetes.

Based on current evidence, ADA recommends hypertension diagnosis and treatment as outlined, emphasizing individualization of blood pressure targets. ADA is aware of hypertension recommendations from other organizations (20a). The ADA Professional Practice Committee continuously reviews and considers all studies, particularly high-quality trials including people with diabetes, for potential incorporation in future recommendations.

### Treatment Strategies

#### Lifestyle Intervention

##### Recommendation

- 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**

Lifestyle management is an important component of hypertension treatment because it lowers blood pressure, enhances the effectiveness of some antihypertensive medications, promotes other aspects of metabolic and vascular health, and generally leads to few adverse effects. Lifestyle therapy consists of reducing excess body weight through caloric restriction, 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 (22).

These lifestyle interventions are reasonable for individuals with diabetes and mildly elevated blood pressure (systolic  $>120$  mmHg or diastolic  $>80$  mmHg) and should be initiated along with pharmacologic therapy when hypertension is diagnosed (Fig. 9.1) (22). A lifestyle therapy plan should be developed in collaboration with the patient and discussed as part of diabetes management.

### Pharmacologic Interventions

#### Recommendations

- Patients with confirmed office-based blood pressure  $\geq 140/90$  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  $\geq 160/100$  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**
- 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). **A**
- Multiple-drug therapy is generally required to achieve blood pressure targets. However, combinations of ACE inhibitors and angiotensin receptor blockers and combinations of ACE inhibitors or angiotensin receptor blockers with direct renin inhibitors should not be used. **A**
- 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  $\geq 300$  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 at least annually. **B**

#### Initial Number of Antihypertensive Medications.

Initial treatment for people with diabetes depends on the severity of hypertension (Fig. 9.1). Those with blood pressure between 140/90 mmHg and 159/99 mmHg may begin with a single drug. For patients with blood pressure  $\geq 160/100$  mmHg, initial pharmacologic treatment with two antihypertensive medications is recommended in order to more effectively achieve adequate blood pressure control (23,24). Single-pill antihypertensive combinations may improve medication adherence in some patients (25).

**Classes of Antihypertensive Medications.** Initial treatment for hypertension should include any of the drug classes demonstrated to reduce cardiovascular events in patients with diabetes: ACE inhibitors (26,27), angiotensin receptor blockers (ARBs) (26,27), thiazide-like diuretics (28), or dihydropyridine calcium channel blockers (29). For patients with albuminuria (urine albumin-to-creatinine ratio [UACR]  $\geq 30$  mg/g), initial treatment should include an ACE inhibitor or ARB in order to reduce the risk of progressive kidney disease (5) (Fig. 9.1). In the absence of albuminuria, risk of progressive kidney disease is low, and ACE inhibitors and ARBs have not been found to afford superior cardioprotection when compared with thiazide-like diuretics or dihydropyridine calcium channel blockers (30).  $\beta$ -Blockers may be used for the treatment of prior myocardial infarction (MI), active angina, or heart failure but have not been shown to reduce mortality as blood pressure-lowering agents in the absence of these conditions (11,31).

**Multiple-Drug Therapy.** Multiple-drug therapy is often required to achieve blood pressure targets (Fig. 9.1), particularly in the setting of diabetic kidney disease. However, the use of both ACE inhibitors and ARBs in combination, or the combination of an ACE inhibitor or ARB and a direct renin inhibitor, is not recommended given the lack of added ASCVD benefit and increased rate of adverse events—namely, hyperkalemia, syncope, and acute kidney injury (AKI) (32–34). 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 the absence of nocturnal blood pressure dipping and the incidence of ASCVD. A meta-

analysis of randomized clinical trials found a small benefit of evening versus morning dosing of antihypertensive medications with regard to blood pressure control but had no data on clinical effects (35). In two subgroup analyses of a single subsequent randomized controlled trial, moving at least one antihypertensive medication to bedtime significantly reduced cardiovascular events, but results were based on a small number of events (36).

**Hyperkalemia and AKI.** Treatment with ACE inhibitors or ARBs can cause AKI and hyperkalemia, while diuretics can cause AKI and either hypokalemia or hyperkalemia (depending on mechanism of action) (37,38). Detection and management of these abnormalities is important because AKI and hyperkalemia each increase the risks of cardiovascular events and death (39). Therefore, serum creatinine and potassium should be monitored during treatment with an ACE inhibitor, ARB, or diuretic, particularly among patients with reduced glomerular filtration who are at increased risk of hyperkalemia and AKI (37,38,40).

### Resistant Hypertension

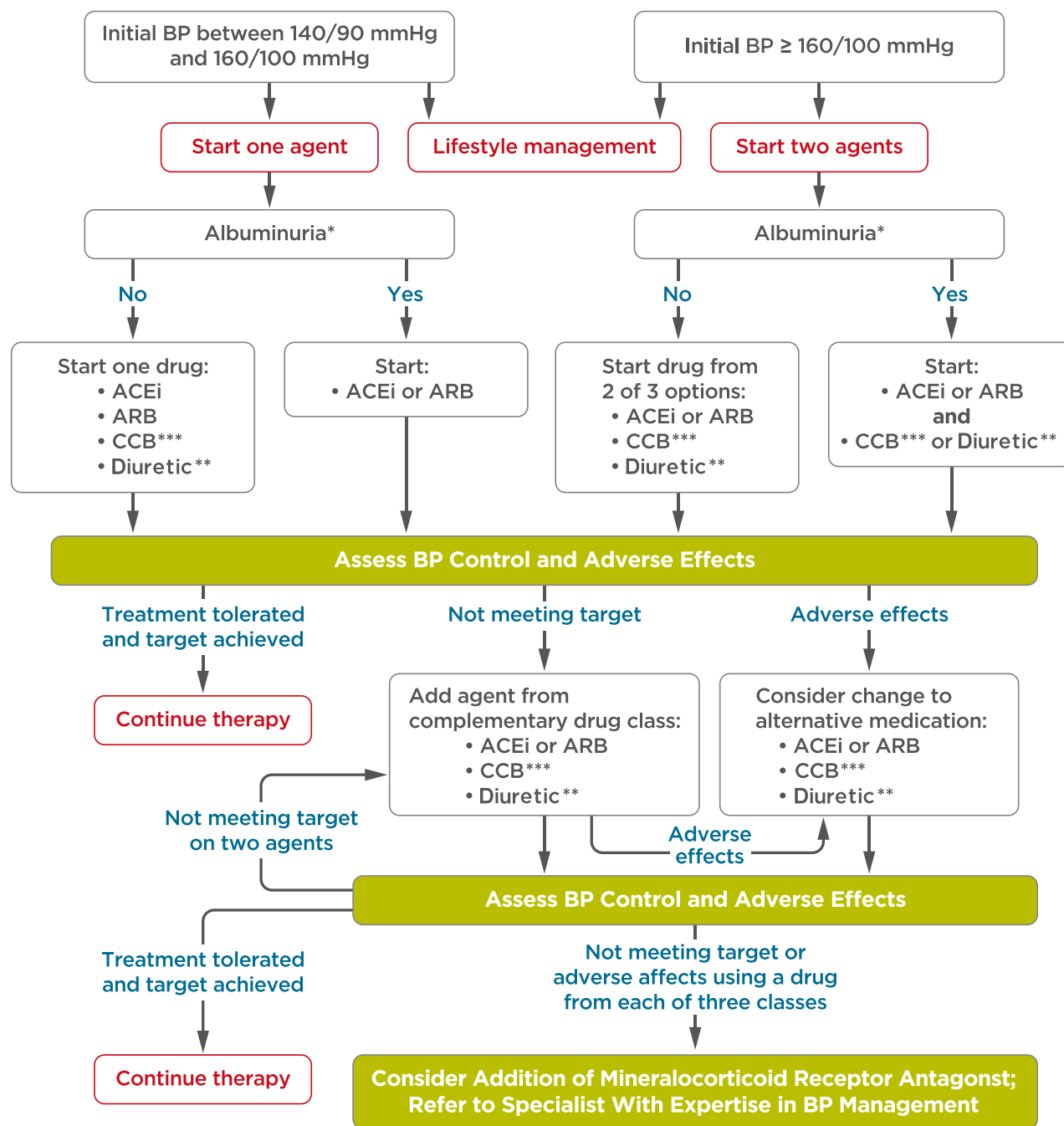
#### Recommendation

- Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. **B**

Resistant hypertension is defined as blood pressure  $\geq 140/90$  mmHg despite a therapeutic strategy that includes appropriate lifestyle management plus a diuretic and two other antihypertensive drugs belonging to different classes at adequate doses. Prior to diagnosing resistant hypertension, a number of other conditions should be excluded, including medication nonadherence, white coat hypertension, and secondary hypertension. In general, barriers to medication adherence (such as cost and side effects) should be identified and addressed (Fig. 9.1). Mineralocorticoid receptor antagonists are effective for management of resistant hypertension in patients with type 2 diabetes when added to existing treatment with a ACE inhibitor or ARB, thiazide-like diuretic, and dihydropyridine calcium channel blocker (41). Mineralocorticoid receptor antagonists also reduce albuminuria and have



## Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes



Downloaded from [http://diabetesjournals.org/care/article-pdf/41/Supplement\\_1/S86/S90/09/0c18s009.pdf](http://diabetesjournals.org/care/article-pdf/41/Supplement_1/S86/S90/09/0c18s009.pdf) by guest on 18 April 2024

**Figure 9.1**—Recommendations for the treatment of confirmed hypertension in people with diabetes. \*An ACE inhibitor (ACEi) or ARB is suggested to treat hypertension for patients with UACR 30–299 mg/g creatinine and strongly recommended for patients with UACR ≥300 mg/g creatinine. \*\*Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. \*\*\*Dihydropyridine calcium channel blocker. BP, blood pressure. This figure can also be found in the ADA position statement “Diabetes and Hypertension” (5).

additional cardiovascular benefits (42–45). However, adding a mineralocorticoid receptor antagonist to a regimen including an ACE inhibitor or ARB may increase the risk for hyperkalemia, emphasizing the importance of regular

monitoring for serum creatinine and potassium in these patients, and long-term outcome studies are needed to better evaluate the role of mineralocorticoid receptor antagonists in blood pressure management.

**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 to moderate gestational hypertension (systolic blood pressure <160 mmHg or diastolic blood pressure <110 mmHg) do not need to be treated with antihypertensive medications as there is no benefit identified that clearly outweighs potential risks of therapy (46). 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 (47). For pregnant women who require antihypertensive therapy, systolic blood pressure levels of 120–160 mmHg and diastolic blood pressure levels of 80–105 mmHg are suggested to optimize maternal health without risking fetal harm. Lower targets (systolic blood pressure 110–119 mmHg and diastolic blood pressure 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, and long-acting nifedipine, while hydralazine may be considered in the acute management of hypertension in pregnancy or severe preeclampsia (46). Diuretics are not recommended for blood pressure control in pregnancy but may be used during late-stage pregnancy if needed for volume control (46,48). ACOG also recommends that postpartum patients with gestational hypertension, preeclampsia, and superimposed preeclampsia have their blood pressures observed for 72 h in the hospital and for 7–10 days postpartum. Long-term follow-up is recommended for these women as they have increased lifetime cardiovascular risk (49). See Section 13 “Management of Diabetes in Pregnancy” for additional information.

## LIPID MANAGEMENT

### Lifestyle Intervention

#### Recommendations

- Lifestyle modification focusing on weight loss (if indicated); the reduction of saturated fat, *trans* fat, and cholesterol intake; increase of dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols intake; and increased physical activity should be recommended to improve the lipid profile in patients with diabetes. **A**
- Intensify lifestyle therapy and optimize glycemic control for patients with elevated triglyceride levels ( $\geq 150$  mg/dL [1.7 mmol/L]) and/or low HDL cholesterol (<40 mg/dL [1.0 mmol/L] for men, <50 mg/dL [1.3 mmol/L] for women). **C**

Lifestyle intervention, including weight loss, 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, n-3 fatty acids, and viscous fiber (such as in oats, legumes, and citrus) intake. Glycemic control may also beneficially modify plasma lipid levels, particularly in patients with very high triglycerides and poor glycemic control. See Section 4 “Lifestyle Management” for additional nutrition information.

### Ongoing Therapy and Monitoring With Lipid Panel

#### Recommendations

- In adults not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and every 5 years thereafter if under the age of 40 years, or more frequently if indicated. **E**
- Obtain a lipid profile at initiation of statins or other lipid-lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter as it may help to monitor the response to therapy and inform adherence. **E**

In adults with diabetes, it is reasonable to obtain a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) at the time of diagnosis, at the initial medical evaluation, and at least every 5 years thereafter in patients under the age of 40 years. In younger patients with longer duration of disease (such as those with youth-onset type 1 diabetes), more frequent lipid profiles may be reasonable. A lipid panel should also be obtained immediately before initiating statin therapy. Once a patient is taking a statin, LDL cholesterol levels should be assessed 4–12 weeks after initiation of statin therapy, after any change in dose, and on an individual basis (e.g., to monitor for medication 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 (50). 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 (51).

### Statin Treatment

#### Recommendations

- 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, the patient and provider should consider using moderate-intensity statin in addition to lifestyle therapy. **C**
- For patients with diabetes aged 40–75 years **A** and >75 years **B** without atherosclerotic cardiovascular disease, use moderate-intensity statin in addition to lifestyle therapy.
- In clinical practice, providers may need to adjust the intensity of statin therapy based on individual patient response to medication (e.g., side effects, tolerability, LDL cholesterol levels, or percent LDL reduction on statin therapy). For patients who do not tolerate the intended intensity

of statin, the maximally tolerated statin dose should be used. **E**

- For patients with diabetes and atherosclerotic cardiovascular disease, if LDL cholesterol is  $\geq 70$  mg/dL on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor) after evaluating the potential for further atherosclerotic cardiovascular disease risk reduction, drug-specific adverse effects, and patient preferences. Ezetimibe may be preferred due to lower cost. **A**
- Statin therapy is contraindicated in pregnancy. **B**

#### 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 statin therapy on ASCVD outcomes in subjects with and without CHD (52,53). Subgroup analyses of patients with diabetes in larger trials (54–58) and trials in patients with diabetes (59,60) 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 (61).

Accordingly, statins are the drugs of choice for LDL cholesterol lowering and cardioprotection. **Table 9.2** shows recommended lipid-lowering strategies, and **Table 9.3** shows the two statin dosing intensities that are recommended for use in clinical practice: high-intensity statin therapy will achieve approximately a 50% reduction in LDL cholesterol, and moderate-intensity statin regimens achieve 30–50% reductions in LDL cholesterol. Low-dose statin therapy is generally not recommended in patients with diabetes but is sometimes the only dose of statin that a patient can tolerate. For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used.

As in those without diabetes, absolute reductions in ASCVD outcomes (CHD

**Table 9.2—Recommendations for statin and combination treatment in adults with diabetes**

Age	ASCVD	Recommended statin intensity <sup>^</sup> and combination treatment*
<40 years	No	None <sup>†</sup>
	Yes	High <ul style="list-style-type: none"> <li>• If LDL cholesterol <math>\geq 70</math> mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)<sup>#</sup></li> </ul>
$\geq 40$ years	No	Moderate <sup>‡</sup>
	Yes	High <ul style="list-style-type: none"> <li>• If LDL cholesterol <math>\geq 70</math> mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)</li> </ul>

\*In addition to lifestyle therapy. <sup>^</sup>For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. <sup>†</sup>Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol  $\geq 100$  mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD. <sup>‡</sup>High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. <sup>#</sup>Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin-based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.

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 (62,63). The *relative* benefit of lipid-lowering therapy has been uniform across most subgroups tested (53,61), including subgroups that varied with respect to age and other risk factors.

#### Risk Stratification

Two broad groups of patients exist for management of cardiovascular risk: those with documented ASCVD (as defined above) and those without; treatment is often referred to as “secondary” and “primary” prevention, respectively. Because risk is higher in patients with ASCVD, more intensive therapy is indicated and has been shown to be of benefit in multiple large randomized cardiovascular outcomes trials (61,64–66).

#### The Risk Calculator

The American College of Cardiology/American Heart Association ASCVD risk calculator is generally a useful tool to estimate 10-year ASCVD risk (my.americanheart.org). However, as diabetes itself confers increased risk for ASCVD and risk calculators in general do not account for the duration of diabetes or the presence of other complications such as albuminuria, the risk calculator has limited use for assessing cardiovascular risk in individuals with diabetes.

Recently, risk scores and other cardiovascular biomarkers have been developed for risk stratification of secondary prevention patients (i.e., those who are already high risk because they have ASCVD) but are not yet in widespread use (67,68). With newer, more expensive lipid-lowering therapies now available, use of these risk assessments may help target these new therapies to “higher risk” ASCVD patients in the future.

**Table 9.3—High-intensity and moderate-intensity statin therapy\***

High-intensity statin therapy (lowers LDL cholesterol by $\geq 50\%$ )	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.

**Primary Prevention (Patients Without ASCVD)**

For primary prevention, moderate-dose statin therapy is recommended for those 40 years and older (55,62,63), though high-intensity therapy may be considered on an individual basis in the context of additional ASCVD risk factors. The evidence is strong for patients with diabetes aged 40–75 years, an age-group well represented in statin trials showing benefit.

The evidence is lower for patients aged >75 years; relatively few older patients with diabetes have been enrolled in primary prevention trials. However, heterogeneity by age has not been seen in the relative benefit of lipid-lowering therapy in trials that included older participants (53,60,61), and because older age confers higher risk, the absolute benefits are actually greater (53,65). Moderate-intensity statin therapy is recommended in patients with diabetes that are 75 years or older. However, the risk-benefit profile should be routinely evaluated in this population, with downward titration of dose 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 (55). 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. Patients below the age of 40 have lower risk of developing a cardiovascular event over a 10-year horizon; however, their lifetime risk of developing cardiovascular disease and suffering an MI, stroke, or cardiovascular death is high. For patients under the age of 40 years and/or who have type 1 diabetes with other ASCVD risk factors, we recommend that the patient and health care provider discuss the relative benefits and risks and consider the use of moderate-intensity statin therapy. Please refer to “Type 1 Diabetes Mellitus and Cardiovascular Disease: A Scientific Statement From the American Heart

Association and American Diabetes Association” (69) for additional discussion.

**Secondary Preventions (Patients With ASCVD)**

High-intensity statin therapy is recommended for all patients with diabetes and ASCVD. This recommendation is based on the Cholesterol Treatment Trialists’ Collaboration involving 26 statin trials, of which 5 compared high-intensity versus moderate-intensity statins. Together, they found reductions in nonfatal cardiovascular events with more intensive therapy, in patients with and without diabetes (53,57,64).

Over the past few years, there have been multiple large randomized trials investigating the benefits of adding nonstatin agents to statin therapy, including three that evaluated further lowering of LDL cholesterol with ezetimibe (65), PCSK9 inhibitors (66), and cholesteryl ester transfer protein [CETP] inhibitors, an investigational class of drugs with some recent supportive data (70). Each trial found a significant benefit in the reduction of ASCVD events that was directly related to the degree of further LDL cholesterol lowering. These three large trials comprised over 75,000 patients and 250,000 patient-years of follow-up, and approximately one-third of participants had diabetes. For patients with ASCVD who are on high-intensity (and maximally tolerated) statin therapy and have an LDL cholesterol  $\geq 70$  mg/dL, the addition of nonstatin LDL-lowering therapy is recommended after considering the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.

**Combination Therapy for LDL Cholesterol Lowering****Statins and Ezetimibe**

The IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a randomized controlled trial in 18,144 patients comparing the addition of ezetimibe to simvastatin therapy versus simvastatin alone. Individuals were  $\geq 50$  years of age, had experienced a recent acute coronary syndrome (ACS), and were treated for an average of 6 years. Overall, the addition of ezetimibe led to a 6.4% relative benefit and a 2% absolute reduction in major adverse cardiovascular events, with the degree of benefit being directly proportional to the change in LDL cholesterol, which was 70 mg/dL in the statin group on average and 54 mg/dL in the combination group (65). In those with

diabetes (27% of participants), the combination of moderate-intensity simvastatin (40 mg) and ezetimibe (10 mg) showed a significant reduction of major adverse cardiovascular events with an absolute risk reduction of 5% (40% vs. 45%) and relative risk reduction of 14% (RR 0.86 [95% CI 0.78–0.94]) over moderate-intensity simvastatin (40 mg) alone (65).

**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 have been approved as adjunctive therapy for patients with ASCVD or familial hypercholesterolemia who are receiving maximally tolerated statin therapy but require additional lowering of LDL cholesterol (71,72).

The effects of PCSK9 inhibition on ASCVD outcomes was investigated in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, which enrolled 27,564 patients with prior ASCVD and an additional high-risk feature who were receiving their maximally tolerated statin therapy (two-thirds were on high-intensity statin) but who still had an LDL cholesterol  $\geq 70$  mg/dL or a non-HDL cholesterol  $\geq 100$  mg/dL (66). Patients were randomized to receive subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg every month based on patient preference) versus placebo. Evolocumab reduced LDL cholesterol by 59% from a median of 92 to 30 mg/dL in the treatment arm.

During the median follow-up of 2.2 years, the composite outcome of cardiovascular death, MI, stroke, hospitalization for angina, or revascularization occurred in 11.3% vs. 9.8% of the placebo and evolocumab groups, respectively, representing a 15% relative risk reduction ( $P < 0.001$ ). The combined end point of cardiovascular death, MI, or stroke was reduced by 20%, from 7.4 to 5.9% ( $P < 0.001$ ). Importantly, similar benefits were seen in prespecified subgroup of patients with diabetes, comprising 11,031 patients (40% of the trial) (73).

**Statins and CETP Inhibitors**

Inhibition of CETP increases HDL cholesterol and further reduces LDL cholesterol.



This class of drugs is not likely to be available for clinical use, but studies provide further insight into the effects of LDL cholesterol lowering on cardiovascular events.

A total of four trials have been conducted, three of which failed to show benefit (74–76). Of these, one showed harm and two were stopped after approximately 2 years and thus did not have sufficient time or power to identify the benefit. The final study, the Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification (REVEAL) trial enrolled 30,449 patients with ASCVD (70). All patients received intensive atorvastatin therapy and were randomized to anacetrapib or placebo.

During the median follow-up of 4.1 years, the primary outcome (coronary death, MI, or coronary revascularization) was significantly reduced with the addition of anacetrapib from 11.8 to 10.8%, with a hazard ratio (HR) of 0.91 ( $P = 0.004$ ). The relative difference in risk was similar across multiple prespecified subgroups, including among 11,320 patients with diabetes (37% of the trial). The benefit appeared to be related to the reduction in LDL (and more broadly non-HDL) as opposed to the raising of HDL. The mean achieved LDL cholesterol was 63 mg/dL vs. 53 mg/dL at the trial midpoint in the placebo and anacetrapib groups, respectively. This study reaffirms the benefit of further lowering of LDL cholesterol on reducing cardiovascular events.

### Treatment of Other Lipoprotein Fractions or Targets

#### Recommendation

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

Hypertriglyceridemia should be addressed with dietary and lifestyle changes including abstinence from alcohol (77). Severe hypertriglyceridemia ( $>1,000$  mg/dL) may warrant pharmacologic therapy (fibrin 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 (78). In a large trial in patients with diabetes, fenofibrate failed to reduce overall cardiovascular outcomes (79).

### Other Combination Therapy

#### Recommendations

- Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. **A**
- Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. **A**

#### Statin and Fibrate

Combination therapy (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) (80).

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  $\geq 204$  mg/dL (2.3 mmol/L) and an HDL cholesterol level  $\leq 34$  mg/dL (0.9 mmol/L) (81).

#### 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 (82).

The much larger Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial also failed to show a benefit of adding niacin to background statin therapy (83). A total of 25,673 patients with prior vascular disease were randomized to receive 2 g of extended-release niacin and 40 mg of laropiprant (an antagonist of the prostaglandin D2 receptor DP<sub>1</sub> that has been shown to improve adherence to niacin therapy) versus a matching placebo daily and followed for a median follow-up period of 3.9 years. There was no significant difference in the rate of coronary death, MI, stroke, or coronary revascularization with the addition of niacin–laropiprant versus placebo (13.2% vs. 13.7%; rate ratio, 0.96;  $P = 0.29$ ). Niacin–laropiprant was associated with an increased incidence of new-onset diabetes (absolute excess, 1.3 percentage points;  $P < 0.001$ ) and disturbances in diabetes control among those with diabetes. In addition, there was an increase in serious adverse events associated with the gastrointestinal system, musculoskeletal system, skin, and, unexpectedly, infection and bleeding.

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

### Diabetes With Statin Use

Several studies have reported a modestly increased risk of incident diabetes with statin use (84,85), which may be limited to those with diabetes risk factors. An analysis of one of the initial studies suggested that although statin use was associated with diabetes risk, the cardiovascular event rate reduction with statins far outweighed the risk of incident diabetes even for patients at highest risk for diabetes (86). 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) (86). 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 (85).

### Statins and Cognitive Function

A recent systematic review of the U.S. Food and Drug Administration's (FDA's) postmarketing surveillance databases, randomized controlled trials, and cohort, case-control, and cross-sectional studies evaluating cognition in patients receiving statins found that published data do not reveal an adverse effect of statins on cognition (87). In addition, no change in cognitive function has been reported in studies with the addition of ezetimibe (65) or PCSK9 inhibitors (66,88) to statin therapy, including among patients treated to very low LDL cholesterol levels. Therefore, a concern that statins or other lipid-lowering agents might cause cognitive dysfunction or dementia is not currently supported by evidence and should not deter their use in individuals with diabetes at high risk for ASCVD (87).

## 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 (with low-dose aspirin and a P2Y<sub>12</sub> inhibitor) is reasonable for a year after an acute coronary syndrome **A** and may have benefits beyond this period. **B**
- Aspirin therapy (75–162 mg/day) may be considered 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  $\geq 50$  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**

### 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 (89,90). 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 (91–93).

The Antithrombotic Trialists' Collaboration published an individual patient-level meta-analysis (89) 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 the effects of aspirin have not been observed in studies of secondary prevention (89). In the six trials examined by the Antithrombotic Trialists' Collaboration, 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 CI 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 effect is an increased risk of gastrointestinal bleeding. The excess risk may be as high as 5 per 1,000 per year in real-world settings. 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 (94).

### 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 (95). This now out-of-date statement included sex-specific recommendations for use of aspirin therapy as primary prevention in persons with diabetes (95). 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  $\geq 50$  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 (e.g., older age, anemia, renal disease) (96–99). While risk calculators such as those from the American College of Cardiology/American Heart Association ([my.americanheart.org](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 (100), but are not generally recommended. Sex differences in the antiplatelet effect of aspirin have been suggested in the general population (101); 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 (102). 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 (103). 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<sub>2</sub> and thus not sensitive to the effects of aspirin (104). "Aspirin resistance" has been described in patients with diabetes when measured by a variety of ex vivo and in vitro methods (platelet aggregation, measurement of thromboxane B<sub>2</sub>) (101), but other studies suggest no impairment in aspirin response among patients with diabetes (105). A recent trial suggested that more frequent dosing regimens of aspirin may reduce platelet reactivity in individuals with diabetes (106); 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 (107). 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 (108). 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, consider ACE inhibitor or angiotensin receptor blocker therapy to reduce the risk of cardiovascular events. **B**
- In patients with prior myocardial infarction,  $\beta$ -blockers should be continued for at least 2 years after the event. **B**
- In patients with type 2 diabetes with stable congestive heart failure, metformin may be used if estimated glomerular filtration rate remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure. **B**
- In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors (see Table 8.1). **A**
- In patients with type 2 diabetes and established atherosclerotic cardiovascular

disease, after lifestyle management and metformin, the antihyperglycemic agent canagliflozin may be considered to reduce major adverse cardiovascular events, based on drug-specific and patient factors (see Table 8.1). **C**

### 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  $\geq 40$  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 (109), in part because these high-risk patients should already be receiving intensive medical therapy—an approach that provides similar benefit as invasive revascularization (110,111). There is also some evidence that silent MI may reverse over time, adding to the controversy concerning aggressive screening strategies (112). In prospective studies, coronary artery calcium has been established as an independent predictor of future ASCVD events in patients with diabetes and is consistently superior to both the UK Prospective Diabetes Study (UKPDS) risk engine and the Framingham Risk Score in predicting risk in this population (113–115). However, a randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic patients with type 2 diabetes and normal ECGs (116). 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—

**Table 9.4—CVOTs completed after issuance of the FDA 2008 guidance**

Intervention	DPP-4 inhibitors			GLP-1 receptor agonists			SGLT2 inhibitors			
	SAVOR-TIMI 53 (129) (n = 16,492)	EXAMINE (145) (n = 5,380)	TECOS (132) (n = 14,671)	ELIXA (140) (n = 6,068)	LEADER (138) (n = 9,340)	SUSTAIN-6 (139)* (n = 3,297)	EXSCEL (141) (n = 14,752)	EMPA-REG OUTCOME (133) (n = 7,020)	CANVAS (135) (n = 4,330)	CANVAS-R (135) (n = 5,812)
	Saxagliptin/ placebo	Alogliptin/ placebo	Sitagliptin/ placebo	Lixisenatide/ placebo	Liraglutide/ placebo	Semaglutide/ placebo	Exenatide QW/ placebo	Empagliflozin/ placebo	Canagliflozin/ placebo	
Main inclusion criteria	Type 2 diabetes and history of or multiple risk factors for CVD	Type 2 diabetes and ACS within 15–90 days before randomization	Type 2 diabetes and preexisting CVD	Type 2 diabetes and history of ACS (<180 days)	Type 2 diabetes and preexisting CVD, kidney disease, or HF at ≥50 years of age or cardiovascular risk at ≥60 years of age	Type 2 diabetes and preexisting CVD, HF, or CKD at ≥50 years of age or cardiovascular risk at ≥60 years of age	Type 2 diabetes with or without preexisting CVD	Type 2 diabetes and preexisting CVD with BMI ≤45 kg/m <sup>2</sup> and eGFR ≥30 mL/min/1.73 m <sup>2</sup>	Type 2 diabetes and preexisting CVD at ≥30 years of age or ≥2 cardiovascular risk factors at ≥50 years of age	Type 2 diabetes and preexisting CVD at ≥30 years of age or ≥2 cardiovascular risk factors at ≥50 years of age
A1C inclusion criteria (%)	≥6.5	6.5–11.0	6.5–8.0	5.5–11.0	≥7.0	≥7.0	6.5–10.0	7.0–10.0	7.0–10.5	7.0–10.5
Age (years) <sup>††</sup>	65.1	61.0	65.4	60.3	64.3	64.6	62	63.1	63.3	63.3
Diabetes duration (years) <sup>††</sup>	10.3	7.1	11.6	9.3	12.8	13.9	12	57% >10	13.5	13.5
Median follow-up (years)	2.1	1.5	3.0	2.1	3.8	2.1	3.2	3.1	5.7	2.1
Statin use (%)	78	91	80	93	72	73	74	77	75	75
Metformin use (%)	70	66	82	66	76	73	77	74	77	77
Prior CVD/CHF (%)	78/13	100/28	74/18	100/22	81/18	60/24	73.1/16.2	99/10	65.6/14.4	65.6/14.4
Mean baseline A1C (%)	8.0	8.0	7.2	7.7	8.7	8.7	8.0	8.1	8.2	8.2
Mean difference in A1C between groups at end of treatment (%)	-0.3 <sup>∧</sup>	-0.3 <sup>∧</sup>	-0.3 <sup>∧</sup>	-0.3 <sup>∧</sup>	-0.4 <sup>∧</sup>	-0.7 or -1.0 <sup>†</sup>	-0.53 <sup>∧</sup>	-0.3 <sup>†</sup>	-0.58 <sup>∧</sup>	-0.58 <sup>∧</sup>
Year started/reported	2010/2013	2009/2013	2008/2015	2010/2015	2010/2016	2013/2016	2010/2017	2010/2015	2009/2017	2009/2017
Primary outcome§	3-point MACE	3-point MACE	4-point MACE	4-point MACE	3-point MACE	3-point MACE	3-point MACE	3-point MACE	3-point MACE	Progression to albuminuria**
	1.00 (0.89–1.12)	0.96 (95% UL ≤1.16)	0.98 (0.89–1.08)	1.02 (0.89–1.17)	0.87 (0.78–0.97)	0.74 (0.58–0.95)	0.91 (0.83–1.00)	0.86 (0.74–0.99)	0.86 (0.75–0.97)§	0.73 (0.47–0.77)
Key secondary outcome§	Expanded MACE	4-point MACE	3-point MACE	Expanded MACE	Expanded MACE	Expanded MACE	Individual components of MACE (see below)	4-point MACE	All-cause and cardiovascular mortality (see below)	40% reduction in composite eGFR, renal replacement, renal death
	1.02 (0.94–1.11)	0.95 (95% UL ≤ 1.14)	0.99 (0.89–1.10)	1.00 (0.90–1.11)	0.88 (0.81–0.96)	0.74 (0.62–0.89)	0.89 (0.78–1.01)	0.89 (0.78–1.01)	0.86 (0.75–0.97)§	0.60 (0.47–0.77)

Continued on p. S98



**Table 9.4—Continued**

	DPP-4 inhibitors			GLP-1 receptor agonists			SGLT2 inhibitors			
	SAVOR-TIMI 53 (129) (n = 16,492)	EXAMINE (145) (n = 5,380)	TECOS (132) (n = 14,671)	ELIXA (140) (n = 6,068)	LEADER (138) (n = 9,340)	SUSTAIN-6 (139)* (n = 3,297)	EXSCEL (141) (n = 14,752)	EMPA-REG OUTCOME (133) (n = 7,020)	CANVAS (135) (n = 4,330)	CANVAS-R (135) (n = 5,812)
Cardiovascular death§	1.03 (0.87–1.22)	0.85 (0.66–1.10)	1.03 (0.89–1.19)	0.98 (0.78–1.22)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.62 (0.49–0.77)	0.96 (0.77–1.18)¶	0.87 (0.72–1.06)¶
MI§	0.95 (0.80–1.12)	1.08 (0.88–1.33)	0.95 (0.81–1.11)	1.03 (0.87–1.22)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	0.87 (0.70–1.09)	0.85 (0.65–1.11)	0.85 (0.61–1.19)
Stroke§	1.11 (0.88–1.39)	0.91 (0.55–1.50)	0.97 (0.79–1.19)	1.12 (0.79–1.58)	0.86 (0.71–1.06)	0.61 (0.38–0.99)	0.85 (0.70–1.03)	1.18 (0.89–1.56)	0.97 (0.70–1.35)	0.82 (0.57–1.18)
HF hospitalization§	1.27 (1.07–1.51)	1.19 (0.90–1.58)	1.00 (0.83–1.20)	0.96 (0.75–1.23)	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	0.65 (0.50–0.85)	0.77 (0.55–1.08)	HR 0.56 (0.38–0.83)
Unstable angina hospitalization§	1.19 (0.89–1.60)	0.90 (0.60–1.37)	0.90 (0.70–1.16)	1.11 (0.47–2.62)	0.98 (0.76–1.26)	0.82 (0.47–1.44)	1.05 (0.94–1.18)	0.99 (0.74–1.34)	—	—
All-cause mortality§	1.11 (0.96–1.27)	0.88 (0.71–1.09)	1.01 (0.90–1.14)	0.94 (0.78–1.13)	0.85 (0.74–0.97)	1.05 (0.74–1.50)	0.86 (0.77–0.97)	0.68 (0.57–0.82)	0.87 (0.74–1.01)††	0.90 (0.76–1.07)##
Worsening nephropathy§	1.08 (0.88–1.32)	—	—	—	0.78 (0.67–0.92)	0.64 (0.46–0.88)	—	0.61 (0.53–0.70)	0.60 (0.47–0.77)	—

—, not assessed/reported; CANVAS-R, CANVAS-Renal; CHF, congestive heart failure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiac event; UL, upper limit. Data from this table was adapted from Cefalu et al. (146) in the January 2018 issue of *Diabetes Care*. \*Powered to rule out an HR of 1.8; superiority hypothesis not prespecified. \*\*On the basis of prespecified outcomes, the renal outcomes are not viewed as statistically significant. ††Age was reported as means in all trials except EXAMINE, which reported medians; diabetes duration was reported as means in all but four trials, with SAVOR-TIMI 53, EXAMINE, and EXSCEL reporting medians and EMPA-REG OUTCOME reporting as percentage of population with diabetes duration >10 years. †A1C change of 0.66% with 0.5 mg and 1.05% with 1 mg dose of semaglutide. ‡A1C change of 0.30 in EMPA-REG OUTCOME is based on pooled results for both doses (i.e., 0.24% for 10 mg and 0.36% for 25 mg of empagliflozin). §Outcomes reported as HR (95% CI). ¶Worsening nephropathy is defined as the new onset of UACR >300 mg/g creatinine or a doubling of the serum creatinine level and an estimated glomerular filtration rate of ≤45 mL/min/1.73 m<sup>2</sup>, the need for continuous renal-replacement therapy, or death from renal disease in EMPA-REG OUTCOME. LEADER, and SUSTAIN-6 and as doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL (530 μmol/L) in SAVOR-TIMI 53. Worsening nephropathy was a prespecified exploratory adjudicated outcome in SAVOR-TIMI 53, LEADER, and SUSTAIN-6 but not in EMPA-REG OUTCOME. ¶¶Truncated data set (prespecified in treating hierarchy as the principal data set for analysis of all-cause mortality and cardiovascular death in the CANVAS Program). †††Significant difference in A1C between groups (P < 0.05). ##Nontruncated data set. †††Truncated integrated data set (refers to pooled data from CANVAS after 20 November 2012 plus CANVAS-R; prespecified in treating hierarchy as the principal data set for analysis for superiority of all-cause mortality and cardiovascular death in the CANVAS Program). ###Nontruncated integrated data (refers to pooled data from CANVAS, including before 20 November 2012 plus CANVAS-R).

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 (117,118). 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 (113,119,120), 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 (121). 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 or ARB therapy in patients with diabetic kidney disease or hypertension, the benefits in patients with ASCVD in the absence of these conditions are less clear, especially when LDL cholesterol is concomitantly controlled (122,123). In patients with prior MI, active angina, or heart failure,  $\beta$ -blockers should be used (124).

#### Diabetes and Heart Failure

As many as 50% of patients with type 2 diabetes may develop heart failure (125). Data on the effects of glucose-lowering agents on heart failure outcomes have demonstrated that thiazolidinediones have a strong and consistent relationship with increased risk of heart failure (126–128). 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) (129). 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. The FDA reported that the hospital admission rate for heart failure in EXAMINE was 3.9% for patients randomly assigned to alogliptin compared with 3.3% for those randomly assigned to placebo (130). Alogliptin had no effect on the composite end point of cardiovascular death and hospital admission for heart failure in the post hoc analysis (HR 1.00 [95% CI 0.82–1.21]) (131). TECOS showed no 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) (132).

A benefit on the incidence of heart failure has been observed with the use of some sodium–glucose cotransporter 2 (SGLT2) inhibitors. In the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), the addition of empagliflozin to standard care led to a significant 35% reduction in the hospitalization for heart failure compared with placebo (133). Although the majority of patients in the study did not have heart failure at baseline, this benefit was consistent in patients with and without a prior history of heart failure (134). Similarly, in the Canagliflozin Cardiovascular Assessment Study (CANVAS), there was a 33% reduction in hospitalization for heart failure with canagliflozin versus placebo (135). Although heart failure hospitalizations were prospectively adjudicated in both trials, the type(s) of heart failure events prevented were not characterized. These preliminary findings, which strongly suggest heart failure–related benefits of

SGLT2 inhibitors (particularly the prevention of heart failure), are being followed up with new outcomes trials in patients with established heart failure, both with and without diabetes, to determine their efficacy in treatment of heart failure.

#### Antihyperglycemic Therapies and Cardiovascular Outcomes

In 2008, the FDA issued a guidance for industry to perform cardiovascular outcomes trials for all new medications for the treatment for type 2 diabetes amid concerns of increased cardiovascular risk (137). Previously approved diabetes medications were not subject to the guidance. Recently published cardiovascular outcomes trials have provided additional data on cardiovascular outcomes in patients with type 2 diabetes with cardiovascular disease or at high risk for cardiovascular disease (see **Table 9.4**). Cardiovascular outcomes trials of DPP-4 inhibitors have all, so far, not shown cardiovascular benefits relative to placebo. However, results from other new agents have provided a mix of results.

EMPA-REG OUTCOME trial was a randomized, double-blind trial that assessed the effect of empagliflozin, a SGLT2 inhibitor, versus placebo on cardiovascular outcomes in 7,020 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, HR in the empagliflozin group 0.86; 95% CI 0.74–0.99;  $P = 0.04$  for superiority) and cardiovascular death by 38% (absolute rate 3.7% vs. 5.9%, HR 0.62; 95% CI 0.49–0.77;  $P < 0.001$ ) (133). The FDA recently added a new indication for empagliflozin, to reduce the risk of major adverse cardiovascular death in adults with type 2 diabetes and cardiovascular disease.

A second large cardiovascular outcomes trial program of an SGLT2 inhibitor, canagliflozin, has been reported (135). The CANVAS Program integrated data from two trials, including the CANVAS trial that started in 2009 before the approval of canagliflozin and the CANVAS-R trial that started in 2014 after the approval of canagliflozin. Combining both these trials, 10,142 participants with type 2 diabetes and

high cardiovascular risk were randomized to canagliflozin or placebo and were followed for an average 3.6 years. The mean age of patients was 63 years and 66% had a history of cardiovascular disease. The combined analysis of the two trials found that canagliflozin significantly reduced the composite outcome of cardiovascular death, MI, or stroke versus placebo (occurring in 26.9 vs. 31.5 participants per 1,000 patient-years; HR 0.86 [95% CI 0.75–0.97];  $P < 0.001$  for noninferiority;  $P = 0.02$  for superiority). The specific estimates for canagliflozin versus placebo on the primary composite cardiovascular outcome were HR 0.88 (0.75–1.03) for the CANVAS trial, and 0.82 (0.66–1.01) for the CANVAS-R, with no heterogeneity found between trials. In the combined analysis, there was not a statistically significant difference in cardiovascular death (HR 0.87 [95% CI 0.72–1.06]). The initial CANVAS trial was partially unblinded prior to completion because of the need to file interim cardiovascular outcome data for regulatory approval of the drug (136). Of note, there was an increased risk of amputation with canagliflozin (6.3 vs. 3.4 participants per 1,000 patient-years; HR 1.97 [95% CI 1.41–2.75]) (135).

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 (GLP-1) receptor agonist, versus placebo on cardiovascular outcomes in 9,340 patients with type 2 diabetes at high risk for cardiovascular disease or with cardiovascular disease. Study participants with a mean age of 64 years and a mean duration of diabetes of nearly 13 years. Over 80% of study participants had established cardiovascular disease. After a median follow-up of 3.8 years, LEADER showed that the primary composite outcome (MI, stroke, or cardiovascular death) occurred in fewer participants in the treatment group (13.0%) when compared with the placebo group (14.9%) (HR 0.87; 95% CI 0.78–0.97;  $P < 0.001$  for noninferiority;  $P = 0.01$  for superiority). Deaths from cardiovascular causes in the were significantly reduced in the liraglutide group (4.7%) compared to the placebo group (6.0%) (HR 0.78; 95% CI 0.66–0.93;  $P = 0.007$ ) (138). The FDA recently approved use of liraglutide to reduce the risk of major adverse cardiovascular events, including heart attack,

stroke and cardiovascular death, in adults with type 2 diabetes and established cardiovascular disease.

Results from a moderate-sized trial of another GLP-1 receptor agonist, semaglutide, were consistent with the LEADER trial (139). Semaglutide, a once-weekly GLP-1 receptor agonist, has not yet been approved by the FDA for the treatment of type 2 diabetes. The preapproval Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) was the initial randomized trial powered to test noninferiority of semaglutide for the purpose of initial regulatory approval. In this study, 3,297 patients with type 2 diabetes were randomized to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 2 years. The primary outcome (the first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke) occurred in 108 patients (6.6%) in the semaglutide group vs. 146 patients (8.9%) in the placebo group (HR 0.74 [95% CI 0.58–0.95];  $P < 0.001$ ). More patients discontinued treatment in the semaglutide group because of adverse events, mainly gastrointestinal.

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial studied the once-daily GLP-1 receptor agonist lixisenatide on cardiovascular outcomes in patients with type 2 diabetes who had had a recent acute coronary event (140). A total of 6,068 patients with type 2 diabetes with a recent hospitalization for MI or unstable angina within the previous 180 days were randomized to receive lixisenatide or placebo in addition to standard care and were followed for a median of approximately 2.1 years. The primary outcome of cardiovascular death, MI, stroke, or hospitalization for unstable angina occurred in 406 patients (13.4%) in the lixisenatide group vs. 399 (13.2%) in the placebo group (HR 1.02 [95% CI 0.89–1.17]), which demonstrated the noninferiority of lixisenatide to placebo ( $P < 0.001$ ) but did not show superiority ( $P = 0.81$ ).

Most recently, the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial also reported results with the once-weekly GLP-1 receptor agonist extended-release exenatide and found that major adverse cardiovascular events were numerically lower with use of extended-release exenatide compared with placebo, although this difference was not statistically

significant (141). A total of 14,752 patients with type 2 diabetes (of whom 10,782 [73.1%] had previous cardiovascular disease) were randomized to receive extended-release exenatide 2 mg or placebo and followed for a median of 3.2 years. The primary end point of cardiovascular death, MI, or stroke occurred in 839 patients (11.4%; 3.7 events per 100 person-years) in the exenatide group and in 905 patients (12.2%; 4.0 events per 100 person-years) in the placebo group (HR 0.91 [95% CI 0.83–1.00];  $P < 0.001$  for noninferiority) but was not superior to placebo with respect to the primary end point ( $P = 0.06$  for superiority). However, all-cause mortality was lower in the exenatide group (HR 0.86 [95% CI 0.77–0.97]). The incidence of acute pancreatitis, pancreatic cancer, medullary thyroid carcinoma, and serious adverse events did not differ significantly between the two groups.

In summary, there are now large randomized controlled trials reporting statistically significant reductions in cardiovascular events for two of the FDA-approved SGLT2 inhibitors (empagliflozin and canagliflozin) and one of the FDA-approved GLP-1 receptor agonists (liraglutide) where the majority, if not all, patients in the trial had ASCVD. The empagliflozin and liraglutide trials further demonstrated significant reductions in cardiovascular death. Once-weekly exenatide did not have statistically significant reductions in major adverse cardiovascular events or cardiovascular mortality but did have a significant reduction in all-cause mortality. In contrast, other GLP-1 receptor agonists have not shown similar reductions in cardiovascular events (Table 9.4). Whether the benefits of GLP-1 receptor agonists are a class effect remains to be definitively established. Additional large randomized trials of other agents in these classes are ongoing.

Of note, these studies examined the drugs in combination with metformin (Table 9.4) in the great majority of patients for whom metformin was not contraindicated or was tolerated. For patients with type 2 diabetes who have ASCVD, on lifestyle and metformin therapy, it is recommended to incorporate an agent with strong evidence for cardiovascular risk reduction, especially those with proven benefit on both major adverse cardiovascular events and cardiovascular death,

after consideration of drug-specific patient factors (Table 8.1). See Fig. 8.1 for additional recommendations on antihyperglycemic treatment in adults with type 2 diabetes.

## 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. Rawshani A, Rawshani A, Franzén S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med* 2017;376:1407–1418
3. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990–2010. *N Engl J Med* 2014;370:1514–1523
4. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. *N Engl J Med* 2007;356:2388–2398
5. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40:1273–1284
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. Segal 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. Omboni S, Gazzola T, Carabelli G, Parati G. Clinical usefulness and cost effectiveness of home blood pressure telemonitoring: meta-analysis of randomized controlled studies. *J Hypertens* 2013;31:455–467; discussion 467–468
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. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;387:957–967
12. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ* 2016;352:i717
13. Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and bayesian random-effects meta-analyses of randomized trials. *Circulation* 2011;123:2799–2810
14. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10- should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. *J Hypertens* 2017;35:922–944
15. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet* 2016;387:435–443
16. Cushman WC, Evans GW, Byington RP, et al.; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575–1585
17. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. 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
18. Bakris GL. The implications of blood pressure measurement methods on treatment targets for blood pressure. *Circulation* 2016;134:904–905
19. Association AD; American Diabetes Association. Glycemic targets. Sec. 6. In *Standards of Medical Care in Diabetes—2017*. *Diabetes Care* 2017;40(Suppl. 1):S48–S56
20. Blood Pressure Lowering Treatment Trialists’ Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet* 2014;384:591–598
- 20a. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. *J Am Coll Cardiol*. In press
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. 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
23. Bakris GL, Weir MR; Study of Hypertension and the Efficacy of Lotrel in Diabetes (SHIELD) Investigators. Achieving goal blood pressure in patients with type 2 diabetes: conventional versus fixed-dose combination approaches. *J Clin Hypertens (Greenwich)* 2003;5:202–209
24. Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SAE, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial. *Hypertension* 2009;53:646–653
25. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med* 2007;120:713–719
26. Catalá-López F, Macías Saint-Gerons D, González-Bermejo J, et al. Cardiovascular and renal outcomes of renin-angiotensin system blockade in adult patients with diabetes mellitus: a systematic review with network meta-analyses. *PLoS Med* 2016;13:e1001971
27. 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
28. Barzilay JI, Davis BR, Bettencourt J, et al.; ALLHAT Collaborative Research Group. Cardiovascular outcomes using doxazosin vs. chlorthalidone for the treatment of hypertension in older adults with and without glucose disorders: a report from the ALLHAT study. *J Clin Hypertens (Greenwich)* 2004;6:116–125
29. 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
30. 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. *BMJ* 2016;352:i438
31. Carlberg B, Samuelsson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? *Lancet* 2004;364:1684–1689
32. Yusuf S, Teo KK, Pogue J, et al.; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547–1559
33. 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
34. Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. *BMJ* 2013;346:f360
35. Zhao P, Xu P, Wan C, Wang Z. Evening versus morning dosing regimen drug therapy for hypertension. *Cochrane Database Syst Rev* 2011 (10): CD004184
36. 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
37. Nilsson E, Gasparini A, Ärnlöv J, et al. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. *Int J Cardiol* 2017;245:277–284
38. Bandak G, Sang Y, Gasparini A, et al. Hyperkalemia after initiating renin-angiotensin system blockade: the Stockholm Creatinine Measurements (SCREAM) project. *J Am Heart Assoc* 2017;6:e005428
39. Hughes-Austin JM, Rifkin DE, Beben T, et al. The relation of serum potassium concentration with cardiovascular events and mortality in community-living individuals. *Clin J Am Soc Nephrol* 2017;12:245–252
40. James MT, Grams ME, Woodward M, et al.; CKD Prognosis Consortium. A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. *Am J Kidney Dis* 2015;66:602–612
41. Iliescu R, Lohmeier TE, Tudorancea I, Laffin L, Bakris GL. Renal denervation for the treatment of resistant hypertension: review and clinical perspective. *Am J Physiol Renal Physiol* 2015;309:F583–F594
42. Bakris GL, Agarwal R, Chan JC, et al.; Mineralocorticoid Receptor Antagonist Tolerability Study—Diabetic Nephropathy (ARTS-DN) Study Group. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *JAMA* 2015;314:884–894
43. Williams B, MacDonald TM, Morant S, et al.; British Hypertension Society’s PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment



- for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 2015;386:2059–2068
44. Filippatos G, Anker SD, Böhm M, et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. *Eur Heart J* 2016;37:2105–2114
45. Bombardieri AS, Klemmer PJ. Mineralocorticoid receptor blockade in chronic kidney disease. *Blood Purif* 2012;33:119–124
46. 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
47. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2014;2:CD002252
48. Al-Balal M, Bozzo P, Einarson A. Use of diuretics during pregnancy. *Can Fam Physician* 2009;55:44–45
49. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after preeclampsia: population based cohort study. *BMJ* 2001;323:1213–1217
50. Chasman DI, Posada D, Subrahmanyam L, Cook NR, Stanton VP Jr, Ridker PM. Pharmacogenetic study of statin therapy and cholesterol reduction. *JAMA* 2004;291:2821–2827
51. 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
52. Mihaylova B, Emberson J, Blackwell L, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. 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
53. 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
54. 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
55. Collins R, Armitage J, Parish S, Sleight 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
56. 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
57. 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
58. 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
59. 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
60. 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
61. Kearney PM, Blackwell L, Collins R, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. 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
62. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013 (1):CD004816
63. 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
64. 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
65. 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
66. Sabatine MS, Giugliano RP, Keech AC, et al.; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713–1722
67. Bohula EA, Morrow DA, Giugliano RP, et al. Atherothrombotic risk stratification and ezetimibe for secondary prevention. *J Am Coll Cardiol* 2017;69:911–921
68. Bohula EA, Bonaca MP, Braunwald E, et al. Atherothrombotic risk stratification and the efficacy and safety of vorapaxar in patients with stable ischemic heart disease and previous myocardial infarction. *Circulation* 2016;134:304–313
69. 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
70. Bowman L, Hopewell JC, Chen F, et al.; HPS3/TIMI55–REVEAL Collaborative Group. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med* 2017;377:1217–1227
71. 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
72. 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
73. Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial [article online]. *Lancet Diabetes Endocrinol* 2017. Available from [http://www.thelancet.com/journals/landia/article/PIIS2213-8587\(17\)30313-3/abstract](http://www.thelancet.com/journals/landia/article/PIIS2213-8587(17)30313-3/abstract). Accessed 28 September 2017
74. Barter PJ, Caulfield M, Eriksson M, et al.; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;357:2109–2122
75. Schwartz GG, Olsson AG, Abt M, et al.; dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;367:2089–2099
76. Lincoff AM, Nicholls SJ, Riesmeyer JS, et al.; ACCELERATE Investigators. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. *N Engl J Med* 2017;376:1933–1942
77. 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
78. Singh IM, Shishehbor MH, Ansell BJ. High-density lipoprotein as a therapeutic target: a systematic review. *JAMA* 2007;298:786–798
79. 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
80. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol* 2005;95:120–122
81. Ginsberg HN, Elam MB, Lovato LC, et al.; ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1563–1574
82. Boden WE, Probstfield JL, Anderson T, et al.; AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365:2255–2267
83. Landray MJ, Haynes R, Hopewell JC, et al.; HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* 2014;371:203–212
84. 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
85. 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
86. 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
87. Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. *Ann Intern Med* 2013;159:688–697
88. Giugliano RP, Mach F, Zavitz K, et al.; EBBINGHAUS Investigators. Cognitive function in a randomized trial of evolocumab. *N Engl J Med* 2017;377:633–643
89. Baigent C, Blackwell L, Collins R, et al.; Antithrombotic Trialists' (ATT) Collaboration. 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
90. 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
91. 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
92. 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
93. 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
94. 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
95. 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
96. 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
97. 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
98. 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
99. Peters SAE, Huxley RR, Woodward M. Diabetes as a risk factor for a 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
100. Dimitriu-Leen AC, Scholte AJHA, van Rosendaal 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
101. 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
102. 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
103. Campbell CL, Smyth S, Montalescot G, Steinhilb SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. *JAMA* 2007;297:2018–2024
104. Davi G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med* 2007;357:2482–2494
105. Zaccardi F, Rizzi A, Petrucci G, et al. In vivo platelet activation and aspirin responsiveness in type 1 diabetes. *Diabetes* 2016;65:503–509
106. 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
107. Vandvik PO, Lincoff AM, Gore JM, et al. 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
108. Bhatt DL, Bonaca MP, Bansal 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
109. 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
110. 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
111. 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
112. 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
113. 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
114. 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
115. 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
116. 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
117. 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
118. 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
119. 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
120. 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
121. Wing RR, Bolin P, Brancati FL, et al.; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369:145–154
122. 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
123. Telmisartan Randomised Assessment Trial 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
124. 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
125. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974;34:29–34
126. 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 In macroVascular Events): a randomised controlled trial. *Lancet* 2005;366:1279–1289

127. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007;298:1189–1195
128. 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
129. 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
130. U.S. Food and Drug Administration. Diabetes medications containing saxagliptin and alogliptin: drug safety communication - risk of heart failure [Internet]. Available from <https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm494252.htm>. Accessed 13 October 2017
131. 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
132. 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
133. 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
134. Fitchett D, Butler J, van de Borne P, et al. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME trial [article online]. *Eur Heart J* 2017. Available from <https://academic.oup.com/eurheartj/article/doi/10.1093/eurheartj/ehx511/4096345/Effects-of-empagliflozin-on-risk-for>. Accessed 29 September 2017
135. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644–657
136. Neal B, Perkovic V, Matthews DR, et al. Rationale, design and baseline characteristics of the CANagliflozin cardiovascular Assessment Study-Renal (CANVAS-R): a randomized, placebo controlled trial. *Diabetes Obes Metab* 2017;19:387–393
137. U.S. Food and Drug Administration. Guidance for industry diabetes mellitus: evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Silver Spring, MD, 2008. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf>. Accessed 3 November 2017
138. 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
139. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–1844
140. Pfeffer MA, Claggett B, Diaz R, et al.; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015;373:2247–2257
141. Holman RR, Bethel MA, Mentz RJ, et al.; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017;377:1228–1239
142. 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
143. 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) randomized trial. *Lancet* 1998;351:1755–1762
144. 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
145. White WB, Cannon CP, Heller SR, et al.; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;369:1327–1335
146. Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a *Diabetes Care* Editors' Expert Forum. *Diabetes Care*. In press