



EDITION

12

BRAUNWALD'S
**HEART
DISEASE**

A TEXTBOOK OF CARDIOVASCULAR MEDICINE

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Diabetes and the Cardiovascular System

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SCOPE OF THE PROBLEM

Diabetes Mellitus

Diabetes mellitus (DM) involves insufficient production of insulin and/or failure to respond appropriately to insulin, resulting in hyperglycemia. Table 31.1 summarizes the current diagnostic criteria.¹ Type 2 DM is characterized by insulin resistance and relative insulin deficiency (>90% of all DM cases), whereas type 1 is defined by absolute insulin deficiency. This chapter focuses on type 2 DM, except when specifically indicated otherwise.

Diabetes, one of the most common chronic diseases in the world, affects an estimated 463 million adults in 2019 (Fig. 31.1).² The mounting incidence and prevalence of type 2 DM, driven by increasing population age, obesity, and physical inactivity, compound with its high global burden (see Chapters 2, 25, and 30), as does the increasing longevity of patients with the disease. DM will affect more than an estimated 700 million persons, 10.9% of the global adult population, by 2045.²

Cardiovascular disease (CVD) remains the principal comorbid condition and primary contributor to mortality in patients with DM, usually in the form of coronary heart disease (CHD), but also in the incremental risk associated with DM for cerebrovascular disease, peripheral vascular disease, heart failure (HF), and atrial fibrillation (AF). For these reasons, continuing effort toward mitigating the risk of CVD in DM remains a global public health imperative.

TABLE 31.1 American Diabetes Association Diagnostic Criteria for Diabetes Mellitus*

1. Fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hr.
Or
2. Two-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
Or
3. Glycated hemoglobin (A_{1c}) $\geq 6.5\%$ (48 mmol/mol). The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.
Or
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

*Criteria 1 to 3 require confirmatory testing; criterion 4 does not.
Modified from American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes. *Diabetes Care*. 2020;43(suppl 1):S14–S31.

Atherosclerotic Vascular Disease

Patients with DM have a two- to fourfold increased risk for CHD, CV mortality, all-cause mortality, and CV hospitalization compared with those without DM (Fig. 31.2).^{3,4} However, the CV risk and mortality in patients with DM remain substantially increased over those without DM, underscoring the unmet clinical need.^{3,5}

Diabetes entails an increased risk for myocardial infarction (MI). Across the spectrum of acute coronary syndrome (ACS) events, in which DM may affect more than one in three patients, those with DM have worse CVD outcomes (see Chapters 36–39).⁶ Despite overall improvements in outcomes during the past several decades for ACS patients with and without DM, the gradient of risk associated with DM persists (Fig. 31.3), although incremental in-hospital mortality risk associated with DM after ACS has declined (Fig. 31.4).⁶ Furthermore, the graded association of increased risk in the setting of ACS extends to glucose values well below the DM threshold (Fig. 31.5).

In addition to CHD, DM increases the risks of stroke (twofold increase, see Chapter 45),⁵ cerebrovascular disease, and peripheral arterial disease. Hyperglycemia affects approximately one in three patients with acute stroke and is associated to a two- to sixfold increased risk for adverse clinical outcomes.

Heart Failure

In the ambulatory setting, DM associates independently with a twofold to fivefold increased risk for HF over that in persons without DM, and patients with DM have worse outcomes once HF has developed.⁷ HF in DM is a key driver of CV morbidity and mortality, leading to the inclusion of HF as a major endpoint in contemporary clinical trials.⁷

Atrial Fibrillation

It remains uncertain as to what degree DM independently augments AF risk, largely because of the difficulty in adjusting for risk factors common to both diseases. In patients with AF, DM increases stroke rate by 2% to 3.5% (see Chapter 66).⁸ The CHA₂DS₂-VASc score includes DM and guidelines recommend anticoagulation for all DM patients who have AF.⁹

Risk Stratification

The high CV risk of patients with DM blurs the concept of primary versus secondary prevention. Recent guidelines classify patients with DM according to CV risk.¹⁰ Very high risk patients are those with DM and established CVD, as well as those with target organ damage such as left ventricular hypertrophy or chronic kidney disease (CKD). Patients with



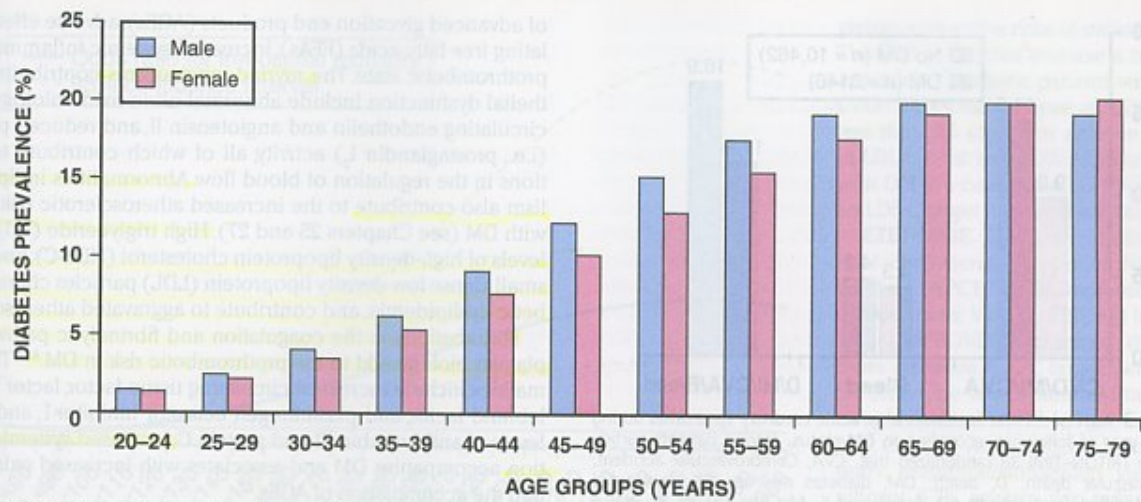


FIGURE 31.1 Diabetes mellitus prevalence by age and sex in 2019. (From Saeedi P, Petersohn I, Salpea P, et al. Global and regional DM prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International DM Federation DM Atlas, 9th edition. *DM Res Clin Pract.* 2019;157:107843.)

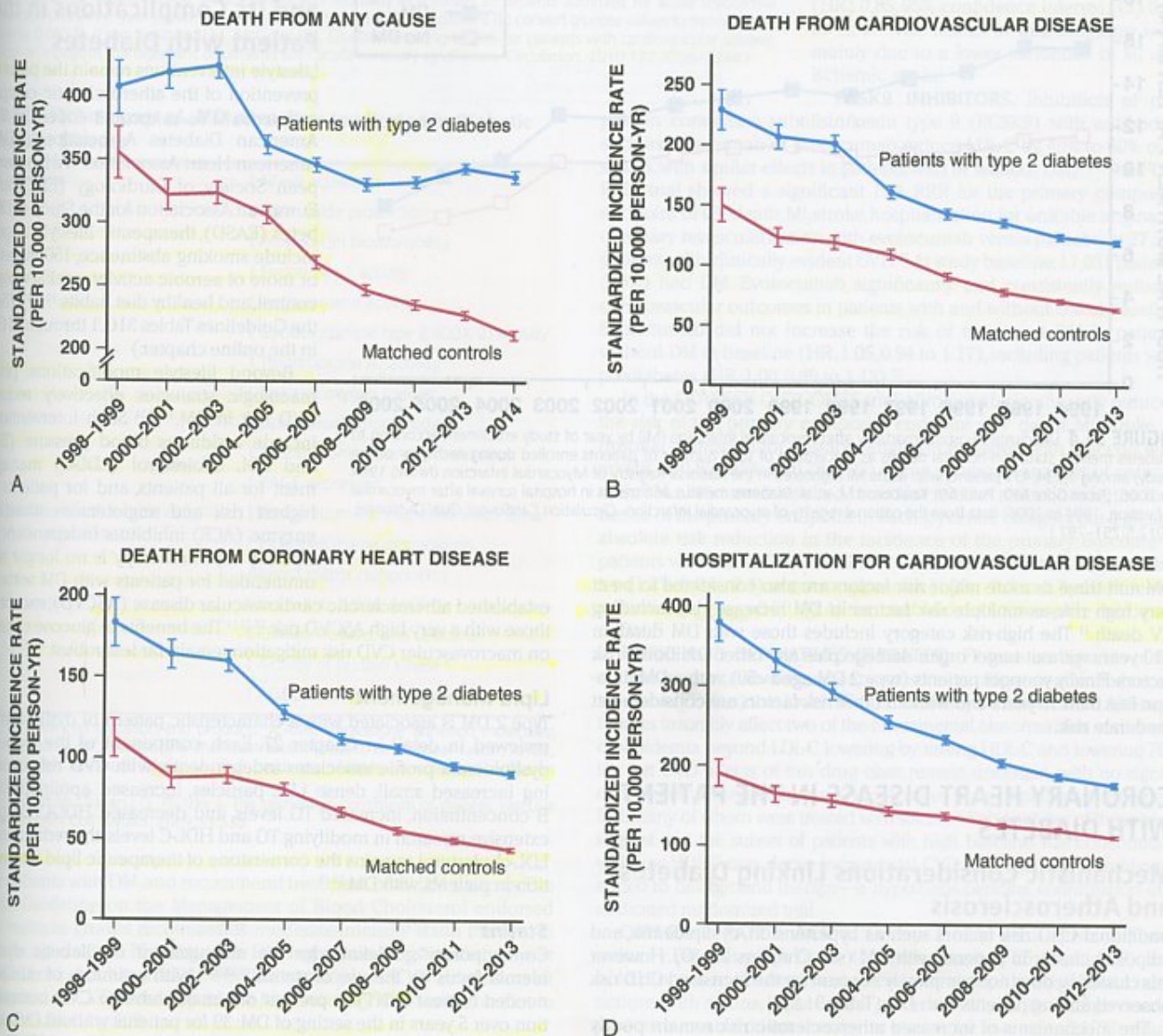


FIGURE 31.2 Major cardiovascular outcomes in patients with type 1 DM and matched controls. Controls were matched for age, sex, and country. I bars represent 95% confidence intervals. (From Rawshani A, Rawshani A, Franzen S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med.* 2017;376:1407-1418.)

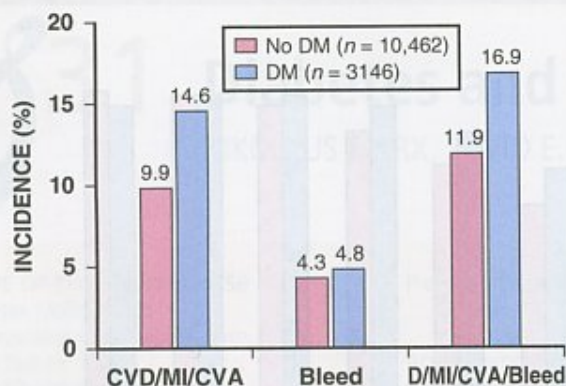


FIGURE 31.3 Adverse clinical outcomes after acute coronary syndromes during more than 1 year of follow-up, according to DM status, among patients participating in the TRITON-TIMI 38 randomized trial. CVA, Cerebrovascular accident; CVD, cardiovascular death; D, death; DM, diabetes mellitus; MI, myocardial infarction. (Modified from Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015.)

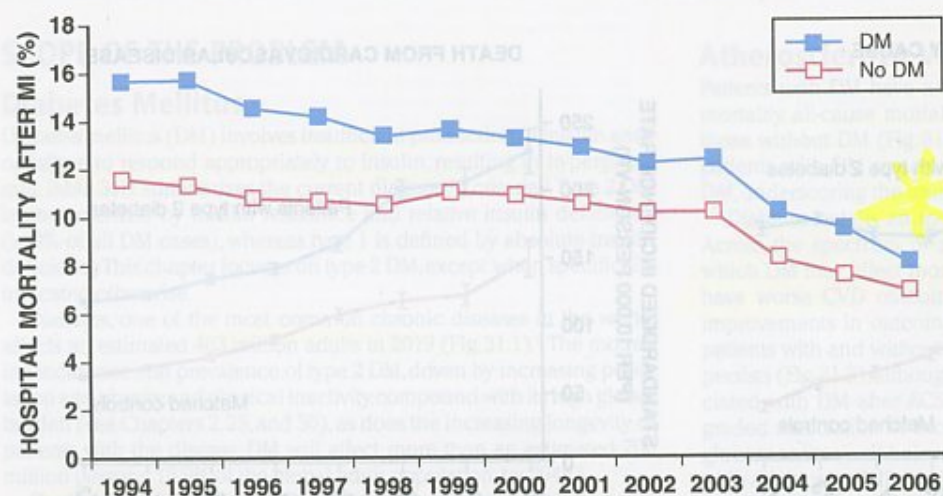


FIGURE 31.4 Unadjusted hospital mortality after myocardial infarction (MI) by year of study enrollment according to diabetes mellitus status (in-hospital deaths as percentage of total number of patients enrolled during each year of the study) among 1,734,431 patients with acute MI registered in the National Registry of Myocardial Infarction (NRM) 1994 to 2006. (From Gore MO, Patel MJ, Kosiborod M, et al. Diabetes mellitus and trends in hospital survival after myocardial infarction, 1994 to 2006: data from the national registry of myocardial infarction. *Circulation Cardiovasc Qual Outcomes*. 2012;5:791–797.)

DM and three or more major risk factors are also considered to be at very high risk, as multiple risk factors in DM increase risk including CV death.¹¹ The high-risk category includes those with DM duration ≥ 10 years without target organ damage plus any other additional risk factors. Finally, younger patients (type 2 DM aged <50) with a DM duration less than 10 years and without other risk factors are considered at moderate risk.

CORONARY HEART DISEASE IN THE PATIENT WITH DIABETES

Mechanistic Considerations Linking Diabetes and Atherosclerosis

Traditional CHD risk factors such as hypertension, dyslipidemia, and adiposity cluster in patients with DM (see Chapters 25–30). However, this clustering does not completely account for the increased CHD risk observed among patients with DM (Table 31.2).¹¹

The mechanisms of increased atherosclerotic risk remain poorly understood. The principal vascular perturbations linked to hyperglycemia include endothelial vasomotor dysfunction, vascular effects

of advanced glycation end products (AGEs), adverse effects of circulating free fatty acids (FFAs), increased systemic inflammation, and a prothrombotic state. The myriad mechanisms contributing to endothelial dysfunction include abnormal nitric oxide biology, increased circulating endothelin and angiotensin II, and reduced prostacyclin (i.e., prostaglandin I_2) activity, all of which contribute to perturbations in the regulation of blood flow. Abnormalities in lipid metabolism also contribute to the increased atherosclerotic risk associated with DM (see Chapters 25 and 27). High triglyceride (TG) levels, low levels of high-density lipoprotein cholesterol (HDL-C), and increased small, dense low-density lipoprotein (LDL) particles characterize diabetic dyslipidemia, and contribute to aggravated atherosclerosis.

Perturbations in the coagulation and fibrinolytic pathways and in platelet biology add to the prothrombotic risk in DM.^{8,12} These abnormalities include increased circulating tissue factor, factor VII, von Willebrand factor, and plasminogen activator inhibitor-1, and decreased levels of antithrombin III and protein C. Increased systemic inflammation accompanies DM and associates with increased oxidative stress and the accumulation of AGEs.¹²

Prevention and Treatment of Coronary Heart Disease and Its Complications in the Patient with Diabetes

Lifestyle interventions remain the pillar of prevention of the atherosclerotic complications in DM. As recommended by the American Diabetes Association (ADA), American Heart Association (AHA), European Society of Cardiology (ESC), and European Association for the Study of Diabetes (EASD), therapeutic lifestyle targets include smoking abstinence, 150 minutes or more of aerobic activity weekly, weight control, and healthy diet habits.^{10,13,14} (See the Guidelines Tables 31G.1 through 31G.4 in the online chapter.)

Beyond lifestyle modifications, pharmacologic strategies effectively reduce CVD risk in DM.^{10,13,14} Such interventions include assiduous blood pressure (BP) and LDL cholesterol (LDL-C) management for all patients, and for patients at highest risk and angiotensin-converting enzyme (ACE) inhibitors independent of BP. Daily aspirin therapy is no longer recommended for patients with DM without

established atherosclerotic cardiovascular disease (ASCVD), except in those with a very high ASCVD risk.^{10,13,14} The benefits of glucose control on macrovascular CVD risk mitigation remain far less robust.^{13,15}

Lipid Management

Type 2 DM is associated with a characteristic pattern of dyslipidemia, reviewed in detail in Chapter 27. Each component of the diabetic dyslipidemia profile associates independently with CVD risk, including increased small, dense LDL particles, increased apolipoprotein B concentration, increased TG levels, and decreased HDL-C. Despite extensive research in modifying TG and HDL-C levels, the reduction of LDL-cholesterol remains the cornerstone of therapeutic lipid intervention in patients with DM.^{10,13}

Statins

Contemporary guidelines for the management of diabetic dyslipidemia focus on the use of statins,^{10,13,16,17} with estimates of numbers needed to treat (NNT) to prevent one major adverse CVD complication over 5 years in the setting of DM: 39 for patients without CVD and 19 among patients with prevalent CVD (see Chapters 25 and 27). These guidelines do not require an increased LDL-C to initiate statin therapy

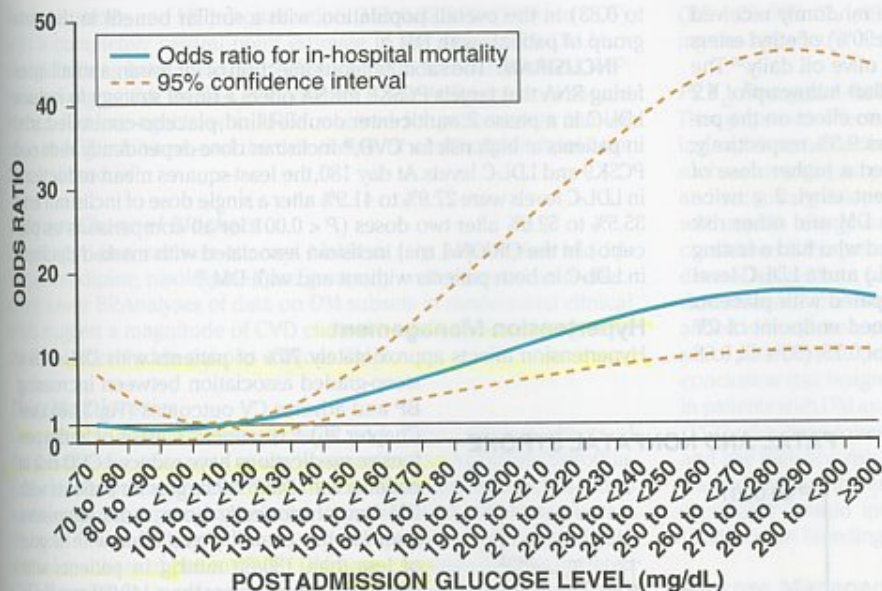


FIGURE 31.5 Postadmission glucose levels and mortality in a cohort of patients admitted for acute myocardial infarction (MI) with hyperglycemia on arrival, after multivariable adjustment (to convert glucose values to mmol/L, multiply by 0.0555). (From Kosiborod M, McGuire DK. Glucose-lowering targets for patients with cardiovascular disease: focus on inpatient management of patients with acute coronary syndromes. *Circulation*. 2010;122:2736–2744.)

TABLE 31.2 Examples of Mechanisms Implicated in Diabetic Vascular Disease

Endothelium	↑ NF-κB activation ↓ Nitric oxide production ↓ Prostacyclin bioavailability ↑ Endothelin 1 activity ↑ Angiotensin II activity ↑ Cyclooxygenase type 2 (COX-2) activity ↑ Thromboxane A₂ activity ↑ Reactive oxygen species ↑ Lipid peroxidation products ↓ Endothelium-dependent relaxation ↑ RAGE expression
Vascular smooth muscle cells and vascular matrix	↑ Proliferation and migration into intima ↑ Increased matrix degradation - Altered matrix components
Inflammation	↑ IL-1β, IL-6, CD36, MCP-1 ↑ ICAMs, VCAMs, and selectins ↑ Activity of protein kinase C ↑ AGEs and AGE-RAGE interactions

AGEs, Advanced glycation end products; ICAMs, intracellular adhesion molecules; IL, interleukin; MCP, monocyte chemoattractant protein; NF, nuclear factor; RAGE, receptor for advanced glycation end products; VCAMs, vascular cell adhesion molecules.

Modified from Orasanu G, Plutzky J. The pathologic continuum of diabetic vascular disease. *J Am Coll Cardiol*. 2009;53:S35.

for patients with DM, and recommend treatment of all DM patients. The 2018 Guideline on the Management of Blood Cholesterol endorsed by multiple groups recommends moderate-intensity statin therapy in adults aged 40 to 75 years with DM regardless of estimated 10-year ASCVD risk. Adults with DM who have multiple ASCVD risk factors or prevalent ASCVD should receive a high-intensity statin with the aim to reduce LDL-C by 50%.

Statin therapy can hasten the onset of DM in patients at risk of developing DM.¹⁸ Nevertheless, the benefits in terms of CV event reduction

greatly exceed the risks of statin-induced DM. The ESC guidelines endorse a treat-to-target approach.¹⁰ Diabetic patients with very high CVD risk should achieve an LDL-C target of less than 55 mg/dL or achieve a decrease in LDL-C of at least 50%. Most other patients with DM are categorized as “high risk,” with an LDL-C target of at least less than 70 mg/dL.

EZETIMIBE. Ezetimibe inhibits the intestinal cholesterol transporter Niemann-Pick C1-like 1 (NPC1L1). The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) assessed the effect of more intensive LDL-C targets with simvastatin/ezetimibe versus standard target control using simvastatin in 18,144 patients following ACS events.¹⁹ After a mean follow-up of 5.7 years, ezetimibe/simvastatin yielded a significant 6.7% relative risk reduction (RRR) for the primary composite endpoint. In the subgroup of patients with DM, the beneficial effect on outcome was stronger than in patients without DM with a hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.78 to 0.94.²⁰ The results in this subgroup were mainly due to a lower incidence of MI and ischemic stroke.

PCSK9 INHIBITORS. Inhibition of pro-protein convertase subtilisin/kexin type 9 (PCSK9) with antibodies such as alirocumab or evolocumab reduce LDL-C by 40% to 60% over statins, with similar effects in patients with or without DM.^{21,22} The FOURIER trial showed a significant 15% RRR for the primary composite endpoint of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization with evolocumab versus placebo in 27,564 patients with clinically evident CVD.²³ At study baseline, 11,031 patients (40%) had DM. Evolocumab significantly and consistently reduced cardiovascular outcomes in patients with and without DM at baseline. Evolocumab did not increase the risk of new-onset DM in patients without DM at baseline (HR, 1.05, 0.94 to 1.17), including patients with prediabetes (HR, 1.00, 0.89 to 1.13).²³

In the ODYSSEY OUTCOMES trial, alirocumab significantly reduced the risk of the primary composite endpoint (CV death, MI, stroke, or hospital admission for unstable angina) compared with placebo, with an HR of 0.85 (95% CI 0.78, 0.93).²⁴ In a subgroup analysis of patients with DM, alirocumab resulted in similar relative reductions in the incidence of the primary endpoint in each glycemic category, but a greater absolute risk reduction in the incidence of the primary outcome in patients with DM (2.3%, 95% CI 0.4 to 4.2) than in those with prediabetes (1.2%, 0.0 to 2.4) or normoglycemia (1.2%, −0.3 to 2.7; absolute risk reduction $p_{interaction}=0.0019$). Alirocumab did not increase the incidence of DM.²⁵

FIBRIC ACID DERIVATIVES (FIBRATES). Fibrates are agonists of the nuclear transcriptional regulator peroxisome proliferator-activated receptor alpha (PPAR-α) that lower TGs and modestly increase HDL-C. Although fibrates favorably affect two of the fundamental abnormalities of diabetic dyslipidemia beyond LDL-C lowering by raising HDL-C and lowering TGs, the net CVD effects of this drug class remain uncertain, with no significant benefit observed in two CV outcomes trials of patients with type 2 DM, many of whom were treated with statins.¹⁶ Sub-analyses of these trials suggest that the subset of patients with high baseline TGs concomitant with low HDL-C may derive incremental CVD risk reduction with fibrates added to background therapy—a hypothesis pending confirmation in a dedicated randomized trial.

OMEGA-3 FATTY ACIDS. Omega-3 fatty acids (fish oil) can reduce circulating TGs up to 40% (see Chapters 25, 27, and 29), and hold promise in the treatment of diabetic dyslipidemia. With no interactions with statins, prescription-grade n-3 fatty acids in high dose is attractive as an add-on therapy to statins for incremental TG reduction. The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial randomized 12,536 patients with impaired fasting

glucose, impaired glucose tolerance, or DM who randomly received either a 1-g capsule containing at least 900 mg ($\geq 90\%$) of ethyl esters of n-3 fatty acids or a capsule containing 1 g of olive oil daily.²⁶ The primary outcome was CV mortality. Over a median follow-up of 6.2 years with 1155 CV deaths to analyze, there was no effect on the primary outcome with fish oil versus control (9.1% vs. 9.3%, respectively; $P = 0.72$). However, the REDUCE-IT trial examined a higher dose of highly purified eicosapentaenoic acid (icosapent ethyl, 2 g twice daily) in patients with established CVD or with DM and other risk factors, who had been receiving statin therapy and who had a fasting TG level of 135 to 499 mg/dL (1.52 to 5.63 mmol/L) and a LDL-C level of 41 to 100 mg/dL (1.06 to 2.59 mmol/L). Compared with placebo, icosapent ethyl significantly reduced the combined endpoint of CV death, non-fatal MI, or non-fatal stroke with a HR of 0.75; (95% CI, 0.68

to 0.83) in the overall population, with a similar benefit in the subgroup of patients with DM.²⁷

INCLISIRAN. The subcutaneous injection of inclisiran, a small interfering RNA that targets PCSK9 mRNA offers a novel strategy to reduce LDL-C. In a phase 2, multicenter, double-blind, placebo-controlled, trial in patients at high risk for CVD,²⁸ inclisiran dose-dependently reduced PCSK9 and LDL-C levels. At day 180, the least-squares mean reductions in LDL-C levels were 27.9% to 41.9% after a single dose of inclisiran and 35.5% to 52.6% after two doses ($P < 0.001$ for all comparisons vs. placebo). In the ORION-1 trial inclisiran associated with marked declines in LDL-C in both patients without and with DM.²⁹

Hypertension Management

Hypertension affects approximately 70% of patients with DM, with a steep graded association between increasing BP and adverse CV outcomes (Fig. 31.6) (see Chapter 26).³⁰ Numerous classes of antihypertensive medications have reduced CVD risk in patients with DM.³⁰ BP targets for patients with DM have historically been more aggressive than for the overall population, with a goal of less than 130/80 mmHg in patients with DM, and a target of less than 140/80 mmHg in those not tolerating the lower goal.^{10,13,30,31}

Renin-Angiotensin-Aldosterone System Antagonists

ACE inhibitors and angiotensin II receptor blockers (ARBs) are cornerstones of therapy for hypertension in DM because of their favorable effects on diabetic nephropathy and CVD outcomes.^{13,14,30,31}

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS. Data from randomized trials of patients with and without hypertension underpin the recommendation for ACE inhibitors as first-line agents for treatment of hypertension in the patient with DM. For example, the Heart Outcomes Prevention Evaluation (HOPE) trial compared ramipril (10 mg daily) with placebo in patients at increased risk for CVD and found that ramipril was superior to placebo in the DM subset of 3577 patients for the primary outcome of CV death, MI, and stroke (RRR, 25%; $P = 0.004$) and for overt nephropathy (RRR, 24%; $P = 0.027$).³⁰ The DM sub-analysis of the EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease) trial,³⁰ which tested perindopril versus placebo; showed an RRR of 19% among the 1502 participants with DM. These results and those from meta-analyses³⁰ support the consideration of ACE inhibitors for all patients with DM who have prevalent CVD, a clustering of CVD risk factors, or nephropathy with or without albuminuria.^{10,13,31}

ANGIOTENSIN II RECEPTOR BLOCKERS. Data on CV outcomes with ARBs are much less robust than those on ACE inhibitors, particularly in patients with DM. The Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial enrolled 5926 patients with intolerance to ACE inhibitors, randomly assigned to receive telmisartan (80 mg daily) or placebo, 2118 of which had DM.³⁰ The overall trial failed to achieve statistical superiority for telmisartan versus placebo on the primary composite of CVD

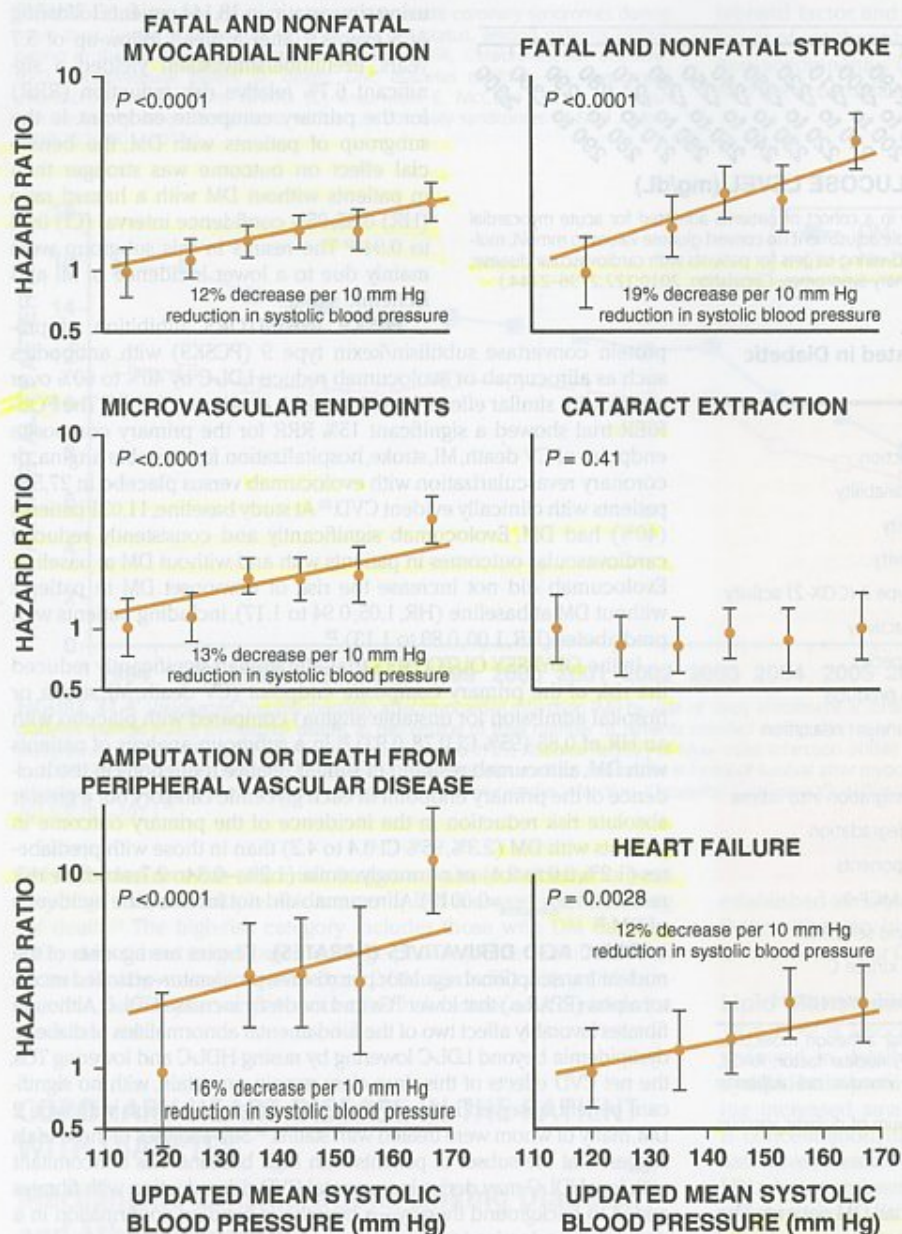


FIGURE 31.6 Hazard ratios (95% confidence intervals as floating absolute risks) as estimate of association between category of updated mean systolic blood pressure and myocardial infarction (MI), stroke, and heart failure (HF), with log linear scales. Reference category (hazard ratio of 1.0) is systolic pressure less than 120 mm Hg for MI and less than 130 mm Hg for stroke and HF; P values reflect contribution of systolic pressure to multivariable model. Data adjusted for age at diagnosis of diabetes mellitus (DM), ethnic group, smoking status, presence of albuminuria, hemoglobin A_{1c} (HbA_{1c}), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglyceride. (Modified from Adler AI, Stratton AM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ*. 2000;321:412.)

death, MI, stroke, and HF hospitalization (HR, 0.92; 95% CI 0.81 to 1.05), with a completely neutral point estimate in the subset with DM. Various guidelines have endorsed ARBs and ACE inhibitors in DM,^{10,13,31} acknowledging the **weaker evidence for ARBs. ACE inhibitors should remain first-line agents, with ARBs reserved for patients with intolerance to ACE inhibitors,** and the two classes of medications should not be combined.^{10,31}

Calcium Channel Blockers

Dihydropyridine calcium channel blockers (e.g., amlodipine, felodipine, nitrendipine, nisoldipine) are generally well tolerated and effectively lower BP. Analyses of data on DM subsets in randomized clinical trials suggest a magnitude of CVD clinical benefit similar to or greater than that observed in cohorts without DM.³⁰

Thiazide Diuretics

Concern about the adverse glycemic and triglyceridemic effects of the thiazide diuretic types of medications, including hydrochlorothiazide, chlorthalidone, indapamide, and bendroflumethiazide, has led to some hesitancy regarding their use in patients with DM. However, randomized trials of chlorthalidone and indapamide that included substantial numbers of patients with DM have consistently demonstrated CVD benefits. In a sub-analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the CVD effects of chlorthalidone compared with both lisinopril and amlodipine were similar in patients with DM or impaired fasting glucose, despite modest but statistically significant increases in incident DM associated with chlorthalidone use.³² Also, indapamide combined with perindopril in the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial of 11,140 patients with DM showed superior CV outcomes.³³ **A meta-analysis of randomized trials further supports the benefits of chlorthalidone and indapamide in the treatment of patients with DM.**^{30,32}

Beta Blockers

Beta blockers are rarely used as routine antihypertensive therapies in patients with DM.^{10,31} Beta blockers offer no benefit over other evidence-based classes of medications, with some concern for increased risk for a composite of CV disease, stroke, and HF based on recent meta-analysis.³⁰ Therefore, use of beta blockers should be primarily limited to patients with HF with reduced ejection fraction (HFrEF) (carvedilol, metoprolol succinate, or bisoprolol) and after MI. Beta blockers have a place in therapy of angina and for rate control of AF.

Antihypertensive Therapy Summary

Four classes of antihypertensive medications reduce CVD risk in patients with DM: ACE inhibitors, ARBs, calcium channel blockers, and thiazide diuretics (specifically, chlorthalidone, indapamide). Other options in resistant hypertension, after eliminating secondary causes, include mineralocorticoid antagonists, alpha blockers, and centrally acting agents. Evidence supports a BP target of at least less than 140/80 mmHg for all patients with DM, with a more intensive systolic BP target of less than 130 mmHg for those patients who can achieve that target without excessive adverse effects.

Antiplatelet Therapy

Daily Aspirin

The ADA and AHA recommend daily aspirin (75 to 162 mg/day) for all patients with DM who have established ASCVD, with use for primary prevention no longer recommended, though it may be considered in those at very highest ASCVD risk.^{10,13,34,35} Substantial evidence based on the setting of secondary ASCVD risk modification supports these recommendations, but **a meta-analysis of primary prevention with aspirin in patients with DM failed to show significant benefit.**³⁶ Two subsequent randomized clinical trials, ASCEND and ACCEPTD trials underscore this finding. The ASCEND trial enrolled 15,480 patients with DM without established ASCVD, randomized to aspirin 100 mg daily versus placebo. There was a modest risk reduction for the primary composite of vascular death, MI, or stroke (RR 0.88; 95% CI, 0.79 to 0.97) in the context of increased risk for major bleeding

(RR 1.29; 95% CI, 1.09 to 1.52), with bleeding hazard counterbalancing the benefits.³⁷

P2Y₁₂ Receptor Antagonists

Though proven effective for patients following ACSs and coronary stenting, aspirin remains the preferred therapy over P2Y₁₂ receptor antagonists such as clopidogrel, prasugrel, or ticagrelor for chronic stable primary and secondary risk prevention. For patients with aspirin indication but with aspirin allergy or intolerance, a P2Y₁₂ receptor antagonist may be considered.¹⁰ For patients with type 2 DM and prevalent coronary artery disease but without prior MI, results from the THEMIS randomized trial demonstrated the net clinical benefit of ticagrelor 60 mg twice daily added to low-dose aspirin versus low-dose aspirin alone in the large subset of patients with prior coronary stenting ($n = 11,154$), leading to the conclusion that ticagrelor should be considered as an add-on to aspirin in patients with DM and a history of percutaneous coronary intervention (PCI) who have tolerated antiplatelet therapy, have high ischemic risk, and low bleeding risk.³⁸ However, the reduction in the primary outcome was achieved at the expense of increased major bleeding, with a highly significant 2.3-fold increase in thrombolysis in myocardial infarction (TIMI) major bleeding, including intracranial bleeding.

Glucose Management

A total of 12 drug classes of glucose-lowering medications are presently available for type 2 DM (Table 31.3), with various mechanisms of action. Typically, two or three drugs simultaneously are used to reduce hyperglycemia.

Cardiovascular Effects of Selected Medications for Diabetes

Until 2008, the approval of drugs for DM depended almost exclusively on the demonstration of glucose lowering, without required proof of improved clinical outcomes. The regulatory landscape for DM drugs underwent major changes in 2008, such that all glucose-lowering agents for type 2 DM needed to demonstrate designated margins of CV safety to achieve and maintain regulatory approval.^{39,40} This led to a rapid proliferation of CV outcome trials of glucose-lowering drugs which have provided rich datasets documenting either CV safety or actual efficacy in improving cardiac and/or renal outcomes (Table 31.4 and Fig 31.7). Heretofore, the available data on the net CV impact of such medications had been quite limited, with older treatment guidelines essentially grounded on the proven microvascular disease benefits demonstrated through glucose control alone.^{41,42} These new data spurred guidelines to endorse specific drug categories depending on patient characteristics, specifically the presence of CV or kidney disease. In 2020, the U.S. Food and Drug Administration (FDA) reversed course and will, going forward, no longer require extensive CV safety testing for new glucose-lowering medications in the absence of specific safety signals. Instead, when a new medication is proposed for glycemic control, its safety database from Phase 3 trials should include sufficient numbers of patients with established CVD, CKD, and age over 65 years, targeting at least 1200 patients with at least one of these conditions/states. Development program sponsors are also advised to use rigorous methods for the collection of adverse CV events and assess them by adjudication.

METFORMIN. Metformin, a biguanide, reduces blood glucose primarily by decreasing hepatic glucose output and perhaps by other mechanisms. Metformin, associated with modest initial weight reduction, has favorable effects on lipid levels, decrease in inflammatory markers, improvement in coagulation profiles, and low risk for hypoglycemia. In the United Kingdom Prospective Diabetes Study (UKPDS) of various glucose-lowering strategies in a population of patients with newly diagnosed type 2 DM, patients who were overweight at study entry were eligible for randomization to a policy of more intensive glucose control with metformin versus usual care. Those treated with metformin had statistically superior outcomes for all DM-related endpoints (RRR, 32%; 95% CI 13% to 47%), DM-related death (RRR, 42%; 95% CI 9% to 63%), and all-cause mortality (RRR, 36%; 95% CI 9% to 55%).³³ A second trial, the HOME study, randomized 390 patients with insulin-treated type 2 DM to metformin versus placebo.³³ The effect on the primary composite outcome, including micro- and macrovascular

TABLE 31.3 Characteristics of Glucose-Lowering Medications for Type 2 Diabetes Mellitus

CLASS	COMPOUND(S)	CELLULAR MECHANISM	MAIN PHYSIOLOGIC ACTION(S)	ADVANTAGES	DISADVANTAGES	COST
Biguanides	Metformin	Activates AMP-kinase ? Other	↓ Hepatic glucose production ? Other	Extensive experience No weight gain No hypoglycemia Likely ↓ CVD events (UKPDS)	GI side effects (diarrhea, abdominal cramping) Lactic acidosis risk (rare) Vitamin B ₁₂ deficiency Multiple contraindications: advanced CKD, acidosis, hypoxia, dehydration, ethanol abuse, other	Low
	Second generation: Glyburide (glibenclamide) Glipizide Glizide* Glimepiride	Closes K _{ATP} channels on beta cell plasma membranes	↑ Insulin secretion	Extensive experience ↓ Microvascular risk (UKPDS)	Hypoglycemia Weight gain ? Blunts myocardial ischemic preconditioning Low durability	Low
Meglitinides (glinides)	Repaglinide Nateglinide	Closes K _{ATP} channels on beta cell plasma membranes	↑ Insulin secretion	↓ Postprandial glucose excursions Dosing flexibility	Hypoglycemia Weight gain ? Blunts myocardial ischemic preconditioning Frequent dosing schedule	High
	Thiazolidinediones Pioglitazone Rosiglitazone*	Activates the nuclear transcription factor PPAR-γ	↑ Insulin sensitivity	No hypoglycemia Durability ↑ HDL-C ↑ Triglycerides (pioglitazone) ↓ Albuminuria ? ↓ CVD events (pioglitazone)	Weight gain Edema/heart failure Bone fractures ↑ LDL-C (rosiglitazone) ? ↑ MI (meta-analyses, rosiglitazone)	Moderate
α-Glucosidase inhibitors*	Acarbose Miglitol Voglibose**	Inhibits intestinal α-Glucosidase	Slows intestinal carbohydrate digestion/absorption	No hypoglycemia ↓ Postprandial glucose excursions Nonsystemic	Generally modest HbA _{1c} efficacy GI side effects (flatulence, diarrhea) Frequent dosing schedule	Moderate
	DPP4 inhibitors Vildagliptin* Sitagliptin Saxagliptin Alogliptin Linagliptin	Inhibits DPP4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations	↑ Insulin secretion (glucose dependent) ↓ Glucagon secretion (glucose-dependent)	No hypoglycemia Well tolerated	Generally modest HbA _{1c} efficacy Urticaria/angioedema ? Pancreatitis Possible ↑ heart failure (saxagliptin; alogliptin)	High
Bile acid sequestrants*	Coarsevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production ? Activation of farnesoid receptor (FXR) in liver	Unknown ? ↑ Hepatic glucose production ? ↑ Incretin levels	No hypoglycemia ↓ LDL-C	Generally modest HbA _{1c} efficacy Constipation ↑ Triglycerides May alter absorption of other medications	High
	Dopamine-2 agonists*	Activates dopaminergic receptors	Modulates hypothalamic regulation of metabolism ↑ Insulin sensitivity	No hypoglycemia ? ↓ CVD events (Cycloset Safety Trial)	Generally modest HbA _{1c} efficacy Dizziness/syncope Nausea Fatigue Rhinitis	High

Continued

TABLE 31.3 Characteristics of Glucose-Lowering Medications for Type 2 Diabetes Mellitus—cont'd

CLASS	COMPOUND(S)	CELLULAR MECHANISM	MAIN PHYSIOLOGIC ACTION(S)	ADVANTAGES	DISADVANTAGES	COST
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TABLE 31.3 Characteristics of Glucose-Lowering Medications for Type 2 Diabetes Mellitus—cont'd

CLASS	COMPOUND(S)	CELLULAR MECHANISM	MAIN PHYSIOLOGIC ACTION(S)	ADVANTAGES	DISADVANTAGES	COST
SGLT2 inhibitors	Dapagliflozin	Inhibits SGLT2 in the proximal renal tubule	Decreases glucose reabsorption, leading to glucosuria	Effective at all disease stages	Diabetic ketoacidosis	High
	Canagliflozin			No hypoglycemia	Genitourinary infections	
	Empagliflozin			Weight loss	Polyuria	
	Ertugliflozin			↓ Blood pressure ↓ Albuminuria	Volume depletion ↑ LDL-C	
GLP-1 receptor agonists	Exenatide	Activates GLP-1 receptors	↑ Insulin secretion (glucose-dependent)	↑ MACE (empa, cana) ↑ HF hospitalization (all) ↑ CV death (empa, cana) ↑ CKD progression (all but ertu)	Reversible ↑ eGFR ? Amputation risk (cana) ? Fracture risk (cana)	High
	Exenatide (weekly)			No hypoglycemia	GI side effects (nausea/vomiting)	
	Liraglutide		↓ Glucagon secretion (glucose-dependent)	Weight reduction	↑ Pulse rate	
	Albiglutide		Slows gastric emptying	↓ CV risk factors	↑ Gallbladder events	
	Dulaglutide		↑ Satiety	↑ MACE (lira, sema, dula)	? Pancreatitis	
	Semaglutide			↓ CV death (lira)	? Mitogenicity/cancer risk	
	Semaglutide (oral)			↓ macroalbuminuria	Injectable	
Amylin mimetics ¹	Lixisenatide				Training requirements (injectables)	High
	Pramlintide ²	Activates amylin receptors	↓ Glucagon secretion Slows gastric emptying ↑ Satiety	↓ Postprandial glucose excursions Weight reduction	Generally modest HbA _{1c} efficacy GI side effects (nausea/vomiting) Hypoglycemia unless insulin dose is simultaneously reduced	
Insulins	Human NPH	Activates insulin receptors	↑ Glucose disposal	Universally effective	Injectable Training requirements Frequent dosing schedule	Variable ³
	Human regular		↓ Hepatic glucose production	Theoretically unlimited efficacy	Hypoglycemia	
	Lispro			↓ Microvascular risk (UKPDS)	Weight gain	
	Aspart				? Mitogenicity/cancer risk	
	Glulisine				Injectable	
	Glargine				Training requirements	
	Detemir				"Stigma" (for patients)	
	Degludec					
	Premixed (several types)					

*Not licensed in the United States.

¹Prescribing highly restricted in the United States; withdrawn in Europe.²Limited use in the United States/Europe.³Not licensed in Europe.

AMP, Adenosine monophosphate; CKD, chronic kidney disease; CVD, cardiovascular disease; DPP4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like protein 1; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MI, myocardial infarction; SGLT2, sodium-glucose cotransporter 2.

PROactive, Prospective Pioglitazone Clinical Trial in Microvascular Events; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; UKPDS, United Kingdom Prospective Diabetes Study. Modified and updated from Inzucchi SE, Bergenstal RM, Buse JB, 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;38:141.

TABLE 31.4 Summary of Completed Cardiovascular Outcomes Trials of Medications for Type 2 Diabetes

TRIAL	DRUG*	PATIENTS (n)	STAGE	NCT
Completed Trials				
SAVOR-TIMI 53 ⁶⁰	Saxagliptin	16,492	Completed	NCT01107886
EXAMINE ⁶¹	Alogliptin	5,380	Completed	NCT00968708
TECOS ⁶³	Sitagliptin	14,671	Completed	NCT00790205
ELIXA ⁶⁶	Lixisenatide	6,068	Completed	NCT01147250
EMPA-REG-OUTCOME ⁷⁵	Empagliflozin	12,500	Completed	NCT01131676
LEADER ⁶⁷	Liraglutide	9,340	Completed	NCT01179048
SUSTAIN 6 ⁷⁰	Semaglutide	3,299	Completed	NCT01720446
CANVAS ⁸¹	Canagliflozin	4,330	Completed	NCT01032629
EXSCEL ⁶⁸	Exenatide LAR	14,752	Completed	NCT01144338
CV Outcomes-ITCA 650	Exenatide ITCA 650	4,156	Completed	NCT01455896
DEVOTE ⁵⁹	Insulin degludec	7,637	Completed	NCT01959529
CANVAS-R ⁸¹	Canagliflozin	5,812	Completed	NCT01989754
CAROLINA ⁴⁶	Linagliptin versus glimepiride	6,000	Completed	NCT01243424
REWIND ⁷²	Dulaglutide	9,600	Completed	NCT01394952
VERTIS ⁸⁵	Ertugliflozin	8,246	Completed	NCT01986881
DECLARE-TIMI 58 ⁸²	Dapagliflozin	17,160	Completed	NCT01730534
CARMELINA ⁴⁷	Linagliptin	6,980	Completed	NCT01897532
VERTIS CV ⁸⁵	Ertugliflozin	3,900	Completed	NCT01986881
CREDENCE ⁸³	Canagliflozin	3,627	Completed	NCT02065791
Ongoing Trials				
SOUL	Oral semaglutide	9,642	Started July, 2019	NCT03914326
SURPASS-CVOT	Tirzepatide vs. dulaglutide	12,500	Started May, 2020	NCT04255433

*All versus placebo except where noted.

NCT, National Clinical Trial [registration number].

complications, was neutral. However, the secondary outcome of major adverse CV events fell in the metformin group (RRR, 39%; 95% CI 6% to 60%), similar in magnitude to the macrovascular risk reductions seen in the UKPDS. Given the relatively small size and few CV events to analyze in both these trials, the CV efficacy of metformin remains uncertain, particularly in statin-treated patients.

Concerns about the potential of metformin to cause lactic acidosis delayed its regulatory approval in the United States and hindered its clinical uptake, stemming from earlier observations with another biguanide, phenformin, that clearly caused lactic acidemia and was removed from the market. In response to this concern, metformin was contraindicated for use in patients with impaired kidney function, for 48 to 72 hours after the administration of iodinated contrast, and in unstable HF. Despite widespread global use of metformin for more than five decades, however, and a substantial aggregated database of comparative clinical trials, no convincing signal for increased lactic acidemia with metformin treatment has emerged.^{43,44}

Given this absence of data supporting the concern for lactic acidosis with metformin, in 2006 the FDA removed the product label warning for its use in patients with HF. More recently, the FDA also adjusted the prescribing guidelines for metformin products with regard to kidney contraindications.⁴⁵ Previously contraindicated with serum creatinine in men of 1.5 mg/dL or higher and in women of 1.4 mg/dL or higher, the updated recommendations allow for use in those with stable, mild-to-moderate CKD. The new cut points are based on the estimated glomerular filtration rate (eGFR) instead of serum creatinine. Metformin is now given to patients with an eGFR less than 60 mL/min/1.73 m², with safety reassessed for those taking metformin with an eGFR less than 45 mL/min/1.73 m², and with metformin contraindicated or to be stopped at an eGFR less than 30 mL/min/1.73 m². These changes should allow use of this effective, safe, and inexpensive medication to hundreds of thousands of patients in the United States alone. Regarding iodinated contrast administration, metformin need not be interrupted if the eGFR is greater than 60 mL/min/1.73 m², but should still be held in patients whose kidney function is below this level until no decrement in kidney function can be documented.

On the basis of safety, tolerability, low hypoglycemia risk, CV clinical outcomes data, and relatively low cost, metformin is widely considered the first-line drug for type 2 DM in the absence of contraindications or intolerance.^{41,42} Metformin is the only oral antihyperglycemic medication routinely recommended to be continued in combination with insulin therapy.

SULFONYLUREAS. Sulfonylureas, in clinical use since the 1950s, are the oldest oral antihyperglycemic medications. They lower glucose by augmenting insulin release through inhibition of adenosine triphosphate (ATP)-dependent potassium (K_{ATP}) channels in pancreatic beta cells. Although sulfonylureas are well tolerated and are relatively potent, their use results in the highest rate of hypoglycemia of any available oral antihyperglycemic drug. They are also associated with weight gain. Although tolbutamide, a first-generation sulfonylurea, increased CV and all-cause mortality in an early randomized trial, no such adverse CV safety signals have emerged from subsequent randomized trials with assignment to second- and third-generation sulfonylureas.³³

There had been concerns about the use of sulfonylureas in CVD cohorts, driven by their associated weight gain, increased risk for hypoglycemia and consequent stimulation of the adrenergic stress-response system with potential adverse CVD effects, and the potential of these drugs to inhibit so-called ischemic preconditioning through blockade of myocardial K_{ATP} channels. In experimental MI in animals, activation of myocardial K_{ATP} channels reduces infarct size, an effect termed ischemic preconditioning. The relevance of these observations in humans was always poorly understood, but this blocking effect is one potential explanation for the increased MI case-fatality rate observed in the more intensively treated patients in the ACCORD trial—a conjecture that remains unproved because of limited ability to analyze outcomes according to drug allocation in that trial.³³ Observations from the UKPDS trial counter the likelihood of such an effect, because an intensive glucose control policy with two different sulfonylureas, chlorpropamide and glibenclamide (glyburide in United States), yielded MI and CV death outcomes similar to those with insulin, metformin, and usual (diet) therapy.³³

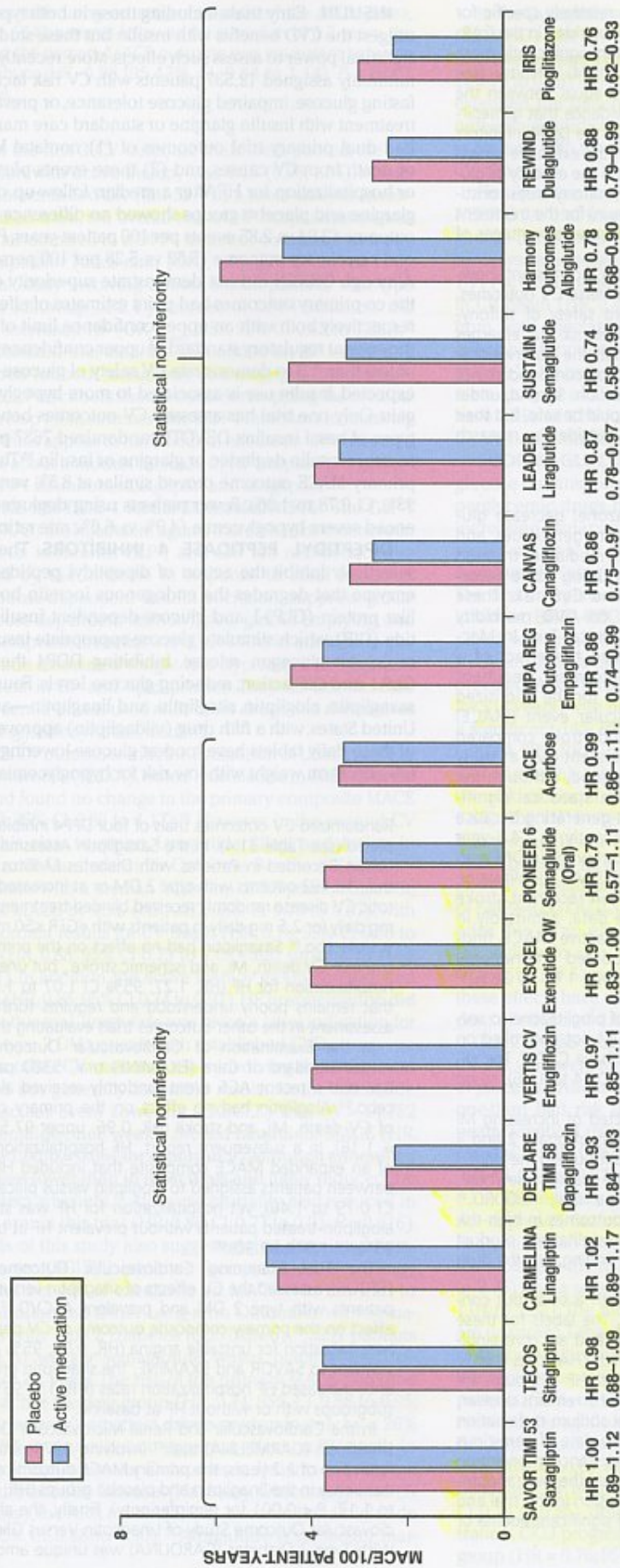


FIGURE 31.7 Summary results of the comparative incident rates (active medication vs. placebo) from large, randomized, placebo-controlled clinical trials of antihyperglycemic medications in patients with stable CV disease / CV risk factors using major adverse CV events (MACE) as primary outcomes. SAVOR TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction); TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin); CARMELINA (Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus); DECLARE TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events-Thrombolysis in Myocardial Infarction); VERTIS CV (Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants with Vascular Disease); EXSCEL (Exenatide Study of Cardiovascular Event Lowering Trial); PIONEER 6 (A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects with Type 2 Diabetes); ACE (Acarbose Cardiovascular Evaluation Trial); EMPA REG Outcome (Empagliflozin Cardiovascular Assessment Study); LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes); CANVAS (Canagliflozin Cardiovascular Assessment Study); Harmony Outcomes (Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease); SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects with Type 2 Diabetes); Harmony Outcomes (Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease); REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes); IRIS (Insulin Resistance Intervention after Stroke). (Data from References 47, 52, 60, 63, 68, 70-73, 75, 81, 82, 85, 88.)

Due to these concerns, sulfonylureas that are relatively specific for pancreatic K_{ATP} channels were developed (e.g., glimepiride). In the CAROLINA trial,⁴⁶ while glimepiride was associated with significantly more hypoglycemia than the dipeptidyl peptidase 4 (DPP4) inhibitor (see below) linagliptin, major adverse CV events were equal between the two randomized groups. This finding is further evidence that glimepiride at least was safe for the heart, since as a group the DPP4 inhibitors are known to be safe themselves.⁴⁷ On the basis of the extensive clinical experience, the availability of low-cost generics, and the efficacy of glucose control demonstrated in several clinical trials, sulfonylureas constitute a category of second-line drugs (after metformin) for the treatment of type 2 DM, but certainly without the CV and/or renal advantages of some of the newer classes.⁴¹

Data from other observational studies have been inconsistent, however, with some^{48–51} finding an association with adverse CV outcomes. This potential discrepancy between the apparent safety of sulfonylureas when studied in randomized trials versus their risk that emerges in observational studies has two explanations. First, the observational studies could be wrong, their findings influenced by confounders not assessable in the datasets, most importantly, indication. Second, under the careful observation of clinical trials the drugs could be safe, but their potential dangers may only emerge when used outside the research setting.

THIAZOLIDINEDIONES

Thiazolidinediones (e.g., rosiglitazone, pioglitazone) decrease glucose levels by increasing insulin sensitivity of target tissues and induce a wide variety of nonglycemic effects mediated through activation of the nuclear receptor PPAR- γ , including some favorable effects on intermediate markers of CVD and CVD risk. These findings engendered interest in their effects on CVD morbidity and mortality.⁴¹ The Prospective Pioglitazone Clinical Trial in Macrovascular Events (the PROactive study) assessed the effect of a glucose-lowering medication on CV clinical outcomes. Treatment with pioglitazone yielded a significant 16% RRR for the prioritized secondary composite major adverse cardiovascular event (MACE) endpoint of all-cause mortality, nonfatal MI, and stroke compared with placebo in patients with type 2 DM and prevalent CVD at study entry, treated during a 34.5-month follow-up period, although the effect on the primary endpoint did not achieve statistical significance.³³ These data were considered hypothesis-generating because of failure to meet the primary outcome. More recently, in a 4.5-year study involving patients with insulin resistance but without DM who had a recent stroke or transient ischemic attack (TIA), pioglitazone versus placebo was associated with a 24% RRR in recurrent stroke or MI (HR, 0.76; 95% CI 0.62 to 0.93).³² These data, admittedly in patients without DM, support the original PROactive MACE findings. In follow-up reports from IRIS, using updated international definitions, pioglitazone reduced ACS by 29%, type 1 MI by 38%,⁵³ and ischemic stroke alone by 28%.⁵⁴

The TOSCA-IT study compared the CV effects of pioglitazone to several sulfonylureas in 3028 patients with type 2 DM not controlled on metformin monotherapy, most of whom did not have CVD.⁵⁵ The HR for the primary MACE outcome was 0.96 (95% CI 0.74 to 1.26), so no apparent benefit.

Rosiglitazone was at one point actually suspected of increasing MI risk.⁴¹ These data from a controversial meta-analysis of phase 2 and 3 data initially led to severe product label restrictions for use in the United States and to withdrawal of rosiglitazone from the market elsewhere. However, a randomized open-label CV outcome trial, RECORD,⁵⁶ showed a neutral effect of rosiglitazone on CV outcomes in high-risk patients taking metformin or sulfonylureas. The rosiglitazone product label has since undergone updating to reflect this finding, but the drug remains infrequently used.

TZD increases the risk for peripheral edema, with a small but consistent increase in risk for new or worsening HF. The labels for these agents warn against their use in patients with HF, and are contraindicated in patients with New York Heart Association (NYHA) class III or IV HF and a caution against their use in any patient with HF. Although the mechanism of the observed increase in edema and HF remains unclear, it appears to result primarily from increased renal sodium reclamation and plasma volume expansion, with no evidence to date of pernicious cardiac effects of these drugs. Notably in insulin resistance intervention after stroke (IRIS), HF outcomes did not differ between the two randomized groups, likely a reflection of HF being an exclusion in the trial and on-trial protocols for study drug dose reduction if significant edema or excessive weight gain occurred.⁵⁷

INSULIN. Early trials including those in both type 1 and type 2 DM suggest the CVD benefits with insulin but these studies all had limited statistical power to assess such effects. More recently the ORIGIN trial⁵⁸ randomly assigned 12,537 patients with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or prevalent type 2 DM to treatment with insulin glargine or standard care management. ORIGIN had dual primary trial outcomes of (1) nonfatal MI, nonfatal stroke, or death from CV causes, and (2) these events plus revascularization or hospitalization for HF. After a median follow-up of 6.2 years, insulin glargine and placebo groups showed no difference in first co-primary outcome (2.94 vs. 2.85 events per 100 patient-years; $P = 0.63$) or the second co-primary outcome (5.52 vs. 5.28 per 100 person-years; $P = 0.27$). Although ORIGIN did not demonstrate superiority of insulin glargine, the co-primary outcomes had point estimates of effect of 1.02 and 1.04, respectively, both with an upper confidence limit of 1.11—well within the current regulatory standard of upper confidence limit for CV effects of less than 1.3 to demonstrate CV safety of glucose-lowering drugs. As expected, insulin use is associated to more hypoglycemia and weight gain. Only one trial has assessed CV outcomes between two different types of basal insulins. DEVOTE randomized 7637 patients with T2DM to either insulin degludec or glargine or insulin.⁵⁹ The incidence of the primary MACE outcome proved similar at 8.5% versus 9.3% (HR, 0.91; 95% CI 0.78 to 1.06). Fewer patients using degludec, however, experienced severe hypoglycemia (4.9% vs. 6.6%; rate ratio, 0.60; $P < 0.001$).

DIIPEPTIDYL PEPTIDASE 4 INHIBITORS. The DPP4 inhibitors selectively inhibit the action of dipeptidyl peptidase 4, a circulating enzyme that degrades the endogenous incretin hormones glucagon-like protein (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP), which stimulate glucose-appropriate insulin secretion and/or inhibit glucagon release. Inhibiting DPP4 therefore potentiates GLP-1 and GIP action, reducing glucose levels. Four DPP inhibitors—saxagliptin, alogliptin, sitagliptin, and linagliptin—are available in the United States, with a fifth drug (vildagliptin) approved elsewhere. Each of these daily tablets have modest glucose-lowering potency and neutral effects on weight with low risk for hypoglycemia.

Randomized CV outcomes trials of four DPP4 inhibitors have been completed (see Table 31.4). In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)—TIMI 53 trial, 16,492 patients with type 2 DM or at increased risk for atherosclerotic CV disease randomly received blinded treatment with saxagliptin, 5 mg daily (or 2.5 mg daily in patients with eGFR ≤ 50 mL/min/1.73 m²) versus placebo.⁶⁰ Saxagliptin had no effect on the primary composite outcome of CV death, MI, and ischemic stroke, but unexpectedly increased hospitalization for HF (HR, 1.27; 95% CI 1.07 to 1.51), an observation that remains poorly understood and requires further exploration and assessment in the other outcomes trials evaluating the DPP4 inhibitors.

In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial, 5380 patients with type 2 DM and a recent ACS event randomly received alogliptin versus placebo.⁶¹ Alogliptin had no effect on the primary composite outcome of CV death, MI, and stroke (HR, 0.96; upper 97.5% confidence limit = 1.16). In a subsequent report, HF hospitalization as the first event of an expanded MACE composite that included HF occurred similarly between patients assigned to alogliptin versus placebo (HR, 1.07; 95% CI 0.79 to 1.46), yet hospitalization for HF was statistically higher in alogliptin-treated patients without prevalent HF at trial entry (HR, 1.76; 95% CI 1.07 to 2.90).⁶²

The Trial Examining Cardiovascular Outcomes with Sitagliptin (TECOS), assessed the CV effects of sitagliptin versus placebo in 14,671 patients with type 2 DM and prevalent ASCVD.⁶³ Sitagliptin had no effect on the primary composite outcome of CV death, MI, stroke, and hospitalization for unstable angina (HR, 0.98; 95% CI 0.88 to 1.09). In contrast to SAVOR and EXAMINE, the sitagliptin group did not experience increased HF hospitalization rates (HR, 1.0; 95% CI 0.83 to 1.20) in subgroups with or without HF at baseline.⁶⁴

In the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA) trial,⁴⁷ involving 6979 patients and a median follow-up of 2.2 years, the primary MACE outcome occurred with equal frequency in the linagliptin and placebo groups (HR, 1.02; 95% CI, 0.89 to 1.17; $P < 0.001$ for noninferiority). Finally, the aforementioned Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (CAROLINA) was unique amongst recent type 2

DM CV outcomes trials using an active comparator, the sulfonylurea, glimepiride. With 6042 patients followed for a median of 6.3 years, the risk of developing the primary MACE outcome was equivalent between the treatment groups (HR, 0.98 [95.47% CI, 0.84 to 1.14]; $P < 0.001$ for noninferiority).

When data from the first 3 CV outcome trials were pooled, the HR for HF hospitalization with active therapy was 1.15 (0.98, 1.34), mainly driven by the outcomes in SAVOR-TIMI 53.⁶⁴ In a meta-analysis involving 84 DPP4 inhibition trials, the overall risk of HF hospitalization was greater in patients randomized to a DPP4 inhibitor compared with placebo or active comparator (odds ratio [OR], 1.19; 95% CI 1.03 to 1.37). In an observational study involving almost 60,000 patients with type 2 DM with average follow-up of 2.4 years, use of DPP4 inhibitors did not associate with increased HF (OR_{adjusted}, 0.88; 95% CI 0.63 to 1.22).⁶⁵ Based on the randomized trial data, the FDA added an HF warning to the prescribing labels for both saxagliptin and alogliptin, but not sitagliptin nor linagliptin. Prescribers should consider stopping the medications if patients develop HF. In summary, the DPP4 inhibitors in relatively short-term clinical trials appear to have neutral effects on CV outcomes, with some concern about a modest increase in HF hospitalization rates with at least two DPP4 inhibitors, saxagliptin and alogliptin.

GLUCAGON LIKE PEPTIDE-1 RECEPTOR AGONISTS. The GLP-1 receptor agonists (RAs) are injectable agents that enhance the incretin system.³⁰ The incretin hormones GLP-1 and GIP are neuroendocrine hormones secreted by the intestine in response to meal ingestion. They stimulate glucose-dependent insulin secretion, suppress glucagon (also in a glucose-dependent fashion), slow gastric emptying, and enhance satiety. Therapeutic benefits with GLP-1 RAs in addition to glucose lowering include associated weight loss (typically 3 to 4 kg), and modest improvement in BP and lipid profiles. They do not increase the risk of hypoglycemia unless used with other drugs that themselves increase the risk (e.g., sulfonylureas, insulin).

The first GLP-1 RA CV outcomes trial, the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA), tested lixisenatide in 6068 patients with recent ACS and found no change in the primary composite MACE outcome (HR, 1.02; 95% CI 0.89 to 1.17).⁶⁶ However, in the second CV outcome trial of this class to report, *Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)*,⁶⁷ involving 9340 patients with a median follow-up of 3.8 years, liraglutide reduced the risk of MACE by 13% (HR, 0.87; 95% CI 0.78 to 0.97), with directionally concordant results for CV death (HR, 0.78; 95% CI 0.66 to 0.93), nonfatal MI (HR, 0.88; 95% CI 0.75 to 1.03), and stroke (HR, 0.89; 95% CI 0.72 to 1.11). In addition, the active therapy group had reduced all-cause mortality (HR, 0.85; 95% CI 0.74 to 0.97). HF hospitalization did not differ. Based on this trial, liraglutide was given a label indication for reducing MACE in type 2 DM patients with established CVD.

The results from other CV outcome trials involving this drug class have shown mixed but generally favorable results. In the Exenatide Study of Cardiovascular Event Lowering (EXSCCEL) Trial ($N = 14,752$ over 3.2 years), exenatide once weekly proved neutral for MACE (HR, 0.91; 95% CI, 0.83 to 1.00; $p = 0.061$ for superiority), although adherence to the study drug was lower than in most trials and likely reduced the trial's power to detect a benefit.⁶⁸ All-cause mortality also reduced in the active therapy arm in this trial (HR, 0.86; CI, 0.77 to 0.91; $P = 0.016$). A post-hoc analysis of this study also suggested that drop-in sodium-glucose cotransporter (SGLT)2 inhibitor therapy (see below) may have attenuated the benefit of exenatide on MACE.⁶⁹ In the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6),⁷⁰ 3297 patients were randomized to weekly semaglutide versus placebo and followed for a mean of 2.1 years. The risk of the primary MACE outcome fell by 26% in the active therapy group (HR, 0.74; 95% CI, 0.58 to 0.95; $P < 0.001$ for noninferiority), an effect driven predominately by a 26% RRR in MI and a 39% in stroke, but no apparent effect on CV death. In the Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease (Harmony Outcomes) trial ($N = 9463$ over 1.6 years), the RRR for MACE 22% lower in the albiglutide group (HR, 0.78, 95% CI, 0.68 to 0.90).⁷¹ Albiglutide is no longer marketed, however.

In the Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes (REWIND) trial ($N = 9901$, 69% of whom had no established CVD at baseline, 5.4 years), dulaglutide showed a RRR of 12% (HR, 0.88, 95% CI 0.79 to 0.99) in MACE, with a 24% RRR in nonfatal stroke.⁷² REWIND extended the benefits of GLP-1 RAs to primary prevention and garnered dulaglutide the first indication by the FDA of reducing CV events in patients with type 2 DM at high CV risk but not necessarily with overt CV disease.

Finally, in the first CV outcome trial involving an oral GLP-1 RA, PIONEER 6 (A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes) ($N = 3183$ over 16 months), there was a non-significant 21% RRR in MACE (HR, 0.79, 95% CI 0.57 to 1.11 $P < 0.001$ for noninferiority), with a large and significant reduction in CV death (HR, 0.49, 95% CI 0.27 to 0.92).⁷³ The combined benefits from both injectable (SUSTAIN 6) and oral (PIONEER 6) earned the injectable formulation by the FDA a label indication to reduce MACE in type 2 DM patients with established CVD. The most comprehensive meta-analysis of GLP-1 RA CV outcome trials, found the category to have RRRs of 12% for MACE, 12% for CV death, 16% for stroke, and 9% for HF hospitalizations (Fig. 31.8).⁷⁴

SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, the newest class of antihyperglycemic drugs, block a SGLT in the proximal tubule of the kidney, increasing urinary excretion of glucose as well as sodium. This effect results not only in glucose lowering but also in modest reductions in body weight (approximately 2 kg) and BP (approximately 4/2 mmHg). The first completed CV outcome trial to assess the effect of an SGLT2 inhibitor, *EMPA-REG OUTCOME*, tested whether empagliflozin compared with placebo influences the incidence of CV events.⁷⁵ The study enrolled a high-risk population of patients with type 2 DM and prevalent ASCVD. It enrolled 7020 patients with longstanding DM (57% for >10 years) with mean follow-up of 3.1 years. The trial demonstrated a significant 14% RRR in the primary MACE (HR, 0.86; 95% CI 0.74 to 0.99). A 38% RRR in CV death (5.9% vs. 3.7%; HR, 0.62; 95% CI 0.49 to 0.77) drove this result. In addition, empagliflozin significantly reduced the risk of hospitalization for HF by 35% (HR, 0.65; 95% CI 0.50 to 0.85). The HF benefit applied to those without prior HF, suggesting that empagliflozin could prevent not only the clinical deterioration of HF but also its occurrence.⁷⁶ The event curves for both CV death and HF hospitalization outcomes diverged during the first few weeks of EMPA-REG OUTCOME, suggesting that the CV benefits likely did not arise due to an effect on atherosclerosis, but from other effects.^{7,77,78} Empagliflozin also led to a 39% RRR in the progression of CKD (HR, 0.61, 95% CI 0.53 to 0.70), and post-hoc inquiries into the mediators of these effects have demonstrated that the benefits are largely independent of effects of the SGLT2 inhibitor on HbA_{1c}.^{79,80}

The CANVAS program involved 10,142 patients with type 2 DM at high CV risk who were randomized to another SGLT2 inhibitor, canagliflozin, or placebo.⁸¹ About two-thirds had established CVD while approximately one-third had risk factors only. The canagliflozin group experienced nearly identical risk reductions to those seen in EMPA-REG OUTCOME for MACE (HR, 0.86; 95% CI, 0.75 to 0.97), HF hospitalization (HR, 0.67; 95% CI, 0.52 to 0.87), and progression of CKD (HR, 0.60; 95% CI, 0.47 to 0.77). The estimate for CV mortality (HR, 0.87; 95% CI, 0.72 to 1.06) did not approach the major reduction observed in EMPA-REG OUTCOME. In addition, two adverse effects of canagliflozin were found in CANVAS: a doubling in the risk of lower limb amputations (HR, 1.97; 95% CI, 1.41 to 2.75) and a smaller increase in the risk of fracture (HR, 1.23; 95% CI, 1.04 to 1.52). The mechanisms behind these complications of therapy are unknown. Other SGLT2 inhibitors have not shown similar effects.

In the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58),⁸² 17,160 patients (59% of whom were without established CVD at baseline) received dapagliflozin or placebo. After a mean follow-up of 4.2 years, the MACE outcome proved equivalent between the two groups (HR, 0.93, 95% CI 0.84 to 1.03) but the other co-primary outcome of CV death and HF hospitalization fell significantly (RRR 17%; HR, 0.83, 95% CI 0.73 to 0.95), driven by a 27% reduction in the risk of HF hospitalization. CKD progression also occurred less often in the dapagliflozin group (HR = 0.76; 95% CI 0.67 to 0.87.)

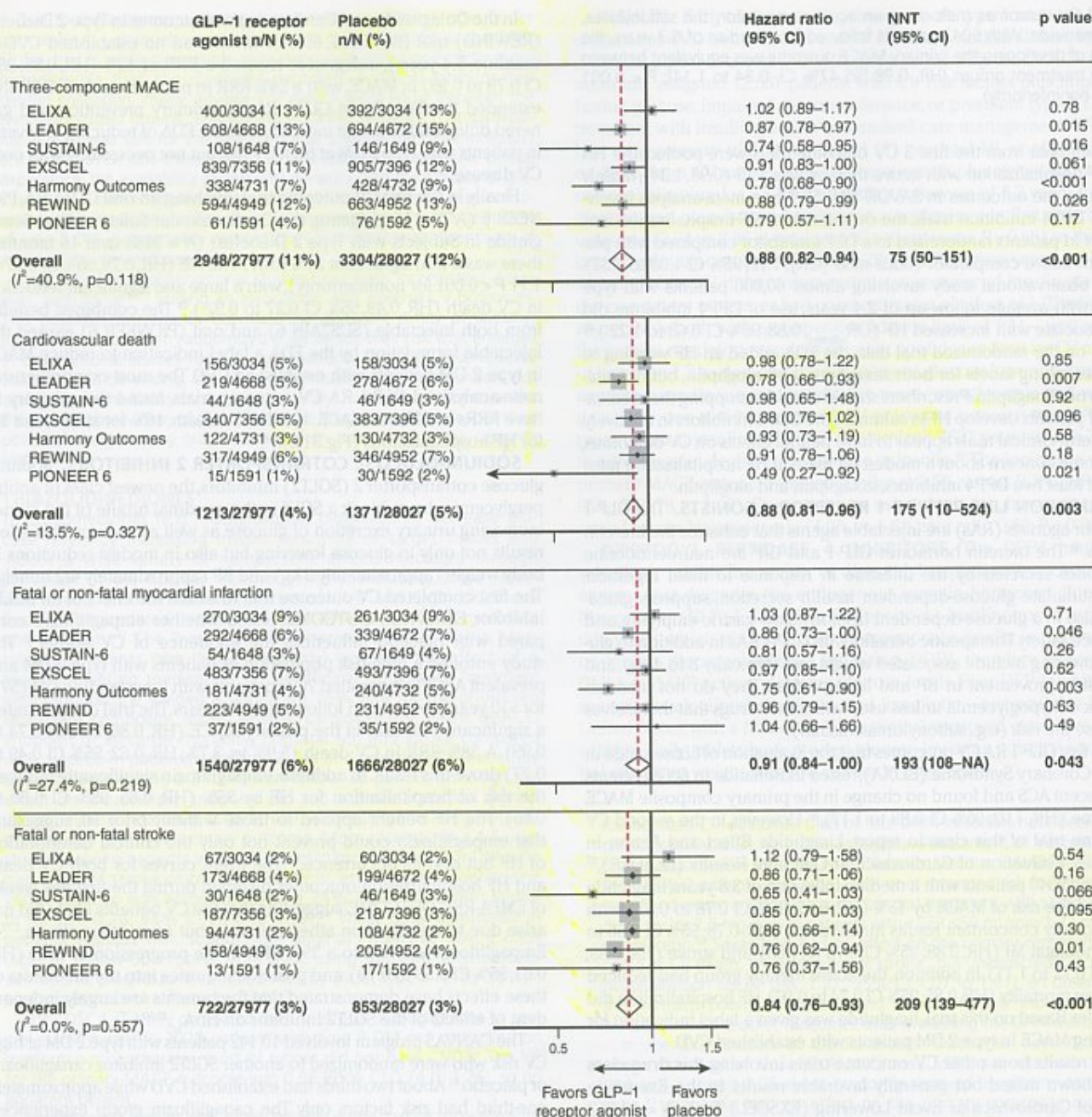


FIGURE 31.8 Meta-analysis of GLP-1 receptor agonist cardiovascular (CV) outcome trials (ELIXA, LEADER, SUSTAIN-6, EXSCEL, Harmony Outcomes, REWIND, PIONEER 6) with outcomes of 3-component major adverse CV events (MACE), CV death, fatal or non-fatal myocardial infarction, stroke, all-cause mortality, hospital admission for heart failure (HHF), composite kidney outcome (including macroalbuminuria), worsening of kidney function, and the composite for the progression of chronic kidney disease (CKD). Hazard ratios (individual and overall) represent the comparison of the incidence rates in the active therapy versus the placebo groups. (From Kristensen SL, Rorth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol.* 2019;7:776–785.)

The Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CRENDENCE) trial primarily assessed the effect of canagliflozin on renal outcomes in 4401 type 2 DM patients with eGFR 30 to 90 mL/min/1.73 m² and prevalent macroalbuminuria.⁸³ The positive primary outcome in favor of canagliflozin, was a 30% RRR in CV death or end-stage kidney disease, a doubling of the creatinine level, or death from renal causes, with the risk of the renal-specific component of the broader composite reduced by 34%. The canagliflozin group also experienced a lower risk of MACE (HR, 0.80; 95% CI, 0.67 to 0.95) and hospitalization for HF (HR, 0.61; 95% CI, 0.47 to 0.80).

The Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease (VERTIS CV) trial,⁸⁴ compared ertugliflozin with placebo in 8238 patients with

type 2 DM and established CVD. This was the only SGLT2i CV outcome trial to miss its primary superiority endpoint (MACE). HF hospitalizations occurred less frequently in the ertugliflozin group, however (HR, 0.70; 95% CI 0.54 to 0.90).⁸⁵

The cardiovascular efficacy of the dual SGLT 1 and 2 inhibitor, sotagliflozin, has been studied in two large-scale randomized trials.^{85a,86} In SCORED, patients with type 2 diabetes and diabetic kidney disease were studied, and in SOLOIST patients with type 2 diabetes during or just after admission for decompensated heart failure were studied. Both trials demonstrated statistical superiority for sotagliflozin versus placebo on the primary composite outcome of CV death/hospitalization for heart failure/urgent heart failure visit, and in SCORED, sotagliflozin also significantly reduced the risk for the prioritized secondary outcome of MACE. Sotagliflozin has not been approved for clinical use

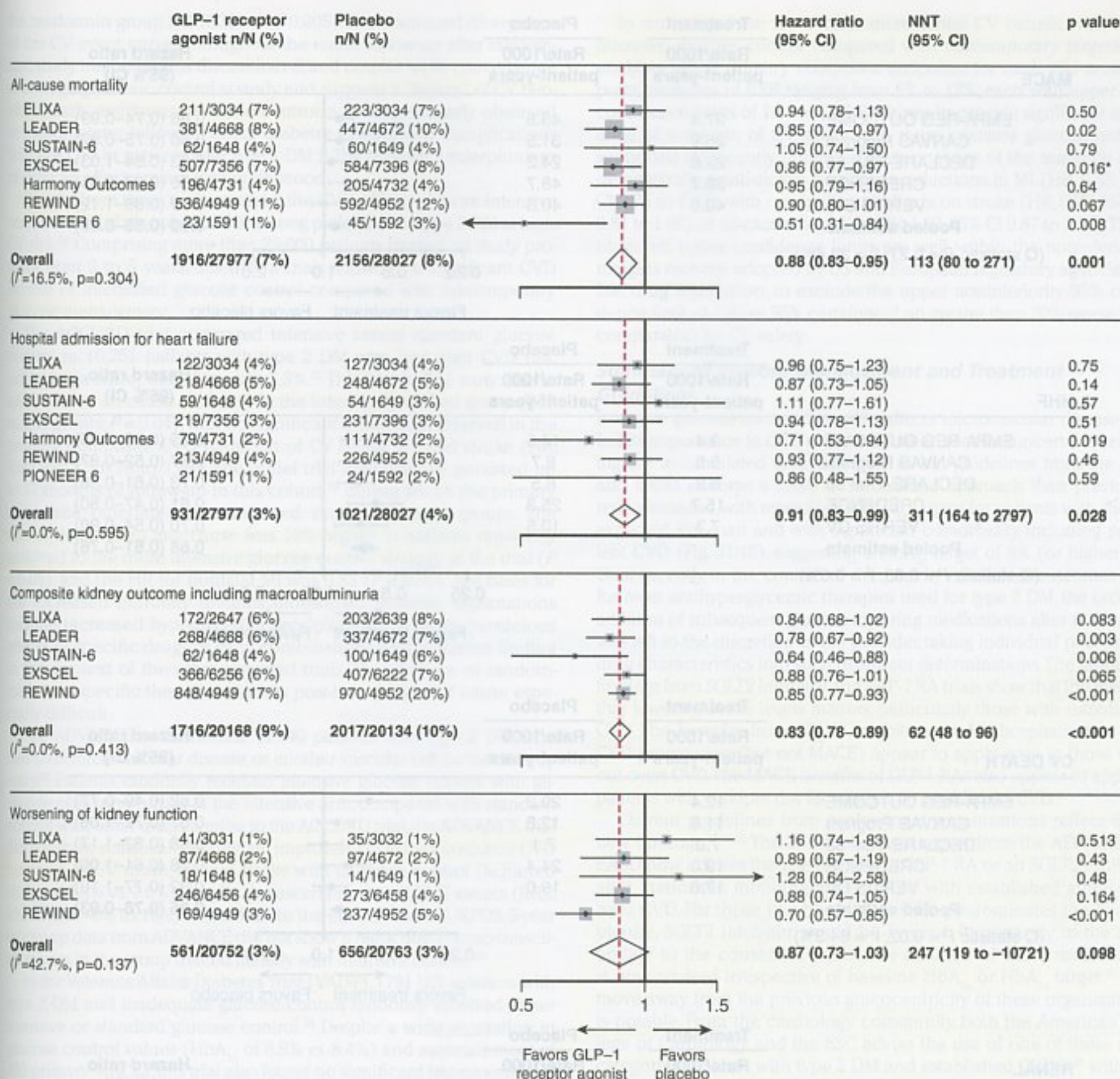


FIGURE 31.8 Continued

for patients with type 2 diabetes and has been approved but is not marketed in Europe for treatment of patients with type 1 diabetes.

In the most recent meta-analysis of SGLT2 inhibitor CV outcome trials,^{86,87} RRRs for MACE, CV death, HF hospitalization, and CKD progression were estimated to be 10%, 15%, 32% and 38%, respectively (Fig. 31.9). The MACE benefit was significant only in those participants with established ASCVD. In contrast, for HF hospitalizations, patients both with and without ASCVD and with or without prior HF appeared to benefit. The greatest variability in the point estimates across trials was in CV death and the greatest consistency was in HF hospitalization. This class is now favored by treatment guidelines as preferred agents in patients with ASCVD, and especially in those with HF or mild-moderate CKD.

OTHER GLUCOSE-LOWERING MEDICATIONS (SEE TABLE 31.3). Data on CVD outcomes are generally limited for other less commonly used glucose-lowering medications.³³ These share the advantage of a very low risk for hypoglycemia, and all most are weight neutral. *Colesevelam*, a bile acid sequestrant initially approved for the treatment of hypercholesterolemia, is also approved for use as a glucose-lowering

drug to treat type 2 DM, and *alpha-glucosidase inhibitors* impair intestinal carbohydrate absorption. The effects of these drugs on CV outcomes remain unknown, with the exception of a reduced incidence of MIs reported with *acarbose* in a DM prevention trial, STOP NIDDM.³³ However, in the larger ACE trial, involving 6522 Chinese patients with CHD and impaired glucose tolerance, *acarbose* had no effect to reduce a CV composite outcome.⁸⁸ Gastrointestinal intolerance has limited their clinical use.⁴¹ The dopamine agonist, *bromocriptine*, activates hypothalamic control of insulin sensitivity, and has actually been demonstrated to be safe and potentially effective in an older CV outcome trial, but is rarely used.

Cardiovascular Effects of More Intensive Versus Less Intensive Glucose Control Strategies

The UKPDS trial randomly assigned 5102 patients with newly diagnosed type 2 DM to intensive glucose control with sulfonylurea or insulin or to management with diet alone; those overweight at study entry ($n = 795$) also could be randomized in the intensive arm to receive metformin.³³ In the insulin and sulfonylurea analyses, resulting

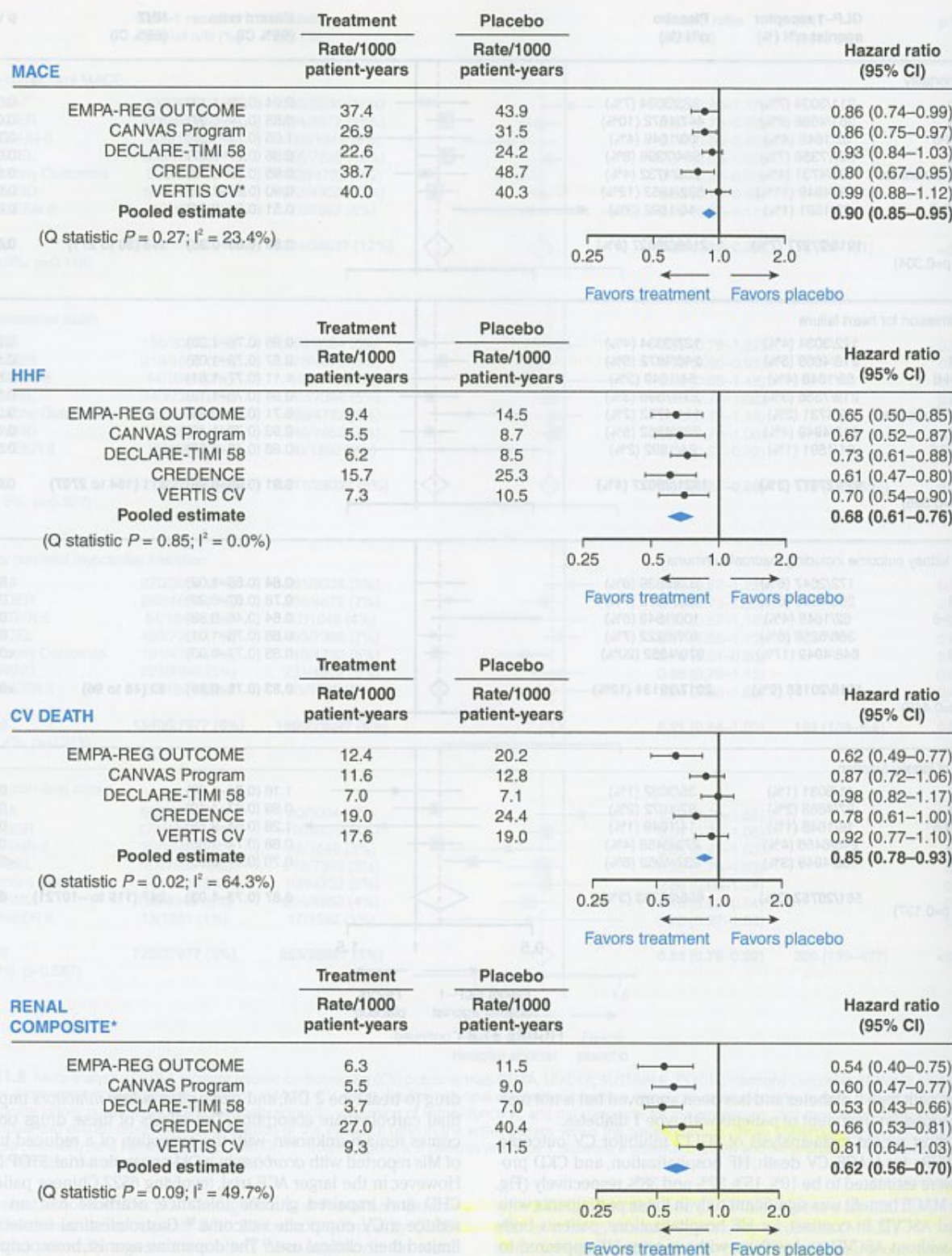


FIGURE 31.9 Meta-analysis of SGLT2 inhibitor cardiovascular (CV) outcome trials (EMPA-REG OUTCOME, CANVAS, DECLARE, CREDENCE, and VERTIS CV) with outcomes of major adverse CV events (MACE), hospitalization for heart failure (HHF), CV death, and the composite for the progression of chronic kidney disease (CKD). Hazard ratios (individual and pooled) represent the comparisons of the incidence rates in the active therapy versus the placebo groups. (From McGuire DK. Metaanalysis Placeholder. 2020.)

in hemoglobin (Hb) A_{1c} levels of 7.0% versus 7.9%, respectively, during an average follow-up of 10 years, intensive control decreased risk for a composite endpoint of all DM-related complications (RRR, 12%; $P = 0.029$) and significantly improved microvascular disease risk (RRR, 25%; $P = 0.01$). Although intensive control showed a trend toward decreased risk of MI (14.8% vs. 16.8%; $P = 0.052$), the number of strokes was increased, although the difference did not achieve statistical significance (5.6% vs. 5.2%; $P = 0.52$). In overweight patients, metformin

yielded better glucose control (HbA_{1c}, 7.4% vs. 8.0%) and significantly decreased risk for MI (RRR, 39%; $P = 0.01$) and all-cause mortality (RRR, 36%; $P = 0.011$). The long-term follow-up of the UKPDS trial cohort has extended these observations to an average duration of 10 years² during which glucose control converged rapidly after discontinuation of the study treatment. These analyses reveal a significantly reduced risk for MI in those originally randomly assigned to intensive control, both in the insulin and sulfonylurea group (RRR, 15%; $P = 0.01$) and in

the metformin group (RRR, 33%; $P = 0.005$). The continued divergence of the CV event curves throughout the entire follow-up after randomized study treatment was discontinued, and despite rapid convergence of average glycemic control at study end, suggests a "legacy" of CV benefit of early assiduous glycemic control, a finding similarly observed in the long-term follow-up of the Diabetes Control and Complications Trial (DCCT) in patients with type 1 DM.³³ The biologic underpinnings of such an effect are not well understood.

Results from three trials assessed the CVD effects of more intensive versus standard glucose control among patients with type 2 DM at high CV risk.³³ Comprising more than 23,000 patients treated on study protocol from 3 to 5 years, this trio of trials showed no significant CVD benefit of intensified glucose control compared with contemporary glucose management.

The ACCORD trial compared intensive versus standard glucose control in 10,251 patients with type 2 DM who had high CVD risk, achieving a HbA_{1c} of 6.4% versus 7.5%.³³ This trial halted early due to an excess of all-cause mortality in the intensively treated group (257 vs. 203 events; $P = 0.04$), with no significant difference observed in the primary composite CVD endpoint of CV death, MI, and stroke (HR, 0.90; 95% CI 0.78 to 1.04). The initial trial observations persisted up to 17 months of follow-up in this cohort,³³ during which the primary composite outcome risks remained similar between groups. The risk of death from any cause was 19% higher in patients randomly assigned to the more intensive glucose control strategy in the trial ($P < 0.05$), and the HR for nonfatal MI was 0.83 ($P < 0.05$). The basis for the increased mortality remains unresolved; possible explanations include increased hypoglycemia precipitating CV death, pernicious effects of specific drugs or drug combinations, and a chance finding in the context of the other reported trials. The absence of randomization to specific therapies renders post-hoc analysis of cause especially difficult.

The ADVANCE trial enrolled 11,140 patients with type 2 DM who had CVD, microvascular disease, or another vascular risk factor at study entry.³³ Patients randomly received intensive glucose control with glazide plus other drugs in the intensive arm, compared with standard control with other drugs. Similar to the ACCORD trial, the ADVANCE trial did not show statistically significant improvement in the composite CVD outcome of CV death, MI, and stroke with intensive control (achieved HbA_{1c} of 6.4% vs. 7.0%), despite the ascertainment of 1147 events (RRR, 6%; 95% CI -6% to 16%). In contrast to the effects seen in UKPDS, 5-year follow-up data from ADVANCE did not show a reduction in macrovascular events in the group treated initially with intensive control.⁸⁰

In the Veterans Affairs Diabetes Trial (VADT), 1791 U.S. veterans with type 2 DM and inadequate glucose control randomly received either intensive or standard glucose control.³³ Despite a wide separation in glucose control values (HbA_{1c} of 6.9% vs. 8.4%) and ascertainment of 499 primary MACEs, this trial also found no significant improvement in CV outcomes with intensive control (29.5% vs. 33.5%; $P = 0.14$). However, follow-up data obtained 3.3 years later in 78% of the initial study population suggest that intensive glucose control compared with standard therapy leads to a significant 17% reduction ($P = 0.04$) of the primary endpoint.⁹⁰

From post-hoc analyses of data for each of these trials and supported by the long-term observations from UKPDS in patients with newly diagnosed DM at study entry, the concept has emerged that more intensive glycemic control may be safer and may have more favorable CV effects when used in patients earlier in the course of DM, particularly among those without prevalent CVD. The corollary to this strategy is that more liberal glycemic targets may be acceptable for selected patients at increased risk, such as very elderly patients and those with a high burden of underlying comorbidities, especially those with prevalent CVD. Although these hypotheses require confirmation in additional clinical trials, the most recent ADA/EASD guidelines for chronic glucose management for patients with type 2 DM endorse such a strategy of targeting intensity of glucose control in the context of global CVD risk, advocating HbA_{1c} target of 8% (or possibly higher) for selected patients, including those with moderate to severe CVD.^{41,42} An overriding consideration of such an approach is the limited evidence of short-term benefits from any reduction in microvascular disease in those with limited life expectancy.

In summary, there is no clear incremental CV benefit with more intensive glucose control compared with contemporary targets, the analyses of the primary composite endpoints for each trial revealed point estimates of RRR ranging from 6% to 12%, each with upper 95% confidence limits of 1.04 to 1.06. Such results provide significant assurance of a margin of CV safety with more intensive glucose control, supported by recently published meta-analyses of the available data, demonstrating statistically significant reductions in MI (HR, 0.83; 95% CI 0.75 to 0.93), with no significant effects on stroke (HR, 0.93; 95% CI 0.81 to 1.06) or all-cause mortality (HR, 1.02; 95% CI 0.87 to 1.19). These observed upper confidence limits are well within the noninferiority margins recently adopted by US and European regulatory agencies for DM drug registration, to exclude the upper noninferiority 95% confidence limit of 1.3 (or 95% certainty of no greater than 30% worse than comparator) for CV safety.

Summary of Glucose Management and Treatment Guidelines

Intensive glucose control favorably affects microvascular disease risk, but its importance in CVD risk modification remains uncertain. Reflecting the accumulated data, the most recent guidelines from the ADA and EASD endorse a more individualized approach than previously recommended, with more liberal HbA_{1c} targets for patients with shorter expected life span and with significant comorbidity, including prevalent CVD (Fig. 31.10), suggesting a HbA_{1c} target of 8% (or higher).^{41,42} Until recently, in the context of the paucity of clinical outcomes data for most antihyperglycemic therapies used for type 2 DM, the ordered addition of subsequent glucose-lowering medications after metformin was left to the discretion of the provider, taking individual patient and drug characteristics into such treatment determinations. The landmark findings from SGLT2 inhibitor and GLP-1 RA trials show that the method that lowers glucose levels matters, particularly those with established CVD. The benefits from SGLT2 inhibitors on HF hospitalization and CKD progression (but not MACE) appear to apply even in those without overt CVD. The MACE benefits of GLP-1 RAs also appear to apply in patients with multiple risk factors but no established CVD.

Current guidelines from professional organizations reflect these new findings.^{10,13,15} The 2018 consensus report from the ADA and the EASD now advises the use of either a GLP-1 RA or an SGLT2 inhibitor after metformin monotherapy in those with established atherosclerotic CVD. For those in whom HF or CKD predominates the clinical picture, SGLT2 inhibitor would be favored. Importantly in the 2019 update to the consensus report, the addition of these medications is now advised irrespective of baseline HbA_{1c} or HbA_{1c} target.¹⁵ This move away from the previous glucocentricity of these organizations is notable. From the cardiology community, both the American College of Cardiology and the ESC advise the use of one of these drug categories in those with type 2 DM and established CVD,^{10,91} with the European group extending this to those at very high and high CV risk. In contrast to the ADA/EASD guidelines, the use of these medications should be considered as first line in those patients not taking metformin.¹⁰

Acute Coronary Syndromes

In view of the high risk associated with DM in the setting of ACS, much investigation has focused on this population. In general, as endorsed by the most recent ACS guidelines,^{92,93} the treatment of patients with DM should mimic that of the overall population (see Chapters 37–39). Some specific therapies also are recommended for patients with DM.

Screening for Diabetes in Acute Coronary Syndrome Patients

One third of ACS patients have previously diagnosed DM.^{6,94} Moreover, many patients present with an ACS event as the first complication of DM, previously undetected DM is also common, affecting up to an additional 20% to 25% of ACS patients.⁹⁴ Therefore, all patients with ACS events warrant screening for DM.^{10,95,96} Given the stress hyperglycemia associated with ACS events that may confound blood glucose testing, screening should extend beyond assessment of fasting blood glucose and include HbA_{1c} testing and/or pre-discharge oral glucose tolerance

APPROACH TO THE MANAGEMENT OF HYPERGLYCEMIA:

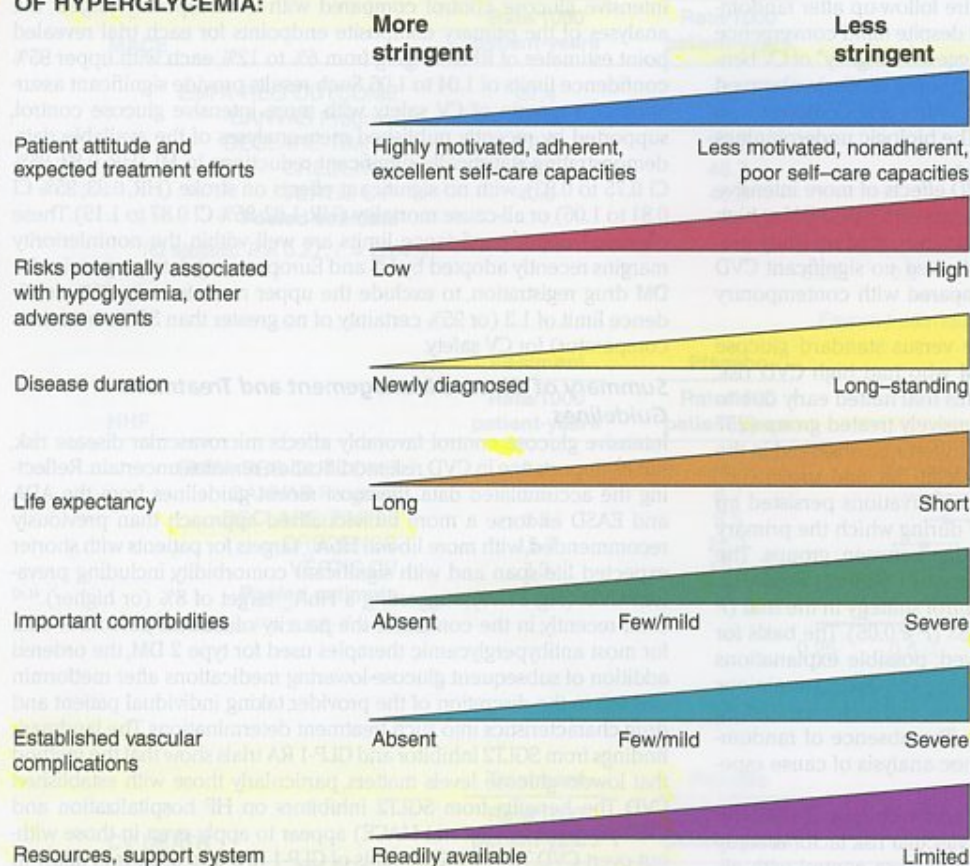


FIGURE 31.10 Modulation of the intensiveness of glucose lowering in type 2 diabetes mellitus (DM). Depiction of patient and disease factors that may be used by the practitioner to determine optimal hemoglobin A_{1c} (HbA_{1c}) targets in patients with type 2 DM. Greater concerns regarding a particular domain are represented by increasing height of the corresponding ramp. Thus, characteristics/predicaments toward the left justify more stringent efforts to lower HbA_{1c}, whereas those toward the right suggest (indeed, sometimes mandate) less stringent efforts. Where possible, such decisions should be made with the patient, reflecting his or her preferences, needs, and values. This "scale" is not designed to be applied rigidly but to be used as a broad construct to guide clinical decision making. (From Inzucchi SE, Bergenstal RM, Buse JB, 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;38:140–149.)

testing.^{10,96} The diagnosis of DM early in the hospital course is important because it influences immediate and later therapeutic decisions.

Insulin Administration and Glucose Control

Research over decades has evaluated the role of myocardial metabolic modulation during ACS events, with insulin delivery as the primary focus of investigation. Almost all trials completed to date evaluating the role of intravenous (IV) insulin in ACS used very high insulin dosing supported by exogenous glucose administration to avoid hypoglycemia, with or without adjunctive delivery of potassium, so-called glucose-insulin-potassium (GIK) therapy. These protocols typically targeted permissive hyperglycemia of 126 to 200 mg/dL during the infusion. This strategy ultimately proved futile in contemporary ACS management in the CREATE ECLA GIK trial of 20,201 patients with ST-segment elevation MI (STEMI), randomized to GIK therapy versus usual care and accumulating 1980 mortality events—demonstrating no benefit of GIK therapy compared with usual care.⁹⁷ These results have led to the abandonment of GIK treatment for ACS patients.

No adequately powered clinical outcomes trial has been completed to date in the ACS setting evaluating targeted glucose control with IV insulin or any other therapy. The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial enrolled 620 patients with hyperglycemia at presentation with MI, randomly assigned to insulin infusion acutely, followed by multidose subcutaneous insulin injection or usual care, with significant mortality reduction demonstrated in the insulin-treated group during long-term follow-up.⁹⁷ DIGAMI used an acute infusion of high-dose insulin (5 units/hr),

coupled with IV glucose administration with protocol-targeted permissive hyperglycemia of 126 to 198 mg/dL, an insulin-dosing protocol used in subsequent GIK trials, including the negative CREATE ECLA GIK trial previously summarized. Often misinterpreted as a trial of intensive glucose control, this study provided the basis of ACCF/AHA guideline recommendations for intensive glucose control in the management of ACS events since 2004. However, in the absence of evidence of beneficial effects of intensive glucose control in ACS populations, and a series of trials in other intensive care unit (ICU) settings demonstrating no significant benefit for the most part,⁹⁸ and increased mortality with intensive glucose control with IV insulin in the medical and surgical ICUs in the largest trial to date, guidelines for the management of hyperglycemia in the ACS setting have changed considerably.⁹⁷ More recently, both ACCF/AHA and ESC guidelines have omitted recommendations with regard to targeted glucose control during the management of ACS events.^{10,99,99} (See the Guidelines Tables 31G.1 through 31G.4 in the online chapter.)

Antiplatelet Medications

ACS patients with or without DM should receive aspirin. Various studies have tested the potential for more intensive antiplatelet therapies to provide particular benefit to ACS patients with DM.

P2Y₁₂ Receptor Antagonists

The incremental efficacy of adding thienopyridine and nonthienopyridine antagonists of the platelet receptor P2Y₁₂ (clopidogrel, prasugrel, and ticagrelor) to aspirin therapy in the treatment of ACS has been demonstrated in randomized clinical trials that included substantial numbers of patients with DM (see Chapters 38 and 39).^{98–101} In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial,⁹⁸ which included 2840 patients with DM, the estimate of treatment benefit of clopidogrel in this subpopulation of 15% RRR was numerically similar to the overall trial results (14.2% vs. 16.7%; $P > 0.05$). Prasugrel added to aspirin, compared with clopidogrel plus aspirin, significantly reduced the CVD risk in the DM subset of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) trial, including patients with ACS undergoing a primary invasive management strategy (12.2% vs. 17.0%; $P < 0.001$).^{101,102} In the DM subset, prasugrel did not lead to a significant increase in major bleeding complications (2.6% vs. 2.5%). The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial, however, which enrolled patients with MI treated medically without revascularization, randomly assigned to treatment with clopidogrel or prasugrel,¹⁰³ found no significant differences were between the groups in the primary composite outcome of CV death, MI, and stroke in the overall trial population, or in the DM subset, in which the interaction of treatment efficacy of prasugrel by DM status observed in the TRITON trial was not evident. In the Platelet Inhibition and Patient Outcomes (PLATO) trial, which enrolled 18,624 patients with an ACS, with or without ST-segment elevation, randomly assigned to receive ticagrelor or clopidogrel, ticagrelor (a nonthienopyridine

P2Y₁₂ antagonist) significantly reduced the primary composite outcome of death from vascular causes, MI, and stroke (9.8% vs. 11.7%; $P < 0.001$).¹⁰¹ Similar findings pertained to the subset of 4662 patients with DM at study entry.⁹⁹

In aggregate, these observations support the incremental benefits of more potent antiplatelet treatment added to aspirin therapy in patients with DM with ACS events, with superiority of both prasugrel and ticagrelor over clopidogrel. The P2Y₁₂ receptor antagonists should be considered in the routine clinical management of patients with DM and ACS.

Renin-Angiotensin-Aldosterone System Antagonists

The ACE inhibitors have several favorable effects in ACS that may particularly benefit patients with DM. Observational data and sub-analyses of patients with DM in randomized trials, suggest greater beneficial effects on HF incidence and mortality in DM. Thus, the routine use of ACE inhibitors for patients with DM is a level I (A) recommendation in ACS.^{10,92,93}

Although ARBs have similar effects on intermediate markers of myocardial structure and function to those of ACE inhibitors, the evidence base for their overall effects on clinical outcomes following an ACS event remains less robust, especially for the subset of patients with DM. For example, in the Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL), a randomized trial comprising patients with MI events complicated by HF, losartan versus captopril associated with a trend toward increased mortality (RR, 1.13; 95% CI 0.99 to 1.28), although the observed differences were not statistically significant.³⁰ In contrast, the Valsartan in Acute Myocardial Infarction Trial (VALIANT), which enrolled patients within 10 days of an acute MI complicated by HF, including 3400 patients with DM, showed no significant difference in mortality between patients randomly assigned to treatment with captopril and those treated with valsartan, and effects in the DM subset mirroring those observed in the overall study cohort.^{30,104} Thus, ARBs should be considered an alternative only for patients intolerant of ACE inhibitors.

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) compared the mineralocorticoid-selective aldosterone antagonist eplerenone to placebo, added to optimal therapy, in a population of 6632 patients with MI and decreased ejection fraction (EF) who had either clinical HF or, in the absence of manifest HF, DM.¹⁰⁵ In the overall study cohort, treatment with eplerenone compared with placebo reduced the risk of CV death by 17% (RR, 0.83; 95% CI 0.72 to 0.94), with numerically similar observations in the subset of 2232 patients with DM. On the basis of this trial, the use of an aldosterone antagonist for patients with DM and reduced EF (with or without clinical HF) after MI is recommended in ACS,^{10,92,93} except in patients with impaired kidney function (creatinine >2.0 mg/dL) or hyperkalemia (potassium concentration $[K^+] >5.0$ mEq/L).

Beta-Adrenergic Blocking Agents

Despite evidence of their incremental effectiveness in the treatment of patients with DM after ACS events, beta blockers continue to be underprescribed in this group.^{6,106} Biologic effects that support the incremental efficacy of beta blockers in the setting of DM include the restoration of the sympathovagal balance in patients with DM with autonomic neuropathy and decreasing fatty acid metabolism within the myocardium, reducing myocardial oxygen demand. Therefore, all patients with ACS should receive beta blockers, independent of their DM status, in the absence of contraindications.^{10,92,93} The selection might consider the variable effects of available beta blockers on glycometabolic parameters, favorable for carvedilol and labetalol and unfavorable for others (e.g., metoprolol, atenolol), although these considerations have uncertain clinical relevance.¹⁰⁶

Primary Invasive Strategy for Non-ST-Segment Elevation Acute Coronary Syndrome

In randomized trials comparing primary invasive versus noninvasive strategies for the treatment of ACS events, the subsets of patients with DM derived similar or greater benefits than those without DM associated with a primary invasive management strategy, although mortality and reinfarction rates were still higher in the groups with DM in both treatment arms (see Chapter 41).^{96,107} Nonetheless, a primary invasive strategy for patients with DM continues to be underused in ACS patients with DM.⁶

Primary Reperfusion Therapy for ST-Segment Elevation Myocardial Infarction

Analyses from trials of primary PCI suggest greater benefit in patients with than in those without DM, with primary PCI proving superior to thrombolysis in these patients.¹⁰⁸ Similarly, in analyses of subsets with DM from randomized trials of thrombolytics, patients with DM derive greater absolute benefit from thrombolytic therapy than patients without DM.⁹³ Therefore, patients with DM and STEMI should undergo reperfusion therapy in the absence of contraindications, preferentially with a strategy of primary PCI when available (see Chapter 38).

Coronary Revascularization Considerations

In patients with DM, the anatomical pattern of CAD influences prognosis and the response to revascularization. Angiographic studies show that patients with DM are more likely to have left main and multivessel CAD, and diffuse and small vessel disease.¹⁰⁹ Current guidelines recommend medical treatment, including anti-ischemic drugs as first-line treatment for patients with DM and stable CAD. For patients requiring revascularization, the optimal strategy remains controversial.

Optimal Medical Therapy Versus Revascularization in Diabetes

Studies examining optimal medical therapy (OMT) versus a revascularization strategy in patients with DM with stable CAD are scarce. The largest such trial, the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trial, randomized 2368 patients with DM with obstructive CAD either to immediate revascularization (coronary artery bypass grafting [CABG] $n = 347$; PCI $n = 765$) in addition to OMT or OMT alone. After 5 years, no significant differences were noted in the combined endpoint of death, MI, or stroke between groups. However, the CABG stratum subgroup, despite having more advanced CAD, showed a significantly higher rate of freedom from major adverse cardiac and cerebrovascular events (MACCE) and death compared with OMT alone (77.5% vs. 69.6%; $P = 0.01$). In contrast, in the PCI stratum compared with OMT alone, there was no difference in freedom from MACCE (77% vs. 78.9%; $P = 0.15$).¹⁰⁸ Thus, BARI-2D demonstrated that OMT is a reasonable therapeutic option in patients with DM and less advanced CAD, independent of the presence of ischemia. Moreover, regarding the indirect comparison between CABG and PCI in this trial, overall mortality was significantly lower with CABG compared with PCI at 5-year follow-up (19.4% vs. 34.5%; $P = 0.003$).¹⁰⁸ Thus, in patients with more extensive CAD and proven ischemia, CABG may be preferred.

The ISCHEMIA trial assessed an initial invasive strategy (angiography and revascularization when feasible) and medical therapy or an initial conservative strategy of medical therapy alone and angiography if medical therapy failed in 5179 patients with CAD and moderate or severe ischemia including 2164 patients with DM.¹¹⁰ The primary outcome was a composite of death from cardiovascular causes, MI, or hospitalization for unstable angina, HF, or resuscitated cardiac arrest. At 6 months, the cumulative event rate was 5.3% in the invasive-strategy group and 3.4% in the conservative-strategy group (difference, 1.9 percentage points; 95% CI, 0.8 to 3.0); at 5 years, the cumulative event rate was 16.4% and 18.2%, respectively (difference, -1.8 percentage points; 95% CI -4.7 to 1.0) suggesting that the initial invasive strategy did not reduce the risk of ischemic cardiovascular events or death from any cause. The results did not differ between patients with or without DM.

Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting

Patients with DM have worse clinical outcomes after revascularization by either PCI or CABG than those without DM. Patients with DM have more recurrent CV events after PCI.¹¹¹ After CABG, patients with DM have elevated risk of wound infections, acute kidney injury, HF, and death.¹⁰⁸ The optimal strategy of coronary revascularization for patients with DM remains controversial.

Several large trials have compared PCI versus CABG,¹¹²⁻¹¹⁵ but given technical advances in both interventional cardiology and coronary surgery over recent decades, the results of these trials may apply only partially today.¹¹⁶ The Coronary Artery Revascularization in Diabetes

(CARDia) trial comparing PCI versus CABG in 510 patients with DM and multivessel CAD found no difference between groups for the primary composite endpoint of death or MI (PCI 13.0% versus CABG 10.5%; $P = 0.39$).¹¹³ However, the addition of repeat revascularization to the composite outcome showed a benefit favoring CABG (11.3% vs. 19.3%; $P = 0.016$) at 1-year follow-up. Important limitations of the CARDia trial were the mixed use of bare-metal stents (BMS, 31%) and first-generation (sirolimus) drug-eluting stents (DES) in the PCI arm and the relatively small sample size.¹¹³

A subanalysis of the 452 patients with DM with left main or three-vessel CAD enrolled in the Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial of PCI versus CABG demonstrated higher rates of MACCE with PCI using paclitaxel-eluting stents (PES) compared with CABG at 1 year (26% vs. 14.2%; $P = 0.003$), and after 5 years of follow-up (46.5% vs. 29.6%; $P < 0.001$).¹¹² Differences driven by more repeat revascularization in the PCI group at 1 year (PCI 20.3% vs. CABG 6.4%; $P < 0.001$) and at 5 years (PCI 35.3% vs. CABG 14.6%; $P < 0.001$). With respect to lesion complexity according to the SYNTAX score, only patients with DM with more complex disease (SYNTAX score ≥ 33) had a treatment benefit of CABG.¹¹²

In contrast to these studies, the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multi-Vessel Disease (FREEDOM) trial studied a cohort of patients with type 2 DM and multivessel disease.¹¹⁵ Among 1900 enrolled patients, the primary composite endpoint (death, MI, or stroke) was lower in patients treated with CABG versus PCI at 1 year (CABG 18.7% vs. PCI 26.6%; $P = 0.005$), and at 5 years of follow-up (CABG 11.8% vs. PCI 16.8%; $P = 0.004$).¹¹⁵ Differences favoring CABG in death (CABG 10.9% vs. PCI 16.3%; $P = 0.049$) and MI (CABG 6.0% vs. PCI 13.9%; $P < 0.001$) at 5 years largely drove this result. Moreover, the incidence of repeat revascularization at 1 year after initial revascularization was significantly higher with PCI versus CABG (12.6% vs. 4.8%; $P < 0.01$). However, stroke risk was conversely higher in the CABG group (5.2% vs. 2.4%; $P = 0.03$), and CV mortality did not differ. Challenging contemporary generalizability, first-generation DES (sirolimus-eluting stent [SES] 51% and PES 43%) were used, and relatively low proportions of women (28.6%), patients with EF less than 40% (2.5%), and patients with less advanced CAD (SYNTAX score < 22 ; 35.5%) were enrolled.¹¹⁵ A collaborative, individual patient data pooled analysis of 11,518 patients with multivessel or LM CAD randomized to CABG or PCI with stents, demonstrated significantly lower all-cause death after CABG versus PCI,¹¹⁷ a finding evident in patients with DM (10.7% vs. 15.7%, respectively; $P = 0.0001$) but not in patients without DM. Consequently, overall current evidence continues to favor CABG as the revascularization modality of choice for patients with DM and multivessel disease.

Based on these trials, the 2014 ACC/AHA guideline upgraded its previous recommendation in favor of CABG over PCI from class II (A) to class I (A) in patients with DM and stable CAD,¹¹⁸ in particular if a left inferior mammary artery (LIMA) graft can be anastomosed to the left anterior ascending (LAD) artery, provided the patient is otherwise a good candidate for surgery. Similarly, the 2019 ESC Guidelines on Diabetes, prediabetes and CVD recommend CABG over PCI in patients with DM and triple-vessel disease. Both CABG and PCI receive a class I recommendation for patients with two-vessel disease with proximal LAD stenosis or left main stenosis with low complexity.¹⁰

HEART FAILURE IN THE PATIENT WITH DIABETES

Scope of the Problem

Diabetes independently predicts HF risk,¹¹⁹ with an associated twofold to fivefold increased risk^{7,120,121} (see Part VI, Heart Failure). Once HF is present, DM portends an especially adverse prognosis for subsequent morbidity and mortality.⁷ In patients with DM and prevalent ASCVD observed in a registry over 4 years, HF at baseline independently associated with increased CV death (HR_{adjusted}

2.5; 95% CI 2.2 to 2.8).¹²¹ Even with state-of-the-art HF therapy like in the PARADIGM HF trial, 21% of all patients had died after median follow-up of 27 months, significantly more compared with patients without DM and a normal HbA_{1c}.¹²²

Mechanistic Considerations

Patients with and without DM share common causes of HF, such as ischemic heart disease, hypertension, left ventricular hypertrophy, and AF. Yet, these common risk factors do not completely account for the incremental HF risk with DM,¹¹⁹ suggesting increased myocardial vulnerability in the setting of DM and probable synergistic effects between such factors and DM that increase HF risk,⁷ yielding the concept of “the ominous octet” of common conditions in DM that may underpin HF risk (Fig. 31.11).

Ischemic Heart Disease and Hypertension

Ischemic heart disease remains the principal risk factor for HF in DM patients. Contributors to this increased risk may include increased disease burden, prevalence of silent or atypical symptoms of ischemia delaying diagnosis and intervention, suboptimal use of therapeutic interventions, perturbed sympathovagal balance, a prothrombotic milieu, impaired coronary endothelial function, and abnormal myocardial metabolism.⁶⁴ Affecting both atherosclerosis and HF risk, hypertension prevalence exceeds 70% in populations with DM. Among patients with type 2 DM, risk of HF increases 12% to 14% for every increment of 10 mm Hg in systolic BP (see Fig. 31.6).³⁰

MYOCARDIAL METABOLISM AND STRUCTURE

The direct effects of hyperglycemia and insulin resistance on myocardial cellular metabolism may contribute to cardiac dysfunction in DM,⁷ with altered energy-substrate supply and impaired metabolic substrate switching under conditions of stress (see Chapters 46 and 47). The myocardium uses predominantly FFAs under aerobic conditions, but increasingly shifts to glycolysis and pyruvate oxidation during ischemia (eFig. 31.1).^{7,123} In T2DM, increased FFA levels activate PPAR- α , a nuclear receptor that controls transcripts of FFA metabolism, shifting energy metabolism towards anaerobic FFA utilization. Together with increasing insulin resistance, this phenomenon minimizes glucose utilization and makes the heart metabolically less flexible. The dominance of FFA utilization in diabetic hearts contributes to energetic inefficiency by augmenting oxygen demand for FFA oxidation compared to glucose oxidation and by mitochondrial uncoupling with associated deterioration of efficiency of ATP production.¹²³

The Heart in the Diabetes Risk Continuum

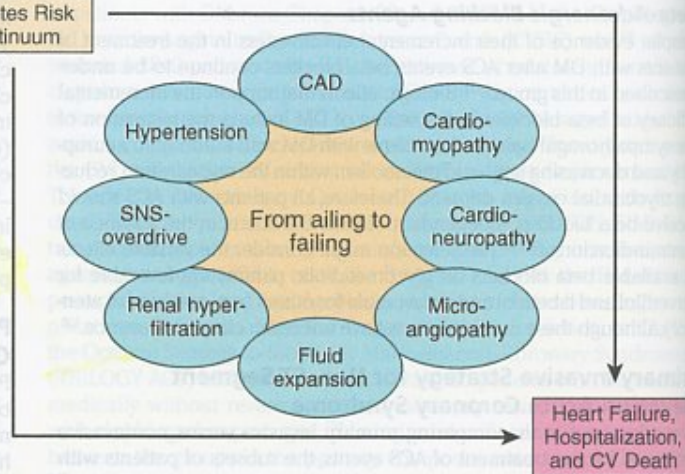


FIGURE 31.11 Heart failure in type 2 diabetes mellitus (DM): the ominous octet—multiple comorbidities commonly associated with type 2 DM that individually and in aggregate contribute to the increased risk for heart failure in such patients. CAD, Coronary artery disease; CV, cardiovascular; SNS, sympathetic nervous system. (From Standl E, Schnell O, McGuire DK. Heart failure considerations of antihyperglycemic medications for type 2 diabetes. *Circ Res*. 2016;118:1830–1843.)

Diabetes causes a variety of morphologic changes in the myocardium, with abnormalities in myocytes, extracellular matrix (ECM), and microvasculature.⁷ Whereas such abnormalities are usually present across causes of cardiomyopathy, they tend to be more common and severe in the setting of DM. In addition, more specific to DM, the myocardial accumulation of AGEs, including macromolecules nonenzymatically modified by glucose, the formation and accumulation of which depend on the severity of hyperglycemia, may contribute to HF risk. Deposition of AGEs within the myocardial ECM adversely affects both systolic and diastolic cardiac function, largely attributable to AGE cross-linking of matrix collagen.

Prevention and Management of Heart Failure in Diabetes

In general, drug therapies for HF generally have similar if not better efficacy in patients with compared with those without DM (see Part VI).

Therapy of Heart Failure with Preserved Ejection Fraction in Diabetes

There is currently no therapy proven to improve the prognosis of patients with HFpEF. The main goal of therapy is to preserve left ventricular function and treat comorbidities such as COPD, hypertension, obesity, AF, and risk for CKD, and consider treatment with RAAS blockers.

Therapy of Heart Failure with Reduced Ejection Fraction in Diabetes

Modulation of the Renin-Angiotensin-Aldosterone System

In patients with DM, meta-analysis of the effects of ACE inhibitors demonstrates a trend to reduce incident HF (RR, 0.87; 95% CI 0.72 to 1.06),³⁰ and in patients with moderate to severe systolic dysfunction, they significantly reduce mortality (RR, 0.84; 95% CI 0.7 to 1.0).^{124,125} numerically similar findings to patients without DM. Likewise, meta-analysis of placebo-controlled trials show reduced incident HF with ARBs (HR, 0.70; 95% CI 0.59 to 0.83).³⁰ Therefore, ACE inhibitors should be first-line agents for the prevention and treatment of HFpEF in patients with DM, with ARBs as alternatives for patients intolerant of ACE inhibitors.^{124,125}

The effect of aldosterone antagonists (e.g., spironolactone, eplerenone) in patients with DM and HFpEF has not been extensively studied. EPHESUS (see above) showed efficacy of eplerenone in the DM subset of 2122 patients. Thus all patients with DM and acute MI with reduced EF should receive eplerenone, except in the presence of contraindications such as kidney dysfunction or hyperkalemia.^{93,96,124}

Angiotensin Receptor-Neprilysin Inhibition (See Chapter 50)

PARADIGM HF compared sacubitril/valsartan to enalapril in patients with HFpEF.¹²⁶ The trial enrolled 8442 patients with class II to IV HF and with EF of 40%. Overall, sacubitril/valsartan significantly reduced the risk for composite outcome of HF hospitalization and CV death (HR, 0.80; 95% CI 0.73 to 0.87), death from any cause (HR, 0.84; 95% CI 0.76 to 0.93), and CV death (HR, 0.80; 95% CI 0.71 to 0.89). In the subset of 2907 patients with DM at baseline (39.4%), sacubitril/valsartan versus enalapril had comparable efficacy on the composite of HF hospitalization and CV death as observed in the overall trial, but there was heterogeneity of the effect on CV death. Morbidity seems to be improved by sacubitril/valsartan over enalapril in patients with or without DM, but there is no clear mortality benefit of sacubitril/valsartan over enalapril in patients with DM. Sacubitril/valsartan therapy led to a greater reduction in HbA_{1c} levels and a lower rate of insulin initiation over 3 years of follow-up compared with enalapril in patients with DM.¹²⁷

Beta Blockers

Beta blockers and diuretic medications significantly reduce incident HF among patients with DM.³⁰ In addition, some beta blockers have demonstrated benefit independent of DM status in the setting of HFpEF (see Chapter 50).¹⁰

Heart Failure Considerations for Glucose Management Strategies and Antihyperglycemic Medications

Poor glycemic control is associated with risk of HF in patients with DM, with a stronger association in women than men. Whether dysglycemia is causal or simply an associated marker of underlying CVD risk remains uncertain. No trials to date have rigorously assessed the effect of targeting glucose control to any specific therapeutic levels, or the comparative effect of existing therapies alone or in combination with regard to their influence on major adverse HF events.⁷ Meta-analyses of available data, however, demonstrate no significant effect of more versus less aggressive glucose control on the risk for HF. Therefore, the role of glucose control in the prevention and treatment of HF is unclear. It is therefore reasonable (as it is with other life-limiting comorbidities) to consider more liberal glycemic targets for patients with DM and advanced HF, such as HbA_{1c} target of less than 8% with the avoidance of hypoglycemia.⁴¹

Some specific considerations warrant attention with regard to drugs and strategies used to treat hyperglycemia in the setting of HF.⁷ Avoidance of hypoglycemic episodes has particular importance in patients with DM and HFpEF, since the stress response to hypoglycemia stimulates the neurohormonal axis implicated in HF pathophysiology. Cautions regarding the use of metformin in the setting of HF were removed in 2006 on the basis of data showing no incremental risk for lactic acidemia,^{43,44} and potential clinical benefit. The product label did retain a caution for use specifically in the setting of acute or decompensated HF. The best available evidence supports consideration of metformin in patients with stable and compensated HF, especially in the context of the available CVD outcomes data, low risk of hypoglycemia, low cost, and favorable tolerability profile. Limited data exist about the use of sulfonylureas in the setting of HF but so far, there are no data suggesting an increased risk of HF hospitalization in patients treated with sulfonylurea. The CAROLINA randomized trial showed similar HF hospitalization risk for glimepiride compared with linagliptin, the later having demonstrated neutrality for HF outcomes versus placebo in the CARMELINA trial.^{45,128}

Thiazolidinedione medications have a propensity to increase plasma volume and to precipitate incident or worsening HF; their use requires caution in patients with any degree of HF, and they are contraindicated in patients with NYHA class III or IV HF.¹²⁹ Data from the aforementioned IRIS trial, however, suggest that with dose reduction/titration, pioglitazone may be used safely without increasing HF risk.⁵⁷

Various cardiovascular outcome trials have assessed the effect of DPP4 inhibitors in patients with DM and high cardiovascular risk. As discussed above, SAVOR-TIMI 53 found that saxagliptin leads to an increased risk for HF hospitalization.¹³⁰ TECOS (sitagliptin) and CARMELINA (linagliptin) showed no such effect.^{64,128} Alogliptin demonstrated a non-significant trend towards an increased HF hospitalization in the EXAMINE trial.⁶² These data suggest that the increase in HF risk is not a class effect of the DPP4 inhibitors, but rather limited to saxagliptin.

As noted previously, SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin) significantly reduced HF hospitalization in placebo-controlled CVOTs in patients with prevalent ACSVD or with risk factors. A meta-analysis of data from six trials of the four available SGLT2 inhibitors demonstrated a highly consistent significant reduction of risk for hospitalization for HF, irrespective of a history of HF at baseline and similar for those with established ASCVD or multiple risk factors (Fig. 31.12).⁸⁶ Data from the DAPA-HF and the EMPEROR-Reduced trials suggest that the beneficial effect of SGLT2 inhibitors in HFpEF extends to HF patients without DM.^{120,131,132} The underlying mechanism of the beneficial effects of SGLT2 inhibitors on HF-related endpoints remain unclear, but may include plasma volume reduction without neurohumoral activation seen with traditional diuretics, effects on cardiac energetics through altered metabolic fuel supply, or direct effects on cardiac function through alterations in mitochondrial ion channels.^{7,79,133,134} Insulin therapy remains an option in patients who fail to achieve benefit with conventional oral glucose-lowering therapies, although some concern persists based on the plausibility that insulin may exacerbate signs and symptoms of HF by increasing renal sodium reclamation, contributing to increased intravascular volume.⁷ In the ORIGIN trial, patients randomly assigned to receive insulin glargine versus usual care tended to have fewer hospitalizations for HF, although this

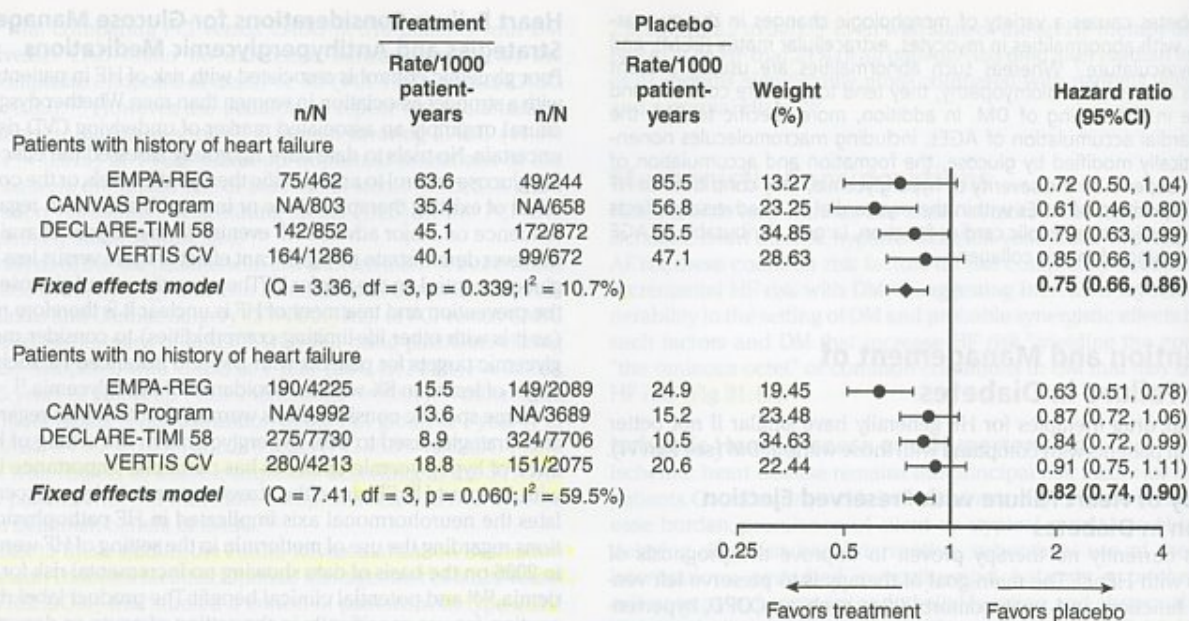


FIGURE 31.12 Meta-analysis of SGLT2 inhibitor cardiovascular (CV) outcome trials (EMPA-REG OUTCOME, CANVAS, DECLARE, and VERTIS CV) with outcome hospitalization for heart failure (HF), stratified by the presence or absence of heart failure at baseline. Hazard ratios (individual and fixed effects model) represent the comparisons of the incidence rates in the active therapy versus the placebo groups. (From McGuire DK. Metaanalysis Placeholder. 2020.)

Drug	Effect on heart failure	
Thiazolidinediones/Glitazones	Unfavorable	● ○ ○
DPP4 inhibitors	Saxagliptin: unfavorable	● ○ ○
	Sitagliptin, Alogliptin, Linagliptin: neutral	○ ● ○
GLP-1 receptor agonists	Lixisenatide, Liraglutide, Semaglutide, Exenatide: neutral	○ ● ○
Insulin	Neutral	○ ● ○
Sulfonylureas	Neutral	○ ● ○
Alpha-Glucosidase inhibitors	Acarbose: neutral	○ ● ○
Metformin	Neutral; potentially beneficial	○ ○ ●
SGLT2 inhibitors	Empagliflozin, Canagliflozin, Dapagliflozin, Ertugliflozin: beneficial	○ ○ ●

FIGURE 31.13 Effect of antidiabetic drugs on heart failure. (From Schütt K, Marx N. Heart failure and diabetes: management and open issues. *Herz*. 2019;44:203–209.)

difference was not statistically significant (4.9% vs. 5.5%; $P = 0.16$). Therefore, in patients with HF who fail to achieve acceptable HbA_{1c} targets with oral agents, insulin remains an acceptable option, if prescribed with caution to avoid hypoglycemia.⁷ GLP-1 RAs lower blood glucose along and weight and BP as well.⁷⁴ The reduction of cardiovascular endpoints in the GLP-1 RA trials most likely resulted from reduced atherosclerosis-related events. GLP-1 RAs had neutral effects on HF hospitalization within each trial, but meta-analyses revealed a modest but significant 9% RRR. Two randomized trials of liraglutide versus placebo in patients with HFREF with or without DM, failed to demonstrate benefit and each had trends toward worse outcomes with liraglutide, so some caution is warranted with regard to GLP-1 RA use in moderate to severe HFREF until further data are available.¹³⁵

In summary, HF is common among patients with DM and associates with a worse prognosis; numerous abnormalities associated with DM may contribute to the increased HF risk.⁷ HF therapy in patients with or without DM generally does not differ except with respect to the

choice of antihyperglycemic agents. Thiazolidinediones and saxagliptin should be avoided, while HF patients should receive SGLT2 inhibitors preferentially. Other drugs, like metformin, SUs, insulin, and GLP-1 RA seem to be safe in most patients with DM and HF and can be used if intensification of glucose lowering is required (Fig. 31.13).¹³⁶

Atrial Fibrillation

Type 2 DM associates independently with AF and aggravates risk for stroke and systemic thromboembolism,^{8,137} resulting in guideline recommendations for systemic anticoagulation for all patients with DM who have AF.¹⁰ Although warfarin has historically been the mainstay of systemic anticoagulation for AF, the direct oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban now offer alternatives. For

each therapy, the sub-analyses of efficacy and safety for patients with DM participating in the pivotal registration trials of these medications suggest similar or even favorably amplified benefit/risk balance.^{8,10} In fact, with similar RRRs with the novel agents versus warfarin and the greater absolute risk for stroke observed in each trial, patients with versus without DM have more favorable NNT for benefit.

SUMMARY AND FUTURE PERSPECTIVES

Overall, DM increases risk for CVD events, notably ASCVD, HF, and AF. Virtually all the recent advances in the care of patients at risk for CVD complications apply to patients with DM, with similar or even greater benefit in this high-risk population. Nonetheless, the gradient of risk associated with DM persists. Further progress requires continued efforts in two areas: first, increased and optimal application of the

existing evidence for CVD risk reduction has paramount importance, with studies consistently demonstrating a substantial gap between the accumulated evidence and its application in patients with DM. Second, continued investigation into specific therapies and strategies targeting the unique risks for CVD associated with DM remains a critical global public health imperative. In that light, largely driven by the regulatory evolution toward requiring CVD safety and efficacy evaluations for all antihyperglycemic medications developed for DM management, a proliferation of randomized CV clinical outcomes trials have recently provided us with substantial new information about reducing CV events in high-risk type 2 DM patients. Currently, members of two glucose-lowering medication classes, SGLT2 inhibitors and GLP-1 RA have proven CV benefits.

GUIDELINES

See the Guidelines Tables 31G.1 through 31G.4 in the online chapter.

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