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CLINICAL GUIDELINE

Cardiovascular Disease and Risk Management: Review of the American Diabetes Association Standards of Medical Care in Diabetes 2018

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Description: The American Diabetes Association (ADA) annually updates its Standards of Medical Care in Diabetes to provide clinicians, patients, researchers, payers, and other interested parties with evidence-based recommendations for the diagnosis and management of patients with diabetes.

Methods: For the 2018 standards, the ADA Professional Practice Committee searched MEDLINE through November 2017 to add, clarify, or revise recommendations on the basis of new evidence. The committee rated the recommendations as A, B, or C depending on the quality of evidence or E for expert consensus or clinical experience. The standards were reviewed and approved by the Executive Committee of the ADA Board of Directors, which includes health care professionals, scientists, and laypersons. Feedback from the larger clinical community informed revisions.

Recommendations: This synopsis focuses on guidance relating to cardiovascular disease and risk management in nonpregnant adults with diabetes. Recommendations address diagnosis and treatment of cardiovascular risk factors (hypertension and dyslipidemia), aspirin use, screening for and treatment of coronary heart disease, and lifestyle interventions.

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Atherosclerotic cardiovascular disease (ASCVD), defined as coronary heart disease, cerebrovascular disease, or peripheral artery disease, is the leading cause of morbidity and mortality in persons with diabetes and is the largest contributor to the direct and indirect costs of diabetes. The 2018 American Diabetes Association (ADA) Standards of Medical Care recommend that cardiovascular risk factors be assessed at least annually in all patients with diabetes. This synopsis focuses on the ADA guidance relating to cardiovascular disease and risk management in nonpregnant adults with diabetes. Recommendations address diagnosis and treatment of cardiovascular risk factors (hypertension and dyslipidemia), aspirin use, screening for and treatment of coronary heart disease, and lifestyle interventions.

Guideline Development and Evidence Grading

To develop the 2018 standards, the ADA Professional Practice Committee, which comprises physicians, adult and pediatric endocrinologists, diabetes educators, registered dietitians, epidemiologists, and public health experts, searched MEDLINE through November 2017 and reviewed studies (particularly high-quality trials that included persons with diabetes) for potential incorporation into recommendations. The committee also solicited feedback from the larger clinical community.

The recommendations were rated as A, B, C, or E. Those with an A rating are based on large, well-designed, multicenter clinical trials or high-quality meta-analyses. Recommendations with lower-quality evidence may be equally important and are based on well-conducted cohort studies (B rating) or uncontrolled studies (C rating). Those with an E rating are consensus recommendations for cases where there is no evidence from clinical trials, clinical trials may be impractical, or there is conflicting evidence.

The ADA funds development of the standards from its general revenues, with no industry support or involvement. Details on the methods, information about the committee members and their conflict-of-interest disclosures, and the complete standards can be downloaded at https://professional.diabetes.org/annals.

Hypertension and Blood Pressure Control

Screening and Diagnosis Recommendations

Blood pressure should be measured at every routine clinical visit. Patients with elevated blood pressure (≥140/90) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. (Grade B recommendation)

All hypertensive patients with diabetes should monitor their blood pressure at home. (Grade B recommendation)

Hypertension coexistent with diabetes is a common risk factor for complications, such as coronary artery disease, cerebrovascular disease, peripheral vascular disease, and diabetic kidney disease. Appropriate treatment of hypertension reduces risk for such complications (1–3).

Blood pressure should be measured by a trained person following the guidelines for the general population (after 5 minutes of rest and while the patient is seated, with feet on the floor and the arm supported at heart level). An average of at least 2 readings obtained on at least 2 occasions should be used to estimate blood pressure (4). White coat hypertension can be confirmed with home self-monitoring or 24-hour ambulatory monitoring (5). Postural changes in blood pressure and pulse may be evidence of autonomic neurop-

athy and therefore require adjustment of blood pressure targets.

Treatment Goal Recommendations

Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mm Hg and a diastolic blood pressure goal of <90 mm Hg. (Grade A recommendation)

Lower systolic and diastolic blood pressure targets, such as 130/80 mm Hg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. (Grade C recommendation)

The ADA Standards of Medical Care emphasize individualization of blood pressure targets. Guidelines from other organizations (4) and large randomized trials (6–10) clearly establish that treating patients with baseline systolic blood pressure of 140 mm Hg or greater to targets below this level is beneficial. More intensive targets may offer additional benefits for some patients but may also incur additional costs. Patients and clinicians should engage in a shared decision-making process to determine individual blood pressure targets (5). Factors that may influence targets include risks of treatment (such as hypotension or drug adverse effects); life expectancy; comorbidities, including vascular and renal complications; patient attitude and expected treatment efforts; and resources and support system. In older adults, individualized blood pressure goals should minimize other risks, such as falls (11, 12).

Lifestyle Intervention Recommendation

For patients with blood pressure >120/80 mm Hg, 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. (Grade B recommendation)

Lifestyle intervention should be initiated along with pharmacologic therapy when hypertension is diagnosed (11). In patients with blood pressure greater than 120/80 mm Hg, lifestyle interventions include losing weight if the patient is overweight or obese; following the DASH (Dietary Approaches to Stop Hypertension) dietary pattern (13), including restricting sodium intake (<2300 mg/d) and increasing intake of potassium, fruits and vegetables (8 to 10 servings per day), and low-fat dairy products (2 to 3 servings per day); avoiding excessive alcohol consumption; and increasing activity levels (11). Decreasing sodium intake to no more than 1500 mg/d may improve blood pressure in certain circumstances (14, 15), but restriction to this level for all patients with diabetes is not recommended (16, 17).

Pharmacologic Intervention Recommendations

Patients with confirmed office-based blood pressure ≥140/90 mm Hg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. (Grade A recommendation)

Patients with confirmed office-based blood pressure ≥160/100 mm Hg 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. (Grade A recommendation)

Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). (Grade A recommendation)

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. (Grade A recommendation)

An ACE inhibitor or angiotensin receptor blocker, at the maximally tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin-to-creatinine ratio ≥300 mg/g creatinine (grade A recommendation) or 30–299 mg/g creatinine (grade B recommendation). If one class is not tolerated, the other should be substituted (grade B recommendation).

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. (Grade B 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. (Grade B recommendation)

Initial treatment for patients with diabetes depends on the severity of hypertension (Figure 1). Several considerations might affect selection of the class of antihypertensive medication. Titration and/or addition of further blood pressure medications is important to avoid clinical inertia and to achieve and maintain blood pressure targets.

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. (Grade A recommendation)

Intensify lifestyle therapy and optimize glycemic control for patients with elevated triglyceride levels (≥150 mg/dL [1.7 mmol/L]) and/or low HDL cholesterol (<40 mg/dL [1.0 mmol/L] for men, <50 mg/dL [1.3 mmol/L] for women). (Grade C recommendation)

Patients should replace saturated fats with unsaturated fats rather than refined carbohydrates (18). Ran-

domized trials do not support use of *n*-3 fatty acid supplements for primary or secondary prevention of ASCVD (19–23). Randomized trials show that a Mediterranean-style diet rich in polyunsaturated and monounsaturated fats can improve glycemic control and lipid levels (18, 24–29).

Lipid Panel Monitoring 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. (Grade E recommendation)

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. (Grade E recommendation)

Statin Treatment Recommendations

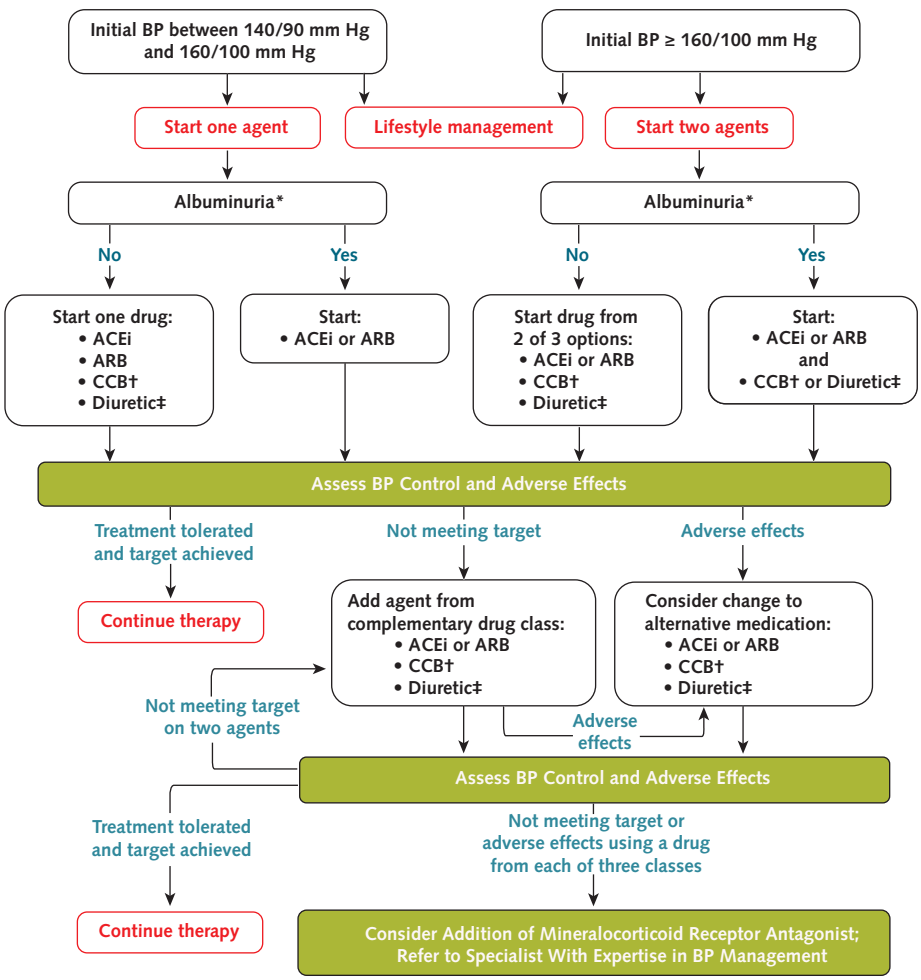
For patients of all ages with diabetes and ASCVD, high-intensity statin therapy should be added to lifestyle therapy. (Grade A recommendation)

For patients with diabetes aged <40 years with additional ASCVD risk factors, the patient and provider should consider using moderate-intensity statin in addition to lifestyle therapy. (Grade C recommendation)

For patients with diabetes aged 40–75 years (grade A recommendation) and >75 years (grade B recommendation) without ASCVD, 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

Figure 1. Recommendations for the treatment of confirmed hypertension in people with diabetes.



This figure can also be found in the American Diabetes Association position statement "Diabetes and Hypertension." ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BP = blood pressure; CCB = calcium-channel blocker; UACR = urinary albumin–creatinine ratio.

* An 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.

† Dihydropyridine calcium-channel blocker.

‡ Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred.

response to medication (e.g., side effects, tolerability, low-density lipoprotein [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. (Grade E recommendation)

For patients with diabetes and ASCVD, if LDL cholesterol is ≥70 mg/dL on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 [proprotein convertase subtilisin/kexin type 9] inhibitor) after considering the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences. Ezetimibe may be preferred due to lower cost. (Grade A recommendation)

Patients with type 2 diabetes have increased prevalence of lipid abnormalities, contributing to their high risk for ASCVD. The American College of Cardiology/American Heart Association ASCVD risk calculator (www.cvriskcalculator.com) has limited use for assessing cardiovascular risk in persons with diabetes because it does not account for the duration of diabetes or the presence of other complications, such as albuminuria (30).

Given that clinical trials show beneficial effects of statin therapy on ASCVD outcomes in patients with and without coronary heart disease (31, 32), statins are the drug of choice for LDL cholesterol lowering and cardioprotection. High-intensity statin therapy achieves a reduction of approximately 50% in LDL cholesterol level, and moderate-intensity regimens achieve reductions of 30% to 50%. Low-dose statin therapy is generally not recommended in patients with diabetes but is sometimes the only dose that a patient can tolerate.

For primary prevention in patients aged 40 to 75 years without clinical ASCVD, moderate-dose statin therapy is recommended (33–35), although high-intensity therapy may be considered for certain patients with additional ASCVD risk factors. Few persons older than 75 years were enrolled in trials of statins; however, the absolute benefits of treatment for them may exceed the benefits for younger persons because increasing age generally confers higher risk for ASCVD (32). Moderate-intensity statin therapy is recommended in patients with diabetes who are older than 75 years, with downward titration of the dose if needed on the basis of risk–benefit profile assessments.

Little evidence from clinical trials exists for patients with type 2 diabetes who are younger than 40 years and for those with type 1 diabetes of any age. Patients younger than 40 years have lower risk for cardiovascular events over a 10-year horizon; however, their lifetime risk for ASCVD and myocardial infarction, stroke, or cardiovascular death is high. For patients younger than 40 years with type 2 diabetes and other ASCVD risk factors and for patients with type 1 diabetes and other ASCVD risk factors, we recommend that the patient and the health care provider discuss relative benefits and risks and consider use of moderate-intensity statin therapy.

For secondary prevention in patients with ASCVD, high-intensity statin therapy is recommended (32, 36, 37). Recent randomized trials investigating the benefits of adding nonstatin agents (ezetimibe [38] and PCSK9 inhibitors [39]) to statin therapy showed reduced risk for ASCVD events with the added therapy that seemed to be related to the degree of further LDL cholesterol lowering. Ezetimibe is indicated to reduce LDL cholesterol levels in patients with hyperlipidemia, and the PCSK9 inhibitors evolocumab and alirocumab have been approved as adjunctive therapy for patients with ASCVD or familial hypercholesterolemia who are receiving maximum tolerated statin therapy but require additional lowering of LDL cholesterol levels (40, 41).

Triglyceride Treatment Recommendation

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

Hypertriglyceridemia should be addressed with dietary and lifestyle changes, including abstinence from alcohol (42). Severe hypertriglyceridemia (>11.3 mmol/L [>1000 mg/dL]) may warrant pharmacologic therapy (fibric acid derivatives, fish oil, or both) to reduce risk for acute pancreatitis.

Combination Therapy Recommendations

Combination therapy (statin/fibrate) has not been shown to improve ASCVD outcomes and is generally not recommended. (Grade A recommendation)

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. (Grade A recommendation)

Combination therapy with a statin and a fibrate is associated with increased risk for abnormal aminotransferase levels, myositis, and rhabdomyolysis. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared with simvastatin alone (43). Combination therapy with a statin and extended-release niacin was evaluated in a trial that was halted early due to lack of efficacy on the primary composite outcome (cardiac death, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome [ACS], or symptom-driven coronary or cerebral revascularization) and a possible increase in ischemic stroke in patients receiving combination therapy (44).

Concerns About Statin Use

Several studies have shown that statin use is associated with a modestly increased risk for incident diabetes; the increased risk may be limited to persons with diabetes risk factors (45–47). In one study, the absolute risk increase was small (1.2% of participants receiving placebo and 1.5% receiving rosuvastatin developed diabetes over 5 years of follow-up), and the cardiovascular event rate reduction with statins outweighed the risk

for diabetes, even for patients at the highest risk for diabetes (47).

Concern that statins or other lipid-lowering agents might cause cognitive dysfunction or dementia should not preclude their use in patients with diabetes who are at high risk for ASCVD. A recent systematic review of the U.S. Food and Drug Administration's (FDA) post-marketing surveillance databases that evaluated cognition in patients receiving statins found that published data do not show an adverse effect of statins on cognition (48).

ANTIPLATELET AGENT RECOMMENDATIONS

Use aspirin therapy (75-162 mg/day) as secondary prevention in those with diabetes and a history of ASCVD. (Grade A recommendation)

For patients with ASCVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used. (Grade B recommendation)

Dual antiplatelet therapy (with low-dose aspirin and a P2Y12 inhibitor) is reasonable for a year after an ACS (grade A recommendation) and may have benefits beyond this period (grade B recommendation).

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 ≥50 years who have at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or albuminuria) and are not at increased risk of bleeding. (Grade C recommendation)

Figure 2. Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes.

	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use Considerations	
Metformin	High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 Inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	• Canagliflozin: not recommended with eGFR <45 • Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 • Empagliflozin: contraindicated with eGFR <30	• FDA Black Box: Risk of amputation (canagliflozin) • Risk of bone fractures (canagliflozin) • DKA risk (all agents; rare in T2DM) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL cholesterol
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	• Exenatide: not indicated with eGFR <30 • Lixisenatide: caution with eGFR <30 • Increased risk of side effects in patients with renal impairment	• FDA Black Box: Risk of thyroid C-cell tumors (liraglutide, albiglutide, dulaglutide, exenatide extended release) • Gastrointestinal side effects common (nausea, vomiting, diarrhea) • Injection site reactions • ?Acute pancreatitis risk
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	• Renal dose adjustment required; can be used in renal impairment	• Potential risk of acute pancreatitis • Joint pain
Thiazolidinediones	High	No	Gain	Potential Benefit: pioglitazone	Increased Risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	• FDA Black Box: Congestive heart failure (pioglitazone, rosiglitazone) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide: not recommended • Glipizide & glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin – Human Insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin – Analogs						High	SQ			

ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CV = cardiovascular; CVD = cardiovascular disease; DKA = diabetic ketoacidosis; DKD = diabetic kidney disease; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; FDA = U.S. Food and Drug Administration; GLP-1 = glucagon-like peptide-1; LDL = low-density lipoprotein; NASH = nonalcoholic steatohepatitis; NPH = neutral protamine Hagedorn; RA = receptor agonist; SGLT-2 = sodium–glucose cotransporter-2; SQ = subcutaneous; T2DM = type 2 diabetes mellitus.

* For description of efficacy, see Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38:140-9. [PMID: 25538310] doi:10.2337/dc14-2441.
† FDA-approved for CVD benefit.

Table. CVOTs Completed After Issuance of the FDA 2008 Guidance*

	DPP-4 Inhibitors			GLP-1 Receptor Agonists	
	SAVOR-TIMI 53 (*n* = 16 492)	**EXAMINE (*n* = 5380)**	**TECOS (*n* = 14 671)**	**ELIXA (*n* = 6068)**	**LEADER (*n* = 9340)**
Intervention	Saxagliptin/placebo	Alogliptin/placebo	Sitagliptin/placebo	Lixisenatide/placebo	Liraglutide/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
A1C inclusion criteria (%)	≥6.5	6.5–11.0	6.5–8.0	5.5–11.0	≥7.0
Age (years)‡	65.1	61.0	65.4	60.3	64.3
Diabetes duration (years)‡	10.3	7.1	11.6	9.3	12.8
Median follow-up (years)	2.1	1.5	3.0	2.1	3.8
Statin use (%)	78	91	80	93	72
Metformin use (%)	70	66	82	66	76
Prior CVD/CHF (%)	78/13	100/28	74/18	100/22	81/18
Mean baseline A1C (%)	8.0	8.0	7.2	7.7	8.7
Mean difference in A1C between groups at end of treatment (%)	–0.3§	–0.3§	–0.3§	–0.3§	–0.4§
Year started/reported	2010/2013	2009/2013	2008/2015	2010/2015	2010/2016
Primary outcome**	3-point MACE 1.00 (0.89–1.12)	3-point MACE 0.96 (95% UL ≤1.16)	4-point MACE 0.98 (0.89–1.08)	4-point MACE 1.02 (0.89–1.17)	3-point MACE 0.87 (0.78–0.97)
Key secondary outcome**	Expanded MACE 1.02 (0.94–1.11)	4-point MACE 0.95 (95% UL ≤ 1.14)	3-point MACE 0.99 (0.89–1.10)	Expanded MACE 1.00 (0.90–1.11)	Expanded MACE 0.88 (0.81–0.96)
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)
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)
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)
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)
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)
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)
Worsening nephropathy**,***	1.08 (0.88–1.32)	–	–	–	0.78 (0.67–0.92)

– = not assessed/reported; A1C = glycated hemoglobin; ACS = acute coronary syndrome; CANVAS = Canagliflozin Cardiovascular Assessment Study; CANVAS-R = Canagliflozin Cardiovascular Assessment Study-Renal; CHF = congestive heart failure; CKD = chronic kidney disease; CVD = cardiovascular disease; CVOT = cardiovascular outcomes trial; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG OUTCOME = BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; EXSCEL = Exenatide Study of Cardiovascular Event Lowering; FDA = U.S. Food and Drug Administration; GLP-1 = glucagon-like peptide-1; HF = heart failure; HR = hazard ratio; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE = major adverse cardiac event; MI = myocardial infarction; QW = once weekly; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53; SGLT2 = sodium–glucose cotransporter-2; SUSTAIN-6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects With Type 2 Diabetes; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UACR = urinary albumin–creatinine ratio; UL = upper limit.

* Data from this table were adapted from Cefalu WT, Kaul S, Gerstein HC, Holman RR, Zinman B, Skyler JS, 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. 2018;41:14-31. [PMID: 29263194] doi:10.2337/dci17-0057.

† Powered to rule out an HR of 1.8; superiority hypothesis not prespecified.

‡ 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.

§ Significant difference in A1C between groups ($P < 0.05$).

‖ 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).

†† On the basis of prespecified outcomes, the renal outcomes are not viewed as statistically significant.

‡‡ Truncated data set (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 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).

*** 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^2, 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.

Table–Continued

GLP-1 Receptor Agonists		SGLT2 Inhibitors		
SUSTAIN-6† (*n* = 3297)	**EXSCEL (*n* = 14 752)**	**EMPA-REG OUTCOME (*n* = 7020)**	**CANVAS (*n* = 4330)**	**CANVAS-R (*n* = 5812)**
Semaglutide/placebo	Exenatide QW/placebo	Empagliflozin/placebo	Canagliflozin/placebo	
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^2 and eGFR ≥30 mL/min/1.73 m^2	Type 2 diabetes and preexisting CVD at ≥30 years of age or ≥2 cardiovascular risk factors at ≥50 years of age	
≥7.0	6.5–10.0	7.0–10.0	7.0–10.5	
64.6	62	63.1	63.3	
13.9	12	57% >10	13.5	
2.1	3.2	3.1	5.7	2.1
73	74	77	75	
73	77	74	77	
60/24	73.1/16.2	99/10	65.6/14.4	
8.7	8.0	8.1	8.2	
–0.7 or – 1.0§‖	–0.53§	–0.3§¶	–0.58§	
2013/2016	2010/2017	2010/2015	2009/2017	
3-point MACE	3-point MACE	3-point MACE	3-point MACE	Progression to albuminuria††
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)
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
0.74 (0.62–0.89)		0.89 (0.78–1.01)		0.60 (0.47–0.77)
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)§§
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)
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)
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)
0.82 (0.47–1.44)	1.05 (0.94–1.18)	0.99 (0.74–1.34)		–
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)¶¶
0.64 (0.46–0.88)	–	0.61 (0.53–0.70)		0.60 (0.47–0.77)

The benefit of aspirin for patients with no previous cardiovascular events is controversial (49, 50). Some randomized trials in diabetic patients have had inconsistent findings or findings among women that differ from those in men (51–53). A meta-analysis of 6 large primary prevention trials found that aspirin reduced the risk for serious vascular events by 12% (relative risk, 0.88 [95% CI, 0.82 to 0.94]) (49). The largest reduction was for nonfatal myocardial infarction, with no statistically significant effect on coronary heart disease death (relative risk, 0.95 [CI, 0.78 to 1.15]) or total stroke. Aspirin reduced overall ASCVD events in men but not in women. Conversely, aspirin had no effect on stroke in men but reduced stroke in women. Of note, secondary prevention studies have not found differences in efficacy between sexes (49).

Aspirin is not recommended for patients at low risk for ASCVD (men and women aged <50 years with diabetes and no other major ASCVD risk factors) because risks for bleeding likely outweigh possible benefits. Clinical judgment should be used for patients at intermediate risk (younger patients with ≥1 risk factor or older patients with no risk factors) until further outcomes research is conducted. Aspirin therapy in patients younger than 21 years is typically contraindicated because of the risk for Reye syndrome.

There is little evidence to support a specific aspirin dose, although expert opinion suggests that 75 to 162 mg/d is optimal (54). Using the lowest possible dose may help reduce adverse effects (55). The most common low-dose tablet in the United States is 81 mg.

The combination of a P2Y12 receptor antagonist and aspirin should be used for at least 1 year in patients who have had an ACS and may have benefits beyond this period. The strongest evidence supports use of clopidogrel or ticagrelor if percutaneous coronary intervention was not performed and clopidogrel, ticagrelor, or prasugrel if it was performed (56). In patients with diabetes and prior myocardial infarction (1 to 3 years before), adding ticagrelor to aspirin significantly reduced risk for recurrent ischemic events, including coronary heart disease and cardiovascular death (57).

CORONARY HEART DISEASE

Screening Recommendations

In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as ASCVD risk factors are treated. (Grade A recommendation)

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). (Grade E recommendation)

Screening of asymptomatic patients with high ASCVD risk is not recommended (58), in part because high-risk patients should already be receiving intensive medical therapy—an approach that provides benefit similar to that of invasive revascularization (59, 60). Studies have shown that a risk factor–based approach to the initial diagnostic evaluation and subsequent follow-up for coronary artery disease fails to identify which patients with type 2 diabetes will have silent ischemia on screening tests (61, 62). Any benefit of newer noninvasive screening methods for coronary artery disease, such as computed tomography and computed tomography angiography, to identify patient subgroups for different treatment strategies remains unproven.

Pharmacologic Treatment Recommendations

In patients with known ASCVD, consider ACE inhibitor or angiotensin receptor blocker therapy to reduce the risk of cardiovascular events. (Grade B recommendation)

In patients with prior myocardial infarction, β-blockers should be continued for at least 2 years after the event. (Grade B recommendation)

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. (Grade B recommendation)

In patients with type 2 diabetes and established ASCVD, 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 Figure 2*). (Grade A recommendation)*

In patients with type 2 diabetes and established ASCVD, 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 Figure 2*). (Grade C recommendation)*

Patients at increased ASCVD risk should receive aspirin, a statin, and an ACE inhibitor or angiotensin-receptor blocker if they have hypertension unless a particular drug class is contraindicated. Although clear benefit exists for ACE inhibitor or angiotensin-receptor blocker 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 (63, 64). In patients with prior myocardial infarction, active angina, or heart failure, β-blockers should be used (65).

Figure 2 summarizes aspects of glucose-lowering agents, including cardiovascular effects, costs, and FDA black box warnings. The Table shows recent cardiovascular outcomes trials that provide relevant data about newer medications for patients with type 2 diabetes who have or are at high risk for cardiovascular disease. Most trials were randomized placebo-controlled trials that examined newer drugs in combination with metformin (unless it was contraindicated or not tolerated). Trials of new agents have had mixed results; empagliflozin, liraglutide, and canagliflozin had the strongest evidence of benefit. In the EMPA-REG OUTCOME trial, empagliflozin reduced the composite outcome of myocardial infarction, stroke, and cardiovascular death by 14% and cardiovascular death by 38% (66). The FDA recently added a new indication for empagliflozin to reduce the risk for cardiovascular death in adults with type 2 diabetes and cardiovascular disease. In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial, the primary composite outcome (myocardial infarction, stroke, or cardiovascular death) occurred in fewer participants in the liraglutide group than the placebo group (13% vs. 14.9%) (67). Deaths due to cardiovascular causes were also reduced in the liraglutide group (4.7%) compared with the placebo group (6.0%) (67). The FDA recently approved use of liraglutide to reduce risk for major adverse cardiovascular events, myocardial infarction, stroke, and cardiovascular death in adults with type 2 diabetes and established cardiovascular disease. The combined results from CANVAS (Canagliflozin Cardiovascular Assessment Study) and the CANVAS renal end points trial (CANVAS-R) found that, compared with placebo, canagliflozin reduced the composite outcome of cardiovascular death, myocardial infarction, or stroke (68). The observed reduction for cardiovascular death alone was not statistically significant (hazard ratio, 0.87 [CI, 0.72 to 1.06]) (68).

LIFESTYLE INTERVENTIONS

Lifestyle interventions, including weight loss, increased physical activity, medical nutrition therapy, and smoking cessation, may beneficially modify ASCVD risk factors in some patients. Intensive lifestyle intervention focusing on weight loss through decreased caloric intake and increased physical activity as performed in the Look AHEAD (Action for Health in Diabetes) trial may improve glucose control, fitness, and some ASCVD risk factors (69). In obese persons with type 2 diabetes, weight loss greater than 5% is needed to produce beneficial outcomes in glycemic control, lipids, and blood pressure, and sustained weight loss greater than 7% is optimal (70).

Smokers with diabetes and persons with diabetes who are exposed to secondhand smoke have heightened risk for ASCVD as well as premature death and microvascular complications. Routine and thorough assessment of tobacco use is essential to prevent smoking or encourage cessation.

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