Circulation

AHA SCIENTIFIC STATEMENT

Clinical Management of Stable Coronary Artery Disease in Patients With Type 2 Diabetes Mellitus

A Scientific Statement From the American Heart Association

ABSTRACT: Although cardiologists have long treated patients with coronary artery disease (CAD) and concomitant type 2 diabetes mellitus (T2DM), T2DM has traditionally been considered just a comorbidity that affected the development and progression of the disease. Over the past decade, a number of factors have shifted that have forced the cardiology community to reconsider the role of T2DM in CAD. First, in addition to being associated with increased cardiovascular risk, T2DM has the potential to affect a number of treatment choices for CAD. In this document, we discuss the role that T2DM has in the selection of testing for CAD, in medical management (both secondary prevention strategies and treatment of stable angina), and in the selection of revascularization strategy. Second, although glycemic control has been recommended as a part of comprehensive risk factor management in patients with CAD, there is mounting evidence that the mechanism by which glucose is managed can have a substantial impact on cardiovascular outcomes. In this document, we discuss the role of glycemic management (both in intensity of control and choice of medications) in cardiovascular outcomes. It is becoming clear that the cardiologist needs both to consider T2DM in cardiovascular treatment decisions and potentially to help guide the selection of glucose-lowering medications. Our statement provides a comprehensive summary of effective, patient-centered management of CAD in patients with T2DM, with emphasis on the emerging evidence. Given the increasing prevalence of T2DM and the accumulating evidence of the need to consider T2DM in treatment decisions, this knowledge will become ever more important to optimize our patients' cardiovascular outcomes.

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The epidemic of type 2 diabetes mellitus (T2DM), linked to the increased burden of obesity, is projected to affect >600 million patients worldwide in the next 2 decades.[1] T2DM has a major impact on survival and quality of life, especially among patients diagnosed at a younger age.[2] Although all complications of T2DM are important, cardiovascular disease in general and coronary artery disease (CAD) specifically continue to be the leading causes of morbidity and mortality in this group.[3] After steady declines in acute myocardial infarction, stroke, and lower limb amputations among patients with T2DM in the past 15 years, there has been a recent resurgence in these morbid ischemic complications, particularly among young and middle-aged adults.[4] These alarming statistics highlight the urgent need to refocus on aggressive cardiovascular risk reduction in patients living with T2DM, especially in those who already have established CAD. Thus, to improve the longevity and quality of life in patients with T2DM, practice guidelines increasingly recognize the prevention of ischemic events as a key management priority.[5,6]

Significant benefits of comprehensive cardiovascular risk reduction strategies in patients with T2DM have been well documented.[7] However, cardiovascular event rates remain high, even among the patients with well-managed T2DM enrolled in contemporary outcomes trials,[8–10] reinforcing the need for additional tools to reduce this risk further. Fortunately, many such tools have emerged in recent years, including advances in anticoagulation and antiplatelet management,[11,12] novel lipid-modifying therapies,[9,13–15] and glucose-lowering agents with potent cardiovascular benefits.[8,10,16–19] Despite this compelling evidence and the plethora of newly available risk-reduction strategies, their adoption in clinical practice has been slow, and large gaps in the quality of care remain.[20] As an example, substantial proportions of patients with T2DM and CAD, including those after an acute coronary syndrome, do not receive therapies with proven cardiovascular benefit such as high-intensity statins, dual antiplatelet therapy, angiotensin converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), and glucose-lowering agents with proven cardiovascular benefits.[21] Although the cost of medications and patient adherence are important considerations that predispose to these gaps, failure to adopt guideline-based recommendations remains a major underlying factor.

These gaps in care highlight a critical opportunity for cardiovascular specialists to assume a more active role in the collaborative care of patients with T2DM and CAD, with the goal of multifactorial risk reduction.[22] Given the availability of many effective tools and the emerging focus on value-based care and population risk management, the time has never been more optimal for this paradigm to be successfully implemented.

MANAGEMENT OF STABLE CAD

Antiplatelet Therapy

Among the factors contributing to an elevated cardiovascular risk in patients with T2DM is a generalized prothrombotic state[23,24] attributable to altered coagulation and platelet function (Table 1).[25,26] Both hyperglycemia and hyperinsulinemia alter the endothelium,[27] disrupting the normal atheroprotective nitric oxide regulatory environment and encouraging a generalized proinflammatory, vasoconstrictive state predisposing to atherothrombosis.[27–29] In addition, dysregulation of platelet receptor density and signaling effects on adhesion, activation, and aggregation[30] result in enhanced platelet activity[31] and impaired antiplatelet therapeutic effect.[32,33] Increased platelet clearance results in a reduced platelet life span and a relative preponderance of large, immature circulating platelets.[34,35] Increased glycoprotein IIb/IIIa receptor density,[36] along with hyperglycemia-mediated increases in adhesion molecules such as von Willebrand factor, vitronectin, and p-selectin,[37,38] furthers this thrombotic propensity and elevates cardiovascular risk.[26,39]

Aspirin and Clopidogrel

In the setting of this platelet-centric thrombogenic milieu, medical management with antiplatelet therapies has been considered a principal focus of secondary preventive care in T2DM. Unfortunately, responsiveness to aspirin[40] and clopidogrel-based dual antiplatelet therapy[41] may be impaired in the setting of T2DM,[41,42] which is further exacerbated in patients with concomitant chronic kidney disease.[43] Because of the increased platelet turnover in patients with T2DM, the decreased responsiveness to antithrombotic medications be improved somewhat by more frequent and higher dosing regimens,[44–46] although the safety of such alternative regimens is not proven. Clopidogrel alone may be a reasonable option compared with aspirin in stable patients with T2DM and CAD (ie, no stent or acute coronary syndrome in the prior year). In the CAPRIE trial (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events), clopidogrel was superior to aspirin in reducing ischemic events with no excess of bleeding in 19 185 patients with prior myocardial infarction, ischemic stroke, or peripheral artery disease.[47] In the subset of 3866 patients with diabetes mellitus, the benefits of clopidogrel over aspirin were even greater.[48] With the availability of less costly generic versions, clopidogrel can be a useful option for secondary prevention, especially in patients with T2DM. Long-term therapy with clopidogrel in addition to aspirin is also an option in select patients with stable CAD and T2DM, with the understanding that there is a balance between decreasing ischemic risks and increasing bleeding

Table 1. Management of Stable CAD

Antithrombotics		
Underlying issue: T2DM is a generalized prothrombotic state caused by both altered coagulation and altered platelet function.		
Aspirin alone	Lowest risk of bleeding but high residual platelet reactivity increases cardiovascular risk	
Clopidogrel alone	Decreased cardiovascular risk without meaningfully increased risk of bleeding vs aspirin alone	
Aspirin+clopidogrel/ticagrelor	Decreased cardiovascular risk with increased risk of bleeding; targets patients with additional risk factor and low risk of bleeding (use risk scores)	
Aspirin+low-dose rivaroxaban	Decreased cardiovascular risk with increased risk of bleeding; targets the aberrant coagulation with T2DM	
Blood pressure		
Underlying issue: Coexisting hypertension increases the risk of MI, stroke, and all-cause mortality.		
Target blood pressure	<140/90 mm Hg in most patients; consider <130/80 mm Hg if additional risk factors for stroke or microvascular complications	
ACE inhibitor/ARB	First-line therapy because of decreased cardiovascular risk with CAD	
Long-acting thiazide diuretic	Good cardiovascular risk reduction but slight increase in glucose	
Calcium channel blockers	Good cardiovascular risk reduction and effective antianginal	
Aldosterone antagonists	Particularly effective in patients with prior MI or LV dysfunction	
β-Blockers	Do not reduce mortality in uncomplicated patients with stable CAD; choose vasodilating β-blocker for less adverse metabolic impact	
Lipids		
Underlying issue: Atherogenic lipid anomalies include hypertriglyceridemia, low HDL-C, and small, dense LDL particles.		
High-intensity statins	Cornerstone of lipid therapy and secondary prevention	
Ezetimibe and PCSK9 inhibitors	Additional cardiovascular risk reduction when LDL is >70 mg/dL despite maximally tolerated statins	
Niacin	Not recommended	
Fibrates	Recommended when triglycerides are very high (eg, >500 mg/dL) to reduce the risk of pancreatitis	
Icosapent ethyl	Consider for further cardiovascular risk reduction when triglycerides remain elevated (>135 mg/dL) despite maximally tolerated statin	
Glycemic control		
Underlying issue: Hyperglycemia increases cardiovascular risk, but impact of glucose-lowering therapies on outcomes is complex, and therapy needs to be individualized.		
Glycemic target	<7.0% if young and healthy (life expectancy >10–20 y); depends on preferences and capacity <8.0% or 8.5% for older patients with comorbidities or at high risk for hypoglycemia; depends on preferences, capacity, and types of treatment used	
Glucose-lowering medications	Cardiovascular effects	Noncardiovascular effects
Metformin (usually first line)	Cardiovascular benefit possible (low-quality evidence)	No associated weight gain or hypoglycemia
SGLT2 inhibitors	Cardiovascular benefit (largely consistent among individual drugs); reduction in MACEs and heart failure hospitalizations	Associated with weight loss, no hypoglycemia, lower blood pressure, and less progression of CKD
GLP-1 receptor agonists	Cardiovascular benefit; reduction in MACEs (some inconsistency among individual drugs)	Associated with weight loss and no hypoglycemia
Thiazolidinediones	Likely cardiovascular benefit (but not heart failure)	No hypoglycemia; associated with weight gain, edema, risk of heart failure, and bone fractures
DPP4 inhibitors	Neutral effect on cardiovascular outcomes	No associated weight gain or hypoglycemia
Insulin and sulfonylureas	Likely neutral effect on cardiovascular outcomes	Associated with weight gain and hypoglycemia

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CKD, chronic kidney disease; DPP4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LV, left ventricular; MACE, major adverse cardiovascular event; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; SGLT2, sodium-glucose cotransporter 2; and T2DM, type 2 diabetes mellitus.

risks.[49] Given the competing risks and benefits, we recommend targeting long-term dual-antiplatelet therapy to those patients with additional high-risk markers (eg, prior myocardial infarction, younger age, tobacco use) with use of a risk calculator[23] along with shared decision-making.

Ticagrelor

Extending the previously documented risk reduction benefit of ticagrelor in patients after myocardial infarction,[50–52] THEMIS (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study)[53] compared dual antiplatelet therapy with

aspirin and low-dose ticagrelor versus aspirin alone among 19 271 patients with T2DM and CAD but without a history of myocardial infarction or stroke. Patients randomized to ticagrelor had a lower risk of the composite of cardiovascular death, myocardial infarction, or stroke over an average follow-up of 40 months (ticagrelor versus placebo: 7.7% versus 8.5%; P=0.04), whereas the incidence of TIMI (Thrombolysis in Myocardial Infarction) major bleeding was higher (2.2% versus 1.0%; P<0.001).[54] Notably, the efficacy and net clinical benefit of ticagrelor were more favorable among patients from THEMIS who had a history of percutaneous coronary intervention (PCI).[55]

Rivaroxaban

The COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies)[56–59] examined whether rivaroxaban improved cardiovascular outcomes in 27 395 patients with stable atherosclerotic vascular disease. Three strategies were tested: rivaroxaban 2.5 mg twice daily plus aspirin, rivaroxaban 5 mg twice daily, and aspirin alone (note that patients requiring dual antiplatelet therapy were excluded). The risk of major adverse cardiovascular events (MACEs) was significantly lower with the combination of rivaroxaban plus aspirin compared with either aspirin alone or rivaroxaban alone. There was an associated increased risk of bleeding with rivaroxaban, although no significant excess in fatal bleeding was noted. The ischemic benefits of rivaroxaban were consistent in the subgroup with diabetes mellitus, suggesting that low-dose anticoagulation added to antiplatelet therapy may be another option for secondary prevention in patients with T2DM and stable CAD.

Platelet Function Testing

T2DM exacerbates cardiovascular risk, inhibiting vascular protective mechanisms and encouraging a thrombotic propensity. Unfortunately, although long-established therapeutics such as aspirin and clopidogrel have shown benefit in reducing recurrent ischemic events, a high proportion of patients continue to have high on-treatment platelet reactivity, making these treatments less effective. Despite initial enthusiasm, multiple large, randomized studies have failed to show any clinical benefit when antithrombotic regimens are adjusted on the basis of platelet function testing.[60–62] Given the greater relative risk (RR) associated with T2DM, antithrombotic therapies have potential to provide greater absolute benefit in these patients. The continued evolution of more potent antiplatelet agents and therapeutic regimens has demonstrated promise in reducing risk and preserving safety in a much broader population of patients with T2DM.

Blood Pressure Control

The prevalence of hypertension in patients with T2DM is ≈2-fold greater than in the general population, with the vast majority of patients with T2DM (70%–80%) having concomitant hypertension.[63] Because both hypertension and T2DM increase with age, it is expected that the prevalence of both conditions will continue to increase in the coming decades as a result of increasing life expectancy. The presence of hypertension in patients with T2DM significantly increases the risk of myocardial infarction, stroke, and all-cause mortality.[63,64] Epidemiological observations have demonstrated that there is a progressive increase in the risk of macrovascular and microvascular events with increasing levels of systolic blood pressure starting at 115 mm Hg.[63–65]

Blood Pressure Target

Similar to the overall primary and secondary prevention cohorts, the optimal blood pressure target for patients with T2DM has been debated, with guideline recommendations changing over time. Early interventional randomized trials showed benefit of aggressive blood pressure reduction in reducing the increased risk of both macrovascular and microvascular events in patients with T2DM.[63] Despite the fact that achieved blood pressures in the aggressive intervention arms of these studies were never <140 mm Hg, previous guidelines recommended a target blood pressure <130/80 mm Hg (and <120/75 mm Hg in those with renal impairment) in patients with T2DM largely on the basis of these trials.[64,65] However, subsequent trials that specifically examined the role of a blood pressure lowering strategy to <130 mm Hg in patients with T2DM and hypertension found no substantive benefit of intensive blood pressure control in reducing the risk of coronary events, although there was evidence for decreased risk of stroke.[5,66–69] The observed stroke reduction is consistent with observational data that have shown a linear relationship between systolic blood pressure and risk of stroke, with a decrease in stroke risk with lowering of systolic blood pressure to levels <120 mm Hg.[64,65] As a result of these studies, most society guideline statements changed their recommendations to a blood pressure target <140/90 mm Hg for patients with T2DM, with the consideration of a goal of <130/80 mm Hg in select high-risk patients when it can be achieved without harm.[5,70]

Intensive blood pressure control has again emerged as potentially beneficial in reducing cardiovascular risk due to SPRINT (Systolic Blood Pressure Intervention Trial), in which there was a notable 25% relative/0.5% absolute reduced risk per year of cardiovascular morbidity and mortality with intensive (<120 mm Hg) as compared with standard (<140 mm Hg) systolic blood pressure control

in patients with hypertension and high cardiovascular risk.[71] Importantly, at least in part due to the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes),[72] patients with T2DM were explicitly excluded from SPRINT, so it is difficult to determine whether the results of SPRINT can extend to patients with T2DM and CAD. There was evidence of benefit of intensive blood pressure lowering in the prediabetes cohort of SPRINT,[71] a subsequent meta-analysis,[73] and a recent large observational study (13% with diabetes mellitus).[73a,74]

It is important to recognize, however, that there are also potential risks of intensive blood pressure reduction (which generally requires multiple antihypertensive drugs).[63–65,69,72,75,76] Excessive blood pressure lowering in patients with concomitant CAD (especially in the presence of left ventricular hypertrophy or dysfunction) can potentially increase the risk of myocardial infarction due to a drop in coronary perfusion pressures across the diseased segments of the coronary arteries secondary to impairment of coronary autoregulation.[64–68] Indeed, data from the INVEST (International Verapamil SR Trandolapril Study), CLARIFY (Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease), ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial), and TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease) studies showed that systolic blood pressure of <120 mm Hg and diastolic blood pressure <70 mm Hg were associated with adverse cardiovascular outcomes except for reduced risk of stroke in those achieving lower blood pressure values.[66–68]

There remains controversy regarding the level of blood pressure target that provides optimal cardiovascular protection in patients with T2DM and coexistent CAD. The 2017 Hypertension Clinical Practice Guidelines recommended a goal blood pressure <130/80 mm Hg in patients with T2DM.[76] However, as described above, such targets might not be optimal for all patients with T2DM and coexistent CAD.[5,63–69,77] There appears to be heterogeneity in the impact of intensive blood pressure lowering on coronary versus cerebral events, and the effects can also vary based on comorbid conditions (eg, recent acute coronary syndrome).[64,65,76] As such, while all patients with T2DM and CAD certainly benefit from a blood pressure of <140/90 mm Hg,[5,63–66,76] lower blood pressure targets of <130/80 mm Hg are likely appropriate for many patients—particularly those at higher risk of stroke (eg, black and Asian patients, those with cerebrovascular disease) and other microvascular complications such as chronic kidney disease.

Choice of Antihypertensive Agents

The choice of antihypertensive agents rests on a number of factors: efficacy in blood pressure reduction (only small differences between classes, on average[78]), side-effect profile, cost and convenience (ie, dosing schedule), and off-target effects. In patients with T2DM and CAD, the last consideration can make drug selection more challenging. In the absence of other considerations, ACE inhibitors/ARBs should be considered first-line treatment for hypertension in patients with T2DM and CAD. ACE inhibitors/ARBs reduce the progression of kidney disease in patients with albuminuria (urine albumin-to-creatinine ratio ≥30 mg/g)[5] and reduce the risk of both incident and recurrent atherosclerotic ischemic events.[79,80] In the HOPE study (Heart Outcomes Prevention Evaluation),[81] 3577 people with diabetes mellitus with cardiovascular disease or at least 1 other cardiovascular risk factor but no proteinuria or heart failure were randomized to ramipril versus placebo. The trial was stopped early (after 4.5 years) because of consistent benefit of ramipril, which was shown to reduce the risk of myocardial infarction by 22% (95% CI, 6–36), stroke by 33% (95% CI, 10–50), and cardiovascular death by 37% (95% CI, 21–51), findings that were independent of changes in blood pressure. In particular groups of patients with CAD—after myocardial infarction[81,82] and with reduced ejection fraction[83,84]—ACE inhibitors/ARBs are even more important.

The majority of patients with hypertension and T2DM will require >1 antihypertensive medication to control blood pressure (in the standard care arm in ACCORD, 30% required 2 and 39% required ≥3 antihypertensive medications[70]). The American Diabetes Association guidelines recommend thiazide-like diuretics (preferably long-acting agents such as chlorthalidone or indapamide) or dihydropyridine calcium channel blockers. Thiazide diuretics are well known to worsen glycemic control through a reduction in both insulin sensitivity and secretion,[85–88] although the clinical implications of this effect are still questioned, given the favorable cardiovascular outcomes in blood pressure trials with these agents.[86] Mineralocorticoid receptor antagonists (spironolactone, eplerenone) can also be effective antihypertensive agents (particularly for those with borderline or low potassium levels)[89] and are important for morbidity and mortality reduction in patients with left ventricular dysfunction.[90,91]

The issue with β-blockers is more complicated. In the setting of primary prevention, β-blockers are generally less preferred compared with ACE inhibitors/ARBs, long-acting thiazide diuretics, and dihydropyridine calcium channel blockers.[92,93] However, many patients with CAD have indications for β-blockers other than just blood pressure reduction. Patients who have had a myocardial infarction and those with chronic

angina, left ventricular dysfunction (ejection fraction <40%), or arrhythmias all benefit from β-blockers. β-Blockers reduce myocardial oxygen demand and are often considered a part of optimal medical therapy (OMT) for all patients with CAD. For the indication of stable coronary disease in the absence of left ventricular dysfunction, β-blockers have not been shown to reduce the risk of mortality or myocardial infarction.[94] Furthermore, the benefit of long-term use of β-blockers after myocardial infarction has been questioned, with the best evidence showing that the benefit is limited to the first 30 days.[95] Thus, β-blockers as antihypertensive agents should be targeted to patients with clear indications such as angina or to those who require additional blood pressure lowering beyond other agents. Furthermore, it is optimal to select a β-blocker with a concomitant vasodilatory effect (eg, carvedilol, labetalol), which will have fewer adverse metabolic effects.[96–98]

Lipid Management

Cardiovascular risk in T2DM is considerably elevated, at least in part as a result of the proatherogenic milieu of diabetic dyslipidemia that arises primarily from a deranged lipoprotein profile.[99] Typical lipid anomalies in T2DM include hypertriglyceridemia, which promotes the presence of small, dense low-density lipoprotein (LDL) particles; reduced levels of high-density lipoprotein cholesterol caused by enhanced high-density lipoprotein cholesterol catabolism; and a predominance of large very LDL particles resulting from a synthesis-catabolism imbalance.[100] LDL cholesterol (LDL-C) levels in individuals with T2DM are often similar to those in individuals without T2DM, but the persistent hypertriglyceridemic state promotes LDL oxidation, and the concurrent hyperglycemia drives LDL glycation, all of which increase the atherogenicity of the LDL particles in T2DM.[100] Other lipid abnormalities that may be present in diabetic dyslipidemia are detailed in Table 2.[101]

Statins

Although healthy lifestyle habits remain a cornerstone of T2DM management, trial data have confirmed the additional benefits of statin therapy in the primary and secondary prevention of CAD.[13,102–112] A large body of evidence indicates that statin-based strategies convey similar LDL-C lowering and relative cardiovascular risk reduction in patients with and those without T2DM.[102–112] However, because of the higher underlying risk of patients with T2DM, statins often result in greater absolute risk reduction. Among the 20 536 adults in the HPS (Heart Protection Study), which tested once-daily 40 mg simvastatin (versus placebo) in a mix of primary and secondary prevention patients, 5963 participants had diabetes mellitus (615 with type 1 diabetes mellitus), and 3982 had both diabetes mellitus and CAD.[108] The diabetes mellitus subanalysis showed that simvastatin was associated with a 22% (95% CI, 13–30) relative decrease in the rate of first major vascular events, regardless of baseline LDL-C levels.[102] In the TNT trial (Treating to New Targets), 10 001 adults with cardiovascular disease were randomized to once-daily 80 mg atorvastatin versus 10 mg atorvastatin,[109] of whom 1051 had diabetes mellitus.[112] Higher-dose atorvastatin was associated with significantly fewer cardiovascular (hazard ratio [HR], 0.85 [95% CI, 0.73–1.00]; *P*=0.044) and cerebrovascular (HR, 0.69 [95% CI, 0.48–0.98]; *P*=0.037) events, with similar risk reduction in those with and those without diabetes mellitus. In the Cholesterol Treatment Trialists' (CTT) Collaboration, which included 90 056 people from 14 randomized statin trials of both primary and secondary prevention (18 686 with diabetes mellitus), there was a 22% RR reduction (RRR) in major coronary events (RR, 0.78 [95% CI, 0.69–0.87]; *P*<0.0001) per 39-mg/dL (1-mmol/L) LDL-C decrease among those with diabetes mellitus,[113] an effect that was indistinguishable for the groups with and without diabetes mellitus.[114]

Multiple studies and meta-analyses have repeatedly shown that statins are associated with a small but significantly increased risk of incident T2DM.[115] This modest risk has been shown to be lower than the risk of incident T2DM associated with thiazide diuretics or nonvasodilating β-blockers[116] and, most important, is far overshadowed by the cardiovascular protective effect of statin therapy.[117,118] Sattar and colleagues[115] reported that although statin treatment for 4 years yielded 1 extra case of T2DM in a group of 255 individuals, 5.4 vascular events were concomitantly prevented. Furthermore, among patients with T2DM, the increase in glucose has also been shown to be rather modest, with an increase in mean glycated hemoglobin (HbA_{1c}) level of 0.12% (95% CI, 0.04–0.20) over a mean follow-up of 3.6 years in a pooled analysis of 9 trials involving

Table 2. Lipid Anomalies in Diabetic Dyslipidemia

High triglycerides and triglycerol-rich lipoproteins
High postprandial triglycerides
High LDL particle number
High small, dense LDL
Low HDL-C
Low small HDL, pre–β-1 HDL, α-3 HDL
Low apolipoprotein AI
High apolipoprotein B
High apolipoprotein C-III
High oxidized and glycated lipids

HDL indicates high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; and LDL, low-density lipoprotein.

9696 participants.[119] Therefore, it is important to recognize that although some patients with T2DM and CAD may be hesitant to take statins for this reason, they should be reassured that despite a potential modest increase in blood sugars, the risk-benefit ratio is clearly in favor of administering statins to people with T2DM and CAD.

Nonstatin LDL-C–Lowering Treatments

Despite their key role in secondary prevention in patients with T2DM and CAD, many patients are unable to tolerate intensive statins because of side effects or do not achieve adequate LDL-C lowering with maximally tolerated statins and need alternative lipid-lowering therapies for secondary prevention. IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) was the first study to demonstrate the benefit of a nonstatin add-on to background statin therapy.[13] Specifically, the addition of 10 mg ezetimibe to 40 mg simvastatin within 10 days of hospitalization for an acute coronary syndrome lowered LDL-C levels by an additional 17 mg/dL (0.4 mmol/L), which was associated with an overall modest, but significant, 2.0% absolute/6.4% relative reduction in the primary composite end point of cardiovascular death, major coronary event, or stroke after a median of 6 years.[13] Of interest is that the ezetimibe-simvastatin combination (versus placebo-simvastatin) lowered the 7-year Kaplan-Meier primary end point event rate in the subcohort with diabetes mellitus by an absolute 5.5% (40.0% versus 45.5%; HR, 0.85 [95% CI, 0.78–0.94]).[120] Furthermore, although the ezetimibe-simvastatin allocation had minimal impact on the incidence of myocardial infarction and stroke among those without diabetes mellitus, the number of these events was significantly lower with ezetimibe-simvastatin treatment in the group with diabetes mellitus ($P_{interaction}$ for myocardial infarction=0.028; $P_{interaction}$ for ischemic stroke=0.031).[120]

The recent availability of the PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors offers new opportunities for managing hypercholesterolemia.[121–124] The FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) randomized 27 564 participants with atherosclerotic cardiovascular disease (11 031 with diabetes mellitus) to either placebo or evolocumab (140 mg every 2 weeks or 420 mg every month) on background statin therapy.[125] In patients with versus without diabetes mellitus, with evolocumab, there were comparable LDL-C reductions (57% versus 60% mean reductions) and RRRs (27% versus 23% RRR) in the primary composite end point of cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina or revascularization.[9] There were also no increase in incident T2DM and no changes in fasting plasma glucose or HbA_{1c} over the median 2.2 years of follow-up.[9]

In the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), 18 924 adults with a recent acute coronary syndrome (5444 with diabetes mellitus) were randomized to either alirocumab every 2 weeks or placebo in addition to maximally tolerated statin therapy.[126] Alirocumab was then titrated between 75 and 150 mg to maintain LDL-C levels between 25 mg/dL (0.65 mmol/L) and 50 mg/dL (1.3 mmol/L). The combination of alirocumab and statins resulted in an absolute risk reduction for time to first MACE of 2.3% in the group with diabetes mellitus relative to 1.2% for those without diabetes mellitus.[14] Although neither PCSK9 inhibitor reduced cardiovascular mortality in these trials,[125,126] the cumulative data from the FOURIER and ODYSSEY OUTCOMES trials suggest that PCSK9 inhibitors effectively lower LDL-C and cardiovascular risk in individuals with CAD regardless of diabetes mellitus status.

The reporting of IMPROVE-IT, FOURIER, and ODYSSEY OUTCOMES also supports the 2010 CTT suggestion that "lower is better" when it comes to LDL-C and cardiovascular risk reduction.[127] This CTT meta-analysis of 26 randomized trials with 170 000 participants had determined that every 39-mg/dL (1.0 mmol/L) reduction in LDL-C culminated in a 10% decrease in all-cause mortality (RR, 0.90 [95% CI, 0.87–0.93]; $P<0.0001$) that was driven primarily by diminished cardiac-related deaths.[127] The proposed linear correlation between LDL-C lowering and cardiovascular risk reduction, coupled with the limited long-term safety data on very low LDL-C levels (<25 mg/dL or 0.65 mmol/L), supports the notion of aiming for low LDL-C levels, especially in those patients with the highest absolute risk of a recurrent event (eg, T2DM, peripheral artery disease, recent incident of acute coronary syndrome, and multiple prior cardiovascular events), but not at the expense of elevating the risk of adverse events.[127]

The evidence to date supports an LDL-C–lowering strategy to reduce the risk of subsequent cardiovascular events in individuals with T2DM and CAD. Accordingly, statins are an essential component in the management of these individuals. However, because patients with both T2DM and CAD represent a high-risk group, additional agents may be needed for LDL-C lowering beyond what is possible with statin monotherapy. In these patients, particularly when LDL-C levels are >70 mg/dL despite maximally tolerated statin, the addition of nonstatin LDL-C–lowering therapies such as ezetimibe and PCKS9 inhibitors should be considered on the basis of the individual's overall cardiovascular risk profile, personal preferences, and drug access.

Non-LDL Target Therapies

Multiple dyslipidemia and cardiovascular risk-lowering trials have tested the combination of a statin with a nonstatin lipid-lowering medication, with often disappointing results. Combinations of statins with fibrates, niacin, or fish oil have thus far generally failed

to demonstrate cardiovascular benefits beyond that achieved with statins alone.[128–132] Of note, when data from several fibrate trials were stratified by lipid profiles, it appeared that individuals with hypertriglyceridemia and low high-density lipoprotein cholesterol levels may have a reduction in cardiovascular risk with the addition of fibrates to background statin therapy.[130,133–135] Furthermore, fibrates or fish oil would be indicated when triglycerides are very high (>500 mg/dL) to reduce the risk of pancreatitis.[5]

REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial) randomized 8179 individuals with either cardiovascular disease or diabetes mellitus and 1 additional risk factor to 2 g icosapent ethyl twice daily or placebo. Patients also had to have triglycerides between 135 and 499 mg/dL (1.5 and 5.6 mmol/L) and LDL-C between 41 and 100 mg/dL (1.1 and 2.6 mmol/L).[15] Overall, there was a significant reduction in the risk of the composite of cardiovascular death, nonfatal myocardial infarction, stroke, coronary revascularization, or unstable angina with icosapent ethyl, an effect that was similar in those with diabetes mellitus (HR, 0.77 [95% CI, 0.68–0.87]) and those without diabetes mellitus (HR, 0.73 [95% CI, 0.62–0.85]). Icosapent ethyl is the first non–LDL-focused lipid therapy to demonstrate cardiovascular benefit and should be considered first-line therapy for patients with T2DM and CAD whose triglycerides remain elevated (>135 mg/dL) despite maximally tolerated statin and lifestyle changes, as now recommended in the American Diabetes Association Standards of Medical Care.[5]

Lifestyle Modification and Weight Management

Lifestyle and health behavior management, including smoking cessation, heart-healthy diet, weight loss (if overweight or obese), sleep and stress management, and exercise/physical activity, is a cornerstone of clinical care for both patients with T2DM and those with CAD. However, there are limited randomized trials for lifestyle and health behavior management in the care of patients with T2DM with comorbid CAD. Instead, evidence to support lifestyle and health behavior management for T2DM and stable CAD has been extrapolated from primary prevention trials and from subgroups of participants with T2DM from studies focusing on the secondary prevention of CAD.[63,136]

Smoking Cessation

Smoking cessation is strongly recommended for all patients with T2DM, regardless of the presence of comorbid CAD.[5] There is robust evidence to support the causal links between cigarette smoking and multiple poor health outcomes.[137–139] In a cohort study of >2600 patients who survived to hospital discharge after a first myocardial infarction, smoking was associated with an increased risk of recurrent events (RR, 1.51 [95% CI, 1.10–2.07] for active smokers compared with nonsmokers).[140] However, smoking cessation can substantially reduce the risk of recurrent CAD events, declining to the level of risk of nonsmokers by ≈3 years after cessation. This benefit of smoking cessation has been shown to be similar for those with and without T2DM.[141] Smoking cessation can be associated with weight gain, which can be particularly problematic in patients with T2DM who may already struggle with obesity and associated insulin resistance. However, data have also shown that weight gain associated with smoking cessation, even among overweight patients with T2DM, does not significantly attenuate the cardiovascular risk reduction observed with smoking cessation.[142]

Diet

The American Diabetes Association Standards of Medical Care in Diabetes dietary guidelines for patients with T2DM emphasize consumption of fruits, vegetables, and low-fat dairy foods.[5] There are no specific recommendations for patients with T2DM and concomitant CAD, primarily because the majority of data on the effects of diet on atherosclerotic outcomes come from primary prevention trials.[7,143,144] The PREDIMED trial (Prevención con Dieta Mediterránea), the largest primary prevention dietary randomized controlled trial to date, randomized 7447 participants at high risk of cardiovascular disease (48.5%; 3614 of 7447 had T2DM) to a Mediterranean diet supplemented with either extravirgin olive oil or mixed nuts versus a control diet.[145] The trial was stopped early because of a 30% reduction in the primary composite outcome of cardiovascular death, myocardial infarction, or stroke observed with the Mediterranean diet, results that were similar in patients with T2DM. There is also evidence that diets rich in low-carbohydrate and low-glycemic-index foods may improve both glycemic control and cardiovascular risk factors.[146,147] The role of low-carbohydrate diets and use of the glycemic index for primary and secondary prevention of CAD warrant further investigation.

Psychosocial Factors and Sleep

Observational data indicate that depression exacerbates the risk of macrovascular complications in people with T2DM. In the REGARDS prospective cohort study (Reasons for Geographic and Racial Differences in Stroke), people with T2DM who reported elevated depressive symptoms or perceived stress had a significantly increased incidence of stroke (HR, 1.57 [95% CI, 1.05–2.33]) and acute cardiovascular disease (HR, 1.57 [95% CI, 1.02–2.40]) over 6 years of follow-up.[148] Similarly, among 1533 people with T2DM in the Denmark arm of the ADDITION study (Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen Detected Diabetes in Primary Care), psychological distress

assessed by the Mental Health Inventory was associated with a 1.8-fold higher risk (95% CI, 1.23–2.53) of having a cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, revascularization, or amputation) compared with a lower Mental Health Inventory score.[149] Whether depression and psychosocial stress increase the risk of adverse atherosclerotic events more in patients with T2DM compared with nondiabetic patients, the mechanisms of these associations,[150] and whether intervention will alter the clinical course of CAD are unknown.

Given its association with obesity, disordered sleep is an underdiagnosed condition among patients with T2DM and significantly contributes to sympathetic activation, inflammation, and endothelial dysfunction.[151] Treatment of obstructive sleep apnea may reduce blood pressure and have other beneficial cardiometabolic effects,[152] despite a lack of clear benefit on cardiovascular outcomes.[153] In addition to obstructive sleep apnea, insufficient or short sleep duration without obstructive sleep apnea has been associated with adverse effects on serum lipids, insulin resistance, and perturbations of the autonomic nervous system associated with CAD.[154]

Physical Activity and Exercise

The American Diabetes Association guidelines recommend that patients interrupt prolonged sitting with light activity every 30 minutes and engage in at least 150 min/wk of moderate to vigorous physical activity.[155] Despite these recommendations, patients with T2DM spend less time engaging in physical activity[156] and have lower exercise capacity compared with those without T2DM,[157,158] factors associated with a higher risk of cardiovascular events.[156,157] Supervised exercise training is preferred to home training because it results in greater improvements in HbA_{1c}, body mass index, waist circumference, blood pressure, exercise capacity, muscle strength, and cholesterol levels.[155,159] Similarly, stable CAD guidelines recommend at least 150 min/wk of moderate to vigorous physical activity and referral at first diagnosis to cardiac rehabilitation, which includes supervised exercise training with a comprehensive secondary prevention program.[160]

Compared with patients without T2DM, patients with T2DM who enroll in cardiac rehabilitation have a greater risk factor burden and lower exercise capacity at baseline, are less likely to complete cardiac rehabilitation, and have a higher mortality.[161–163] Although some studies of exercise-based interventions in patients with T2DM with CAD have demonstrated improvements in exercise capacity,[164] waist circumference,[156] and endothelial function,[165] others have shown no significant improvements in HbA_{1c} or exercise capacity and poor adherence to the intervention.[156,166] However, 1 study of patients with T2DM (n=68, 63% with CAD) randomized to a T2DM-tailored cardiac rehabilitation program or usual care found that the T2DM-focused cardiac rehabilitation program significantly improved blood pressure, waist circumference, exercise capacity, HbA_{1c}, and cholesterol.[167] Furthermore, patients with T2DM who attend cardiac rehabilitation achieve relative improvements in exercise capacity[162,163] and relative reductions in hospitalizations and mortality similar to those in patients without T2DM.[168] Therefore, it is recommended that patients with T2DM and CAD receive individualized T2DM assessment and management as a part of cardiac rehabilitation.[169,170]

Weight Management

Because it is challenging for obese patients with T2DM to lose weight with diet and exercise alone,[171] clinicians should consider referring obese individuals to nutrition or structured weight loss programs.[172] Several weight loss medications of relatively modest efficacy are now available,[172] although safety data in patients with concomitant CAD are limited. The 2 notable exceptions are lorcaserin, which had a neutral effect on MACEs in the CAMELLIA-TIMI 61 study (Cardiovascular and Metabolic Effects of Lorcaserin in Patients Who Have Excess Weight and/or Obesity),[173] and liraglutide, which reduced MACEs in the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), at least in the lower doses used for T2DM.[17] The risks and benefits of pharmacological management of obesity are complex and outside the scope of this statement. Guidelines also recommend consideration of bariatric surgery (sometimes referred to as metabolic surgery),[174] with the most common procedures including Roux-en-y gastric bypass and sleeve gastrectomy. In addition to weight loss, clinical trials of bariatric surgery in patients with T2DM have consistently shown improvement in cardiovascular risk factors, including better glycemic control, lower blood pressure, higher high-density lipoprotein cholesterol, and lower triglyceride levels.[175–177] Although this improvement in cardiovascular risk factors would be expected to translate into a reduction in ischemic events, randomized controlled trials have thus far been inadequately powered to assess cardiovascular events and mortality, although observational studies have consistently shown cardiovascular risk reduction with such procedures.[176,178,179] An observational matched cohort study of 12 264 Swedish patients with diabetes mellitus showed a 58% RRR (HR, 0.42 [95% CI, 0.30–0.57]; $P<0.001$) in all-cause mortality over a median follow-up of 3.5 years with gastric bypass versus control, with 5-year absolute risks of death of 1.8% (95% CI, 1.5–2.2) in the gastric bypass group versus 5.8% (95% CI, 5.0–6.8) in the control group.[180] Despite these potential benefits, bariatric surgery remains underused among eligible patients.[181] Although bariatric surgery has risks,[178] which are likely higher in patients with existing

CAD, it may be another effective tool for cardiovascular risk reduction in the subset of patients with obesity, particularly in those with body mass indexes ≥35 kg/m^2.

Glycemic Control

For several decades, T2DM guidelines instructed clinicians to strictly control blood glucose levels of patients with T2DM to reduce the risk of complications, including heart disease. The prevailing concept was that risk reduction could be achieved by a clinical focus on reaching target values of HbA_{1c}, agnostic to the strategies used. However, 3 major clinical trials of intensive glycemic control (lowering HbA_{1c} levels to <6%–6.5%) demonstrated no reduction in major cardiovascular events compared with less intensive glycemic control in patients with T2DM.[182–184] In contrast, several cardiovascular outcomes trials (CVOTs) demonstrated that drugs that lowered HbA_{1c} to similar levels had different effects on cardiovascular outcomes.[8,10,17,185,186] The results of these studies suggest that the strategy used to achieve glycemic control matters because the total effect of a specific glucose-lowering agent is not conveyed by the degree to which it lowers glucose. This evidence is shifting our previous glucocentric approach to T2DM care toward one that considers the actual method of glycemic management.

Glycemic Targets in Patients With CAD

The first major clinical trial of glycemic control among patients with T2DM was UKPDS (UK Prospective Diabetes Study).[187,188] This trial showed that more intensive glycemic control (achieved median HbA_{1c}, 7.0%) compared with standard treatment (HbA_{1c}, 7.9%) was associated with a reduction in the risk for myocardial infarction (RR, 0.84 [95% CI, 0.71–1.00]) among newly diagnosed patients with T2DM, but this did not reach statistical significance (P=0.052).[187] In the 10-year follow-up of UKPDS, despite the loss of differences in HbA_{1c} levels between the 2 groups by 1 year, the risk of myocardial infarction was lower among patients originally randomized to intensive glycemic control (RR, 0.85 [95% CI, 0.74–0.97]).[189] Notably, the study was conducted before the widespread use of cardioprotective therapies such as statins and renin-angiotensin system inhibitors, and it excluded patients with long-standing T2DM or those with a myocardial infarction in the prior year. Nevertheless, the findings suggest that glycemic control, if instituted early in the course of T2DM, may lower the risk of cardiovascular events, but the effect is modest.

Subsequent clinical trials of intensive versus standard glycemic control among patients with long-standing T2DM and with multiple risk factors for cardiovascular disease did not show similar benefits.[182–184] These trials included a substantial proportion of patients with established macrovascular disease (ACCORD, 35.2%; ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation], 32.3%; and VADT [Veterans Affairs Diabetes Trial], 40.3%) and generally targeted HbA_{1c} levels <6.5%.[182–184] One trial was stopped early because of an increased risk of death among patients randomized to intensive glycemic control.[184] The other 2 trials demonstrated no benefit with respect to the primary outcome, major cardiovascular events, with no heterogeneity of effect based on the presence or absence of established macrovascular disease.[182,183] Several factors have been postulated as playing a potential role in the observed lack of benefit. These include weight gain and increased risk of hypoglycemia associated with intensive glycemic control strategies, the specific agents used to achieve glucose control, and the timing of the intervention (ie, inability to reverse established atherosclerotic changes late in the course of T2DM). Taken together, these trials suggest that the general strategy of targeting HbA_{1c} levels to <6.5% among patients with T2DM does not reduce the risk of subsequent cardiovascular disease.

The American Diabetes Association Standards of Medical Care recommend that a reasonable HbA_{1c} goal for many nonpregnant adults is still <7%.[190] A less stringent goal such as <8% or <8.5% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing T2DM.[190] The rationale for these recommendations is that intensive glycemic control generally reduces the risk of microvascular end points, even if it does not reduce major cardiovascular events. Notably, the evidence for microvascular benefit with intensive glycemic control is more robust in the UKPDS study[187] compared with the 3 more recent trials (ACCORD, ADVANCE, and VADT).[182–184] Moreover, the last trial showed minimal, if any, effect on hard clinical microvascular outcomes such as blindness, need for dialysis or transplantation, renal death, or clinical neuropathy.[191] Therefore, the microvascular benefits may be more likely to be realized by patients early in the course of T2DM and with longer life expectancy. The relatively intense efforts to achieve an HbA_{1c} <7% among patients with long-standing T2DM increase the risks associated with polypharmacy, contribute to treatment burden (including financial burden), and may increase the risk of hypoglycemia.[192]

Hypoglycemia

Intensive glycemic control in all major clinical trials was shown to increase the risk of severe hypoglycemia 2- to 3-fold.[182–184,187,193] More than just a nuisance, hypoglycemia can cause direct harm, including falls, injuries and fractures, motor vehicle accidents, and even coma and death.[194] Because insulin-induced severe

hypoglycemia is thought to cause death by inducing fatal cardiac arrhythmias, there have been long-standing concerns about the impact of hypoglycemia on cardiovascular events, especially in patients with preexisting cardiovascular disease. Indeed, multiple studies have shown a strong relationship between hypoglycemia (severe or not severe) and cardiovascular events and mortality.[195–201] Yet, whether hypoglycemia is a marker of vulnerability or a causal mediator of cardiovascular events remains unclear.[202] Regardless of the causality, the occurrence of hypoglycemia should be minimized in all patients with T2DM, especially among patients with preexisting cardiovascular disease.

Impact of Specific Glucose-Lowering Drugs on CAD Outcomes

Sulfonylureas and Insulin

Given the known high risk for CAD in patients with T2DM and the varying physiological actions of glucose-lowering agents, clinicians have long wondered whether any specific T2DM medication offered unique advantages or disadvantages (over and above any benefits of glycemic control) to the cardiovascular system. For years, concerns have been raised about the traditional T2DM drugs, the sulfonylureas, which reduce blood glucose by depolarizing β-cell membranes, resulting in insulin release. Hyperinsulinemia, hypoglycemia, and blunting of ischemic preconditioning have been raised as specific concerns. However, although sulfonylureas have been associated with increased cardiovascular mortality in retrospective observational studies, most large controlled clinical trials have generally proved sulfonylureas (particularly second-generation agents) to be safe and cardiovascular neutral.[183,187,203,204] In the CAROLINA randomized trial (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) of 6033 patients with T2DM and cardiovascular risk factors, there was no difference in the risk of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in patients treated with glimepiride versus linagliptin, albeit with a marked increased risk of hypoglycemia with the sulfonylurea.[204] Sulfonylurea use has been linked to improved microvascular outcomes, specifically retinopathy and albuminuria, in the context of intensive glycemic control in the UKPDS study.[187] Insulin therapy has raised similar concerns with respect to cardiovascular safety and has been associated with adverse cardiovascular outcomes and mortality in observational studies.[205,206] However, these data are challenging to interpret because insulin tends to be reserved for those patients with more advanced disease. As with the sulfonylureas, randomized trials have shown insulin to be associated with a reduced risk of microvascular complications in the context of intensive glycemic control; insulin appears safe from a cardiovascular standpoint, but it does not reduce adverse cardiovascular events.[184,187] Accordingly, sulfonylureas and insulin can be used cautiously as glucose-lowering therapies in a patient with stable CAD, but careful attention should be paid to avoiding hypoglycemia and excess weight gain. Given these adverse effects, neither insulin nor sulfonylureas should be first-line therapies for most patients with established CAD, especially given the documented cardiovascular benefits associated with the use of other glucose-lowering drugs.

Metformin

In contrast to sulfonylureas and insulin, metformin may actually improve cardiovascular outcomes and is not associated with either hypoglycemia or weight gain. Within a substudy of the UKPDS (n=1704 randomized to metformin [n=324] versus sulfonylureas/insulin), metformin was associated with fewer myocardial infarctions (11.0 per 1000 person-years versus 18.0 per 1000 person-years; 39% RRR) and deaths (13.5 per 1000 person-years versus 20.6 per 1000 person-years; 36% RRR).[188] Follow-up studies involving metformin appeared to support a potential cardiovascular benefit, but these studies were small and the findings were not robust.[207,208] A large trial is currently recruiting through the US Veterans Affairs to examine the cardiovascular benefit of metformin versus placebo in patients with prediabetes and atherosclerotic cardiovascular disease (results expected in 2024). Nonetheless, this agent continues to be the most popular glucose-lowering agent in the United States and Europe for people with T2DM, including those with CAD, and remains the drug most frequently recommended as first-line therapy in treatment guidelines.

Thiazolidinedione

Thiazolidinediones are insulin-sensitizing agents and thus were attractive options with potential cardiovascular benefits, given the link between insulin resistance and CAD. An early cardiovascular outcome trial, PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events), suggested a cardiovascular benefit from the thiazolidinedione pioglitazone in 5238 patients with T2DM with preexisting macrovascular disease. Although the primary outcome of the trial, a broad cardiovascular composite, was not significantly reduced (HR, 0.90 [95% CI, 0.80–1.02]), pioglitazone resulted in a 16% RRR in the secondary outcome of MACEs (11.6% versus 13.6%).[209] Given the neutral primary outcome, this secondary finding was considered hypothesis generating. Subsequently, a major controversy emerged involving rosiglitazone, with a well-publicized meta-analysis of small phase 3 trials suggesting an increase in myocardial ischemic events (odds ratio, 1.43 [95% CI, 1.03–1.98]).[210] However, rosiglitazone was later demonstrated to be neutral for major cardiovascular events in the RECORD trial (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia

in Diabetes).[211] Finally, in the IRIS trial (Insulin Resistance Intervention After Stroke), which involved 3876 patients with stroke and insulin resistance (but notably not T2DM), pioglitazone produced a 24% RRR in stroke or myocardial infarction (9.0% versus 11.8%).[212] In a post hoc analysis of IRIS, pioglitazone was also associated with a 29% RRR in acute coronary syndrome (4.3% versus 6.0%) and 38% RRR in myocardial infarction (1.7% versus 2.7%).[213]

Despite their likely atherosclerotic benefit, thiazolidinediones unfortunately also increase the risk of heart failure as a result of their sodium retentive properties at the distal nephron, and this risk is accentuated at higher doses and when the drugs are used with insulin. Thus, they remain contraindicated in patients with established heart failure and must be used with some caution in patients with CAD, given the underlying risk of heart failure in this group. Notably, in IRIS, there was no increased risk of heart failure hospitalizations with pioglitazone, but patients with known heart failure were excluded, and there were protocols in place for study drug dose reduction with any signs of fluid overload. Thiazolidinediones can be used in patients with CAD but without known heart failure and may have important atherosclerotic benefits; however, the clinician must be vigilant for any signs of fluid overload so as to reduce the risk of overt heart failure.

Dipeptidyl Peptidase 4 Inhibitors

Partially in response to the rosiglitazone controversy, the US Food and Drug Administration released guidance to the pharmaceutical industry in 2008 that essentially mandated large CVOTs to demonstrate cardiovascular safety of any new glucose-lowering agent.[214] The first drug category to report outcomes in these CVOTs was the DPP4 (dipeptidyl peptidase 4) inhibitors, oral agents that increase concentrations of endogenous incretin hormones, increasing insulin and decreasing glucagon secretion in a glucose-dependent manner. These medications are somewhat less powerful than traditional agents but do not result in any hypoglycemia or weight gain and are generally well tolerated. In 4 trials to date, the DPP4 inhibitors have been shown to be neutral in terms of cardiovascular outcomes.[185,186,215,216] Notably, 1 drug in this class, saxagliptin, led to a 26% increase in heart failure hospitalization in the SAVOR-TIMI 53 trial (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus), with no clear explanation of the mechanism.[186] Alogliptin also showed a trend toward increased heart failure hospitalizations in the EXAMINE trial (Cardiovascular Outcomes Study of Alogliptin in Patients With Type 2 Diabetes and Acute Coronary Syndrome),[185] and both now carry relevant warnings in their labels. Subsequent observational studies, CVOTs, and meta-analyses have not shown an excess heart failure risk with DPP4 inhibitors.[217,218]

Sodium-Glucose Cotransporter 2 Inhibitors

The first drug class to show clear benefits on cardiovascular outcomes was the SGLT2 (sodium-glucose cotransporter 2) inhibitors. These oral agents reduce blood glucose by increasing glucosuria and are associated with modest reductions in body weight and blood pressure. Their main side effects include increased urination and genitourinary infections. In the EMPA-REG OUTCOME trial (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), empagliflozin reduced MACEs by 14% (HR, 0.86 [95% CI, 0.75–0.99]) in patients with established cardiovascular disease, which was driven primarily by a significant reduction in cardiovascular mortality (3.7% versus 5.9%; 38% RRR).[8] Empagliflozin also reduced all-cause mortality (5.7% versus 8.3%; 32% RRR), hospitalizations for heart failure (2.7% versus 4.1%; 35% RRR),[219] and progression of chronic kidney disease (12.7% versus 18.8%; 39% RRR).[220] The event curves for cardiovascular death and heart failure hospitalization diverged early, suggesting that the effects of the drug were not mediated through the traditional reduction in atherosclerosis but perhaps instead through a rapid effect on hemodynamics. A follow-up analysis showed that these benefits were also consistent regardless of HbA_{1c} before and during therapy.[221] There were mixed results with canagliflozin in CANVAS (Canagliflozin Cardiovascular Assessment Study) involving 10 142 patients with established or at high risk for cardiovascular disease. Canagliflozin reduced MACEs (26.9 per 1000 person-years versus 31.5 per 1000 person-years; 14% RRR), heart failure hospitalization (5.5 per 1000 person-years versus 8.7 per 1000 person-years; 33% RRR), and chronic kidney disease progression (6.6 per 1000 person-years versus 9.0 per 1000 person-years; 40% RRR) at rates similar to empagliflozin, but there was no significant reduction in cardiovascular death.[19] These benefits were somewhat counterbalanced by a doubling of amputation rates (6.3 per 1000 person-years versus 3.4 per 1000 person-years) and more bone fractures in the canagliflozin arm of CANVAS, adverse effects that have not been reported to date with other SGLT2 inhibitors and were not observed in a subsequent trial of canagliflozin.[222] Finally, in DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events), dapagliflozin did not significantly reduce MACEs in 17 160 patients with established or at high risk for cardiovascular disease. Dapagliflozin significantly reduced the risk of the dual primary composite outcome of cardiovascular death or heart failure hospitalization (4.9% versus 5.8%; 17% RRR) and reduced progression of chronic kidney disease.[16] Notably, DECLARE enrolled more patients without preexisting cardiovascular disease (59%) than either CANVAS (34%) or EMPA-REG OUTCOME (0%), meaning that at least some of the

benefits of SGLT2 inhibition extend to those without overt cardiovascular disease.[222,223] Updated drug labels for empagliflozin and canagliflozin now include indications for cardiovascular benefits.

Glucagon-Like Peptide-1 Receptor Agonists

The final category reporting CVOT results was the GLP-1 (glucagon-like peptide-1) receptor agonists, injectables that mimic the effects of the DPP4 inhibitors while also delaying gastric emptying and centrally decreasing appetite. Side effects include nausea and vomiting and possibly an increase in gallbladder disease. Their use is associated with a stronger effect on HbA_{1c} and weight loss than either DPP4 inhibitors or SGLT2 inhibitors. Unlike these other drug classes, there has been greater inconsistency in the outcomes of the CVOTs for the different GLP-1 receptor agonists. ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) was the first to report and showed that the short-acting GLP-1 receptor agonist lixisenatide had no impact on MACEs in 6068 patients after an acute coronary syndrome.[224] In the second GLP-1 receptor agonist CVOT, LEADER, liraglutide led to a 13% RRR in MACEs (13.0% versus 14.9%) and a 22% RRR in cardiovascular death (4.7% versus 6.0%) in 9340 patients with overt or at high risk for cardiovascular disease.[17] In SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects With Type 2 Diabetes; n=3297), semaglutide produced a 26% RRR in MACEs (6.6% versus 8.9%) but no reduction in cardiovascular mortality.[10] The next CVOT, EXSCEL (Exenatide Study of Cardiovascular Event Lowering Trial; n=14 752), found extended-release exenatide to be neutral for MACEs.[225] Finally, Harmony Outcomes (n=9463) reported a 22% RRR in MACEs (7.1% versus 9.0) with albiglutide in patients with T2DM and atherosclerotic cardiovascular disease,[18] but this GLP-1 receptor agonist is no longer marketed as a result of the manufacturer's decision.

On the basis of these studies, it is now clear that although glucose lowering itself has, at best, only modest impact on cardiovascular events, the method by which glucose is lowered may. Accordingly, guideline committees have amended their recommendations for the management of patients with T2DM on the basis of the presence or absence of cardiovascular disease. In both a consensus report from the American Diabetes Association and European Association for the Study of Diabetes and an expert consensus decision pathway from the American College of Cardiology, use of either a GLP-1 receptor agonist or an SGLT2 inhibitor demonstrated to improve cardiovascular outcomes is advised in patients with high cardiovascular risk regardless of HbA_{1c}.[226–228] If heart failure or chronic kidney disease dominates the clinical picture, an SGLT2 inhibitor is preferred.

MANAGEMENT OF STABLE ANGINA

Workup of Angina

Current US guidelines recommend that most patients with stable ischemic heart disease undergo noninvasive ischemic testing at some point to gain prognostic information.[160,229] A variety of noninvasive tests are available that incorporate electrocardiography, radionuclide scintigraphy, echocardiography, or coronary computed tomography angiography (CTA). Although these tests have been the focus of guidelines for the assessment of stable angina, studies designed to answer clinical questions about the management of stable CAD in T2DM are lacking.

Anatomic Versus Functional Testing

Two large studies have tested CTA versus functional testing in the workup for stable angina. The SCOT-HEART trial (Scottish Computed Tomography of the Heart) was an open-label randomized comparison of CTA with standard care (which could include stress testing, angiography, or continued medical management) in 4146 subjects with stable chest pain (444 with diabetes mellitus) from 2010 to 2014.[230] At the 5-year follow-up, the rate of the composite end point of death caused by CAD or nonfatal myocardial infarction was lower in the CTA group than in the standard care group (2.3% versus 3.9%; HR, 0.59 [95% CI, 0.41–0.84]; *P*=0.004). This difference was caused primarily by a lower rate of nonfatal myocardial infarction in the CTA group than in the standard care group (HR, 0.60 [95% CI, 0.41–0.87]). This effect was similar in the subset of patients with diabetes mellitus (primary end point HR, 0.36 [95% CI, 0.15–0.87]). Revascularization rates were similar in the 2 groups and probably did not play a major role in the difference between the groups in the rate of the primary end point. The authors speculated that the mechanism by which myocardial infarctions were prevented may be, in part, related to more appropriate use of preventive therapies in the CTA group that may have been prompted from the test results.

The findings of the SCOT-HEART trial are in contrast to those of PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain), which randomly assigned 8966 patients with stable chest pain (1908 with diabetes mellitus) to either CTA or functional testing and showed no difference in outcomes over a median of 2 years of follow-up.[231] Further analysis showed that a substantial proportion of myocardial infarctions occurred in patients with nonobstructive CAD identified by CTA, disease that would not be detected by functional testing and could prompt important changes in prevention strategies. However, there was a significant interaction by diabetes mellitus (*P*=0.02); patients with diabetes mellitus who were randomized to CTA had a lower risk of cardiovascular death or nonfatal

myocardial infarction compared with those randomized to functional stress testing (1.1% versus 2.6%; adjusted HR, 0.38 [95% CI, 0.18–0.79]; *P*=0.01), whereas there was no significant difference in outcomes in patients without diabetes mellitus.[232] Overall, CTA may provide an advantage over stress testing in the management of patients with T2DM and stable angina, mostly for its ability to diagnose nonobstructive CAD and therefore inform medical management.

Medical Therapy Options

Despite advances in interventions that prevent and slow the progression of atherosclerosis and revascularization technologies to reduce myocardial ischemia, about one-third of patients with stable CAD report chronic angina.[233] Increasing burden of chronic angina not only affects patients' quality of life[234,235] but also is associated with increased hospitalizations and healthcare costs.[236] However, angina remains both underrecognized[237,238] and undertreated.[239,240] Patients with angina and concomitant T2DM are a particularly challenging group because they often have more diffuse and extensive CAD that may not be as amenable to revascularization.[241,242] Even among patients who are candidates, residual angina after revascularization is quite common, with ≈20% to 30% of patients reporting angina at 1 year after revascularization.[243–245] Thus, medical management of angina can play a particularly important role in improving the quality of life of patients with T2DM and stable coronary disease.

Antianginal Efficacy

Options for medical management of stable angina have 1 of 2 mechanisms: increasing myocardial oxygen supply (nitrates, calcium channel blockers) or decreasing myocardial oxygen demand (β-blockers, calcium channel blockers, ranolazine, ivabradine). Guidelines generally recommend β-blockers or calcium channel blockers as first-line therapy, with long-acting nitrates and ranolazine considered when β-blockers or calcium channel blockers are contraindicated, poorly tolerated, or insufficient to control symptoms (Table 3).[246,247] For the indication of stable coronary disease, none of these medications have been shown to reduce the risk of mortality or myocardial infarction.[94,248–251] In addition, both a meta-analysis and a systematic review found similar effects on angina and exercise duration among β-blockers, calcium channel blockers, and nitrates.[251,252] Therefore, selecting medications for the treatment of stable angina should focus on other factors specific to the patient (eg, effects on blood pressure or heart rate, side effects, costs, glycemic effects).

Effects of Antianginals on Glucose

There are 2 special considerations in the choice of antianginal medications for patients with concomitant T2DM. First, many β-blockers (eg, metoprolol, atenolol) that effectively treat angina also have adverse metabolic effects. β-Blockers reduce heart rate and myocardial contractility (thereby reducing myocardial oxygen demand), but this can induce compensatory peripheral vasoconstriction, which leads to increased insulin resistance and a more atherogenic lipid profile.[96,97,253] β-Blockers that have a concomitant vasodilatory effect (eg, carvedilol, labetalol, nebivolol), however, have neutral or beneficial effects on metabolic parameters.[96–98] In head-to-head trials, patients with T2DM who were treated with vasodilating (versus nonvasodilating) β-blockers had small but significant decreases in HbA_{1c} levels (0.1%–0.2%), improved insulin sensitivity, lower cholesterol levels, less weight gain, and less progression to microalbuminuria.[96,254–256]

A second consideration of pharmacological treatment of angina in patients with T2DM is the impact of ranolazine on both angina and blood glucose. Ranolazine reduces myocardial ischemia at the cellular level and is the only antianginal medication to be tested and found effective specifically in patients with T2DM.[257] In addition to its antianginal effects, ranolazine appears to reduce HbA_{1c} by ≈0.5% to 0.7% via a reduction in glucagon secretion.[258] Both the antianginal effect[259] and the glucose-lowering effect[260–262] of ranolazine appear to be enhanced in patients with poorly controlled T2DM.

Table 3. Management of Stable Angina

Medical therapy	
Underlying issue: No antianginal medications reduce morbidity or mortality in stable CAD and have similar impact on reducing angina.	
β-Blockers	Preference for vasodilating β-blockers with less adverse metabolic effects
Calcium channel blockers	Avoid nondihydropyridines in patients with LV dysfunction or with β-blockers
Long-acting nitrates	Long-term use can cause tolerance and endothelial dysfunction
Ranolazine	No hemodynamic effects; moderate reduction in HbA_{1c}
Revascularization	
Underlying issues: Both surgical and percutaneous revascularization outcomes are impaired in the setting of T2DM, with increased risk of both procedural complications and recurrent ischemic events.	
Multivessel CAD, left main disease, complex coronary anatomy	CABG is associated with lower MACEs compared with PCI
	Use of the IMA to the anterior wall is an important driver of benefit of CABG
	Typically achieve more complete revascularization with CABG vs PCI
	Newest-generation drug-eluting stents have narrowed the gap between CABG and PCI

CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; HbA_{1c}, glycated hemoglobin; IMA, internal mammary artery; LV, left ventricular; MACE, major adverse cardiovascular event; PCI, percutaneous coronary intervention; and T2DM, type 2 diabetes mellitus.

The metabolic impact of β-blockers and ranolazine is modest, and other considerations may make other antianginal medications preferable in patients with angina and concomitant T2DM. Most important is the recognition of angina among patients with stable coronary disease, understanding that patients with T2DM have at least as high a burden of angina as those without T2DM. Once angina is recognized and quantified, effective antianginal medications can be applied, with selection of those medications that are T2DM friendly, when no other competing considerations are present.

Revascularization Options

OMT with risk modification remains the foundation of management in patients with T2DM and CAD.[263,264] However, as coronary anatomic burden and complexity increase, particularly among those with large ischemic burden or frequent angina, the benefit of revascularization combined with OMT becomes manifest.[263,265–267] Both surgical and percutaneous revascularization outcomes are impaired in the setting of T2DM, with an increased risk of adverse procedural events and of long-term lesion development, progression, and restenosis.[25,268,269] The relative benefit and risk of each revascularization strategy vary by the extent and complexity of CAD and the patient's underlying comorbid state.[270] Therefore, individualized consideration of the need for and optimal choice of revascularization strategy is required.[271] In patients with multivessel CAD, left main disease, and complex coronary anatomy, coronary artery bypass grafting (CABG) is associated with reduced long-term MACEs compared with PCI, albeit with a small increased early risk of stroke[272,273] (30-day stroke rate for CABG versus PCI, 1.8% versus 0.3%[274]). The reduced MACEs observed after CABG are driven largely by a lesser need for repeat revascularization with CABG than with PCI, particularly in the initial years after revascularization.[273] Several lines of evidence, however, suggest that the more complete revascularization that can be achieved in bypassed territories accounts for a gradual accrual of benefit beyond 4 to 5 years after CABG, whereas there is an accompanying hazard associated with incomplete PCI over this time course.[275,276]

Importance of the Internal Mammary Artery

BARI (Bypass Angioplasty Revascularization Investigation),[277] which randomized patients with multivessel CAD to CABG or balloon angioplasty, provides a framework to understand the beneficial impact of durable revascularization, particularly of the left anterior descending artery.[278] In this trial, significantly improved survival was noted in the subgroup of patients with diabetes mellitus who were randomized to CABG, a difference that continued to accrue out to 10 years from study entry.[279] Much of the observed long-term benefit of CABG over balloon angioplasty was attributable to a durable surgical conduit bypassing the entire proximal vessel, resulting in a documented early survival advantage after myocardial infarction in patients treated with left internal mammary artery (IMA) grafts.[280] A consistent effect has been identified throughout subsequent contemporary revascularization trials,[266] including in pooled analysis.[281] Bilateral IMA implantation is less commonly used than single IMA implantation because of concern about increased sternal wound infection rates.[282–284] Although pooled analysis from retrospective studies suggests the safety of skeletonized bilateral IMA harvest[285,286] and the potential for superior long-term survival associated with this approach,[284] the only large-scale randomized experience with bilateral IMA to date failed to demonstrate early[287] or 5-year superiority compared with single IMA.[288]

PCI With Drug-Eluting Stents

Although patients with T2DM are at increased risk for the full spectrum of ischemic events compared with those without T2DM, the issue of restenosis after PCI has been an area of particular concern in those with T2DM.[289] Approximately 15% of patients with T2DM will require target vessel revascularization within 2 years after bare metal stenting,[290] which is reduced by 60% to 70% with the use of drug-eluting stents.[291] As PCI technology has advanced, the benefit of CABG over PCI in patients with T2DM has therefore been challenged. The FREEDOM trial[274] (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) was the first large-scale investigation of contemporary CABG (94% IMA implantation to the left anterior descending artery) compared with drug-eluting stent–based PCI (first-generation paclitaxel- or sirolimus-eluting stents) among 1900 patients with diabetes mellitus and CAD. With excellent adherence to OMT in both cohorts, the primary composite outcome of 5-year rates of death resulting from any cause, nonfatal myocardial infarction, or nonfatal stroke occurred more frequently in the PCI group (26.6% versus 18.7%; P=0.005), as did the individual outcomes of death (16.3% versus 10.9%; P<0.05) and nonfatal myocardial infarction (13.9% versus 6%; P<0.001), although stroke was more common after CABG (5.2% versus 2.4%; P=0.03). Impressively, these results were consistent across all prespecified subgroups.[274,275,292] Extended follow-up (mean, 7.5 years) of the original 1900 randomized patients found a significant 25% relative survival benefit for CABG compared with PCI (81.7% versus 75.7%; P=0.01), with survival curves diverging beyond 2 years and continuing to widen throughout follow-up, suggesting a robust long-term benefit.[293] There was also a small favorable benefit in quality of life favoring CABG from 6 months to 2 years, although there was no further accrual of benefit beyond 2 years.[294]

Meta-Analytic Results

A pooled patient-level data analysis of 11 518 patients from 11 multivessel revascularization trials found a survival advantage at 5 years associated with CABG compared with PCI among the 4386 patients with diabetes mellitus in the studies (84.5% versus 90.0%; *P*=0.0004).[272] Pooled analysis of patient-level data from BARI2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes),[263] COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation),[264] and FREEDOM[274] showed a reduction in 5-year composite rates of death, myocardial infarction, or stroke in patients with diabetes mellitus randomized to OMT+CABG compared with OMT+PCI or OMT alone.[272,295] When the additional end point of need for subsequent revascularization was included in the composite, OMT+CABG was again superior to other strategies regardless of baseline angina severity.[296]

Diabetes mellitus is associated with marked and widespread vascular perturbation leading to enhanced cardiovascular risk. In particular, the increased vascular disease burden and progressive nature of CAD in patients with T2DM lead to an increased propensity toward postrevascularization target and nontarget vessel ischemic events, especially in those with more advanced T2DM as reflected by insulin requirements.[265,297] Because both percutaneous and surgical revascularization outcomes are impaired in the presence of T2DM, primary and secondary medical preventive therapy remains the foundation of care. When revascularization is indicated,[271] optimal approaches include PCI with newest-generation drug-eluting stents and CABG with IMA implantation. For patients with complex CAD or multiple comorbidities, an individualized, patient-centric heart team approach to revascularization strategy, including consideration of coronary anatomy, risk profile, presentation features, and patient preference, is essential, with the understanding that CABG with OMT will offer improved outcomes in the majority of patients with T2DM and multivessel CAD and is the revascularization strategy recommended by current US and European society guidelines.[229,298] Ongoing medical, surgical, and percutaneous developments require continuous reassessment of RRs and benefits associated with these modalities to ensure optimal outcome in patients with T2DM.

SUMMARY AND CONCLUSIONS

A remarkable transformation in the care of patients with T2DM is occurring. Clinical trials have uncovered several new drugs that not only reduce glucose but also improve cardiovascular and renal outcomes. These advances build on concurrent improvements in the management of other risk factors in patients with T2DM such as elevated LDL-C, triglycerides, and hypertension. The options in antithrombotic therapy for patients with T2DM have also expanded. Our understanding of diagnostic modalities to assess CAD burden in patients with T2DM has been refined, as well as the appropriate roles of lifestyle management, medical therapy, and percutaneous or surgical revascularization. Thus, the expanding knowledge base needed for the care of patients with T2DM necessitates a broad range of physicians to understand and apply the evidence that can directly improve clinical outcomes.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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