Circulation

AHA SCIENTIFIC STATEMENT

Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes: A Scientific Statement From the American Heart Association

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ABSTRACT: Cardiovascular disease remains the leading cause of death in patients with diabetes. Cardiovascular disease in diabetes is multifactorial, and control of the cardiovascular risk factors leads to substantial reductions in cardiovascular events. The 2015 American Heart Association and American Diabetes Association scientific statement, "Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence," highlighted the importance of modifying various risk factors responsible for cardiovascular disease in diabetes. At the time, there was limited evidence to suggest that glucose-lowering medications reduce the risk of cardiovascular events. At present, several large randomized controlled trials with newer antihyperglycemic agents have been completed, demonstrating cardiovascular safety and reduction in cardiovascular outcomes, including cardiovascular death, myocardial infarction, stroke, and heart failure. This AHA scientific statement update focuses on (1) the evidence and clinical utility of newer antihyperglycemic agents in improving glycemic control and reducing cardiovascular events in diabetes; (2) the impact of blood pressure control on cardiovascular events in diabetes; and (3) the role of newer lipid-lowering therapies in comprehensive cardiovascular risk management in adults with diabetes. This scientific statement addresses the continued importance of lifestyle interventions, pharmacological therapy, and surgical interventions to curb the epidemic of obesity and metabolic syndrome, important precursors of prediabetes, diabetes, and comorbid cardiovascular disease. Last, this scientific statement explores the critical importance of the social determinants of health and health equity in the continuum of care in diabetes and cardiovascular disease.

Key Words: AHA Scientific Statements ■ antihypertensive agents ■ cardiovascular diseases ■ diabetes complications ■ hypoglycemic agents ■ life style ■ social determinants of health

The prevalence of diabetes has increased sharply in the United States over the past 4 decades with >34.2 million Americans with diabetes.[1] More than 90% to 95% of the diabetes population are classified as type 2 diabetes (T2D).[1] Type 1 diabetes, characterized by an inability to produce insulin because of autoimmunity, accounts for 5% to 10% of cases. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in type 1 diabetes and T2D.[2] From 1998 to 2015, rates of cardiovascular mortality in the United States have declined in those with and without diabetes, with a 25% greater decline in diabetes populations; but disparities still persist, with cardiovascular mortality remaining higher in those with diabetes in the United States and similar findings in other western countries.[2–4]

CVD comprises a group of disorders of the heart and blood vessels including coronary heart disease, cerebrovascular disease, heart failure, peripheral artery disease (PAD), congenital heart disease, etc. In this scientific statement, the focus is mostly on components of the major adverse cardiovascular events (MACE) including coronary artery disease (CAD), cerebrovascular disease,

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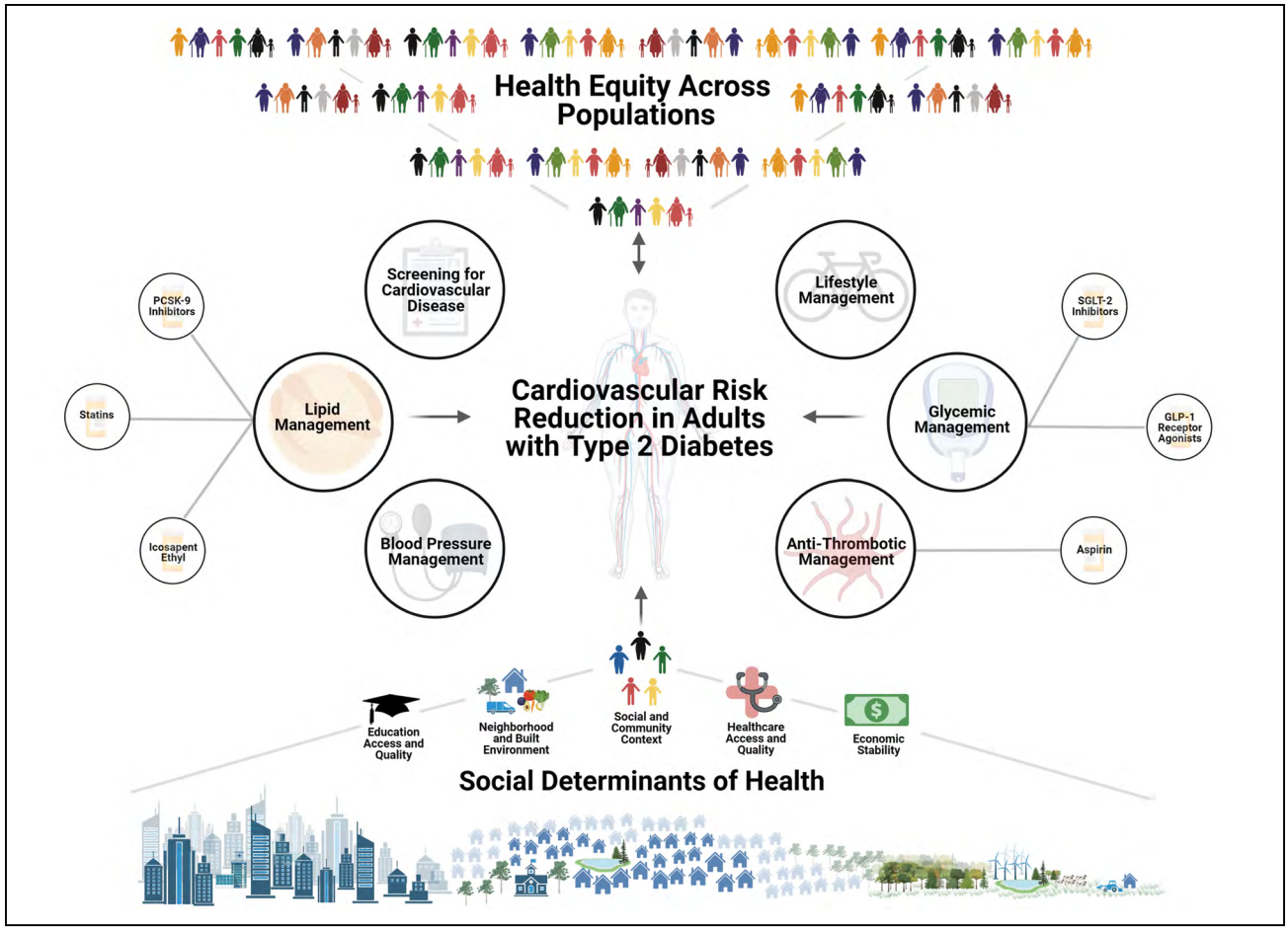

Figure 1. Cardiovascular risk reduction in adults with type 2 diabetes: central illustration.
GLP-1 indicates glucagon-like peptide 1; PCSK-9, proprotein convertase subtilisin/kexin type 9 serine protease; and SGLT-2, sodium-glucose cotransporter-2.

and heart failure. Atherosclerosis begins with the deposition of lipoproteins in the arterial wall. In the subendothelial space, foam cells accumulate and low-density lipoprotein (LDL) particles are oxidized, which ultimately leads to vascular modifications. Acute coronary and cerebrovascular syndromes occur when arterial plaque deposits become unstable and rupture.[5] Several factors in the development of atherosclerosis and CVD are often comorbid in individuals with T2D; these include hypertension,[6] insulin resistance,[7] hyperglycemia,[8] obesity,[9] and dyslipidemia.[10] Insulin resistance promotes macrovascular abnormalities through formation of atheroma plaques, diastolic dysfunction, and ventricular hypertrophy.[7] Hyperglycemia promotes the development of CVD through advanced glycosylated end products and oxidative stress among other factors.[11] Both insulin resistance and hyperglycemia promote CAD, cerebrovascular disease, and heart failure.

Lifestyle change, weight reduction, and cardioprotective therapeutics are vital tools in primary and secondary prevention of CVD. Since the "Update on Prevention of CVD in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association" in 2015,[12] there have been a number of important clinical trials advancing our understanding of lifestyle, blood pressure (BP), blood glucose, antithrombotic, and cholesterol management in primary and secondary prevention of CVD. This scientific statement (1) synthesizes the current science and best practices for the comprehensive management of cardiovascular risk factors in adults with T2D and (2) provides additional context on the importance of the social determinants of health (SDoH) and health equity in cardiovascular risk factor management from the individual to the population level (Figure 1).

DEFINITIONS AND DIAGNOSTIC CRITERIA

The pathophysiological progression to T2D includes metabolic syndrome and prediabetes with glucose dysregulation attributable to liver, skeletal muscle, and adipocyte insulin resistance, along with proinflammatory cytokines. These processes cause hepatic glucose production and impaired glucose uptake in skeletal muscle, and adipocytes leading to hyperglycemia and lipolysis.

The combined impact of these effects causes eventual β-cell decline with decreased insulin secretion and T2D. According to the International Diabetes Federation, metabolic syndrome is defined as having ≥3 of the following: (1) a waist circumference ≥35 inches for women or 40 inches for men, (2) elevated triglycerides (≥150 mg/dL), (3) a high-density lipoprotein cholesterol (HDL-C) <40 mg/dL in men or <50 mg/dL in women, (4) hypertension (≥130/85 mm Hg), and (5) elevated fasting plasma glucose (FPG; ≥100 mg/dL).[13] Even for obesity without metabolic syndrome, there is a 45% higher relative risk of CVD events compared with individuals who have a normal body mass index (BMI).[14] A diagnosis of prediabetes is based on FPG levels between 100 mg/dL and 125 mg/dL, glucose ranging from 140 mg/dL to 199 mg/dL in response to an oral glucose tolerance test (2-hour post glucose load), or a hemoglobin A1c (A1c) between 5.7% and 6.4%.[15] The diagnostic cutoff values for diabetes based on FPG, A1c, oral glucose tolerance test, and random glucose are ≥126 mg/dL, ≥6.5%, ≥200 mg/dL, and ≥200 mg/dL, respectively.[15] All 4 methodologies are considered suitable for the diagnosis of diabetes with a follow-up second abnormal test, although they are not perfectly concordant with one another. The 2-hour glucose measurement of an oral glucose tolerance test is the preferred test for assessing postmeal glucose tolerance and is a more sensitive diagnostic marker for both prediabetes and diabetes compared with A1c and FPG.[16] A1c has distinct advantages to plasma glucose testing because it is able to assess average blood glucose levels over a longer time frame (3 months) and has less inter/intraday variability attributable to external factors like stress. However, the A1c test alone with a ≥6.5% cutoff identifies only 30% of prevalent diabetes compared with A1c, oral glucose tolerance test, or FPG combined.[15,17] In relation to CVD, each of these disease states carries significant risk, and the combination of metabolic syndrome with diabetes increases CVD risk nearly 5-fold.[18,19]

LIFESTYLE MANAGEMENT

Lifestyle modification is a critical component of cardiovascular risk factor reduction in adults with T2D.[20–23] Lifestyle management of T2D includes diabetes self-management education and support, medical nutrition therapy, physical activity, smoking cessation, and psychosocial care. In adults with T2D, greater adherence to an overall healthy lifestyle is associated with a substantially lower risk of incident CVD and CVD mortality (Table 1).[24,25]

The Look AHEAD trial (Action for Health and Diabetes) tested the impact of intensive lifestyle intervention focused on weight loss and increased physical activity versus diabetes support and education on adverse cardiovascular events among overweight adults with T2D.[40] The intensive lifestyle intervention included a calorie goal of 1200 to 1800 kcal per day (with <30% from fat and >15% from protein), the use of meal replacement products, and at least 175 minutes of moderate-intensity physical activity per week. The intensive lifestyle intervention did not reduce the rate of MACE in Look AHEAD. However, it produced greater weight loss and reductions in A1c versus control, in particular, in the first year.[40] In post hoc analyses, individuals who lost ≥10% of their body weight or had a >2 metabolic equivalent increase in fitness in the first year of the trial experienced reductions in cardiovascular outcomes compared to those with stable weight/weight gain or stable fitness/fitness loss.[36] Similarly, although the intensive lifestyle intervention did not lower the risk of heart failure (HF) compared with control, sustained, long-term improvements in weight loss and cardiorespiratory fitness were associated with lower risk of HF in the entire cohort.[41] Furthermore, intensive lifestyle intervention yielded improvements in other cardiovascular risk factors,[40,42] sleep apnea,[43] fitness,[44] renal disease,[45] peripheral neuropathy,[46] and depressive symptoms.[47] Thus, among patients with T2D with overweight or obese status, intensive lifestyle intervention results in moderate and sustained weight loss, control of cardiovascular risk factors, and substantial cardiovascular benefit for those with greater weight loss and fitness.[36,41,48]

Physical Activity

Physical activity is important in cardiovascular risk reduction among individuals with T2D (Table 1). Consistent with other prevention guidelines,[21] the American Diabetes Association (ADA) recommends ≥150 minutes of moderate-to-vigorous intensity aerobic activity per week, over at least 3 days, with no more than 2 consecutive days without activity for most adults with T2D.[20,49] Recommendations also include 2 to 3 sessions per week of resistance exercise on nonconsecutive days, decreasing time spent sedentary with prolonged sitting being interrupted every 30 minutes, and flexibility and balance training 2 to 3 times per week.[20] Shorter durations (≥75 minutes per week) of vigorous activity or interval training may also be considered.[20]

Increased physical activity and exercise have been shown to improve glycemic control, lipids, BP, insulin sensitivity, and inflammatory biomarkers in T2D.[49–53] Physical activity has also been associated with lower risk of CVD and mortality in T2D.[54] Structured exercise training recommendations by health care workers, consisting of aerobic exercise, resistance training, or both, are more effective than physical activity advice alone.[53]

Nutrition

For adults with T2D, a tailored nutrition plan is a key component for cardiovascular risk reduction, and a heart-

Table 1. Risks of All-Cause Mortality, and Cardiovascular and Microvascular Events Associated With Control of Lifestyle Factors

	Lifestyle factors	Physical activity/exercise	Smoking	Alcohol
Total mortality	Bariatric surgery:[26] HR=0.33; 95% CI 0.21–0.52	Low vs higher:[27] HR=1.41; 95% CI 1.16–1.72	vs nonsmokers:[28] RR=1.55; 95% CI 1.46–1.64 vs never smokers: Former: RR=1.19; 95% CI 1.11–1.28 Daily smoking:[29] HR 1.52; 95% CI 1.27 –1.83 Women: HR=1.78; 95% CI 1.23–2.59 Men: HR=1.45; 95% CI 1.18–1.80 Cessation: HR=0.70; 95% CI 0.57–0.87 BARI 2D vs never smokers:[30] Current smokers: HR=1.49; 95% CI 0.97–2.29 Former smokers: HR=1.37; 95% CI 1.04–2.79	Moderate vs none (for wine):[31] HR=0.77; 9.5% CI 0.62–0.95 Alcohol consumers vs nonconsumers (6 g/d):[32] RR=0.64; 95% CI 0.49–0.82 NS at higher levels
CV mortality	≥3 low-risk factors:[33] HR=0.48; 95% CI 0.40–0.59 ≤2 risk factor control vs all:[34] HR=2.0; 95% CI 1.3–3.3	Low vs higher:[27] HR=1.54; 95%CI 1.07–2.22 Increase from inactive to 150 min moderate-intensity aerobic activity per wk:[35] RR=0.83; 95% CI 0.77–0.89	vs nonsmokers:[28] RR=1.49; 95% CI 1.29–1.71 vs never smokers[28] Former: RR=1.15; 95% CI 1.00–1.32 BARI 2D vs never smokers:[30] Current smokers: NS Former smokers: NS	Alcohol consumers vs nonconsumers:[32] <6 g/d: RR=0.72; 95% CI 0.52–1.00 6 to <18 g/d: RR=0.57; 95% CI 0.42–0.76 ≥18 g/d: RR=0.34; 95% CI 0.22–0.53
Total CVD	None vs 3 of 4 factors:[25] HR=4.17; 95% CI 1.02–17.09 ≥3 low-risk factors:[33] HR=0.48; 95% CI 0.40–0.59 >10% weight loss first y:[36] Primary outcome: RR=0.79; 95% CI 0.64–0.98 Secondary outcome: RR=0.79; 95% CI 0.64–0.98 ≤2 risk factor control vs all:[34] HR=1.7; 95% CI 1.2 – 2.5	Low vs higher: HR=1.18; 95% CI 1.02–1.36 Increase from inactive to 150 min moderate-intensity aerobic activity per wk:[35] RR=0.83; 95% CI 0.77–0.89	Compared with nonsmokers:[28] RR=1.44; 95% CI 1.34–1.54 vs never smokers: [28] Former: RR=1.09; 95% CI 1.05–1.13 vs smokers:[37] Quit ≤4 y: HR=0.49; 95% CI 0.11–2.19 Quit >4 y: HR=0.57; 95 %CI 0.28–1.15 Nonsmokers: HR=0.49; 95% CI 0.22–1.09	
Coronary heart disease/coronary artery disease	≥3 low-risk factors:[33] HR=0.53; 95% CI 0.42–0.66 Bariatric surgery:[26] HR=0.64; 95% CI 0.42–0.99	Low vs higher:[27] HR=1.19; 95% CI 1.00–1.42 Increase from inactive to 150 min moderate-intensity aerobic activity per wk:[35] RR=0.80; 95% CI 0.75–0.86	vs nonsmokers:[28] RR=1.51; 95% CI 1.41–1.62 Compared with never smokers:[28] Former: RR=1.14; 95% CI 1.00–1.30 BARI 2D vs never smokers:[30] Current smokers: No Former smokers: No	Heavy drinking and highest depressive symptoms:[38] Odds ratio=1.02; 95% CI 1.00–1.04 Alcohol consumers vs nonconsumers:[32] <6 g/d: RR=0.75; 95% CI 0.61–0.93 6 to <18 g/d: RR=0.57; 95% CI 0.39–0.83 ≥18 g/d: RR=0.59; 95% CI 0.41–0.81
Heart failure		Increase from inactive to 150 min moderate-intensity aerobic activity per wk:[35] RR=0.81; 95% CI 0.76–0.86	vs nonsmokers:[28] RR=1.43; 95% CI 1.19–1.72	

(*Continued*)

Table 1. Continued

	Lifestyle factors	Physical activity/exercise	Smoking	Alcohol
CV events	>10% weight loss first y:[36] RR=0.76; 95% CI 0.63–0.91 Achieving 5 factors vs ≤2:[39] HR=0.60; 95% CI 0.47–0.77 Bariatric surgery:[26] HR=0.60; 95% CI 0.42–0.86		vs smokers: Quit ≤4 y: HR=0.36; 95% CI 0.04–2.97 Quit >4 y: HR=0.42; 95% CI 0.16–1.10 Nonsmokers: HR=0.15; 95% CI 0.04–0.57	Moderate vs none:[31] adjusted HR=0.83; 95% CI 0.72–0.95

BARI 2D indicates Bypass Angioplasty Revascularization Investigation 2 Diabetes; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; NS, nonsignificant; and RR, relative risk.

Details on some of the studies noted in Table 1.

Population-based prospective cohort study of newly diagnosed patients with type 2 diabetes (n=867); composite first CV event: CV mortality, nonfatal MI, and nonfatal stroke and revascularization; risk in those who did not change any health behavior vs those who adopted 3 out of 4 (physical activity, alcohol intake, smoking, and diet).[25]

Retrospective cohort study over 5 years.[26]

Observational study from Swedish National Diabetes Register (n=15 462; low=never or 1 to 2 times per week; higher=3 times per week or more; adjusted for age, sex, diabetes duration, diabetes treatment, smoking, systolic blood pressure, low- and high-density lipoproteins, triglycerides, body mass index, and albuminuria.[27]

Meta-analysis and systematic review of 89 prospective, cohort studies.[28]

ADVANCE trial (The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation): all-cause mortality; major cardiac events (CVD death, nonfatal stroke, or nonfatal MI); all CV events (major+ peripheral artery disease or transient ischemic attack); coronary events (fatal and nonfatal MI; nephropathy [new or worsening renal disease]); adjusted for CVD risk factors and weight change.[29]

Adjusted for factors that differed by smoking status and smoking status as a time-dependent covariate.[30]

Meta-analysis of 7 prospective studies.[32]

Umbrella review of systematic reviews and meta-analyses.[33]

Nonrandomized analysis (n=2265) of survival and CV events (composite death, MI, or stroke) and control of 6 risk factors (nonsmoker, non–high-density lipoprotein <130 mg/dL, triglycerides <150 mg/dL, systolic blood pressure <130 mm Hg, diastolic blood pressure < 80 mm Hg, hemoglobin A1c <7%) in BARI2D; time-varying number of risk factors in control adjusted for baseline numbers of risk factors in control. Clinical characteristics and randomization assignment.[34]

Systematic review of 36 prospective cohort studies; increase from being inactive to achieving recommended PA levels of 150 minutes of moderate-intensity aerobic activity per week; adjusted for body weight.[35]

Composite. End point of CVD death, MI, stroke, or angina hospitalization in Look AHEAD; these events plus coronary artery bypass grafting, carotid endarterectomy, percutaneous coronary intervention, hospitalization for heart failure, peripheral vascular disease, or total mortality.[36]

Prospective community-based cohort study data from Framingham Offspring Study from 1984 to 2011; total CVD events–coronary heart disease, cerebrovascular events, peripheral artery disease, and congestive heart failure; age and sex-adjusted; multiple cardiac risk factor adjusted; and 4-year weight change adjusted.[37]

Evaluation of Diabetes Treatment annual survey, n=1413; adjusting for socioeconomic, lifestyle, and diabetes-related covariates.[38]

TECOS trial (Trial Evaluating Cardiovascular Outcomes with Sitagliptin; n=13 616) attainment of 5 secondary prevention goals (aspirin use, lipid control [low-density lipoprotein cholesterol <70 mg/dL or statin use], systolic blood pressure <140 mm Hg, diastolic blood pressure < 90 mm Hg, angiotensin-converting enzyme or angiotensin receptor blocker use, nonsmoking) on CV death, MI, or stroke.[39]

healthy dietary pattern is recommended to improve glycemic control, achieve weight loss when needed, and improve other atherosclerotic CVD (ASCVD) risk factors. The ADA recommendations support various healthy dietary approaches to achieve glycemic control and weight management,[20,23] although the effects of dietary interventions on CVD outcomes in individuals with T2D has not been widely studied. The Mediterranean, Paleolithic, low-carbohydrate, high-protein, vegetarian, and nut-enriched diets have demonstrated benefits on glycemic control and weight loss in T2D, with the Mediterranean diet producing the greatest improvements in glycemic control and a 29% CVD reduction over 4.8 years.[55–60] Very low–energy diets can lower A1c, BMI, cholesterol, and BP.[61,62] Very low–carbohydrate versus moderate carbohydrate diets yield a greater decrease in A1c, more weight loss and use of fewer diabetes medications in individuals with diabetes.[63–65] For those who are unable to adhere to a calorie-restricted diet, a low-carbohydrate diet reduces A1c and triglycerides.[63–65] Very low–carbohydrate diets were effective in reducing A1c over shorter time periods (<6 months) with less differences in interventions ≥12 months.[65a–65d] For individuals using very low–carbohydrate dietary approaches, it is important for health care professionals to maintain medical oversight and adjust diabetes medications to prevent hypoglycemia.[20] Overall, weight loss of 5% to 10% is associated with A1c reductions of 0.6% to 1.0% and reduced diabetes medications.[66] Thus, the ADA recommends an individualized nutrition plan focusing on total calorie and metabolic goals, using a medical nutrition program as needed to achieve goals.

Obesity and Weight Management

Overweight (BMI >25 kg/m^2), obesity (BMI >30 kg/m^2), and central/visceral adiposity are associated with adverse CVD outcomes.[66,67] Obesity increases CVD risk ≈2-fold, and diabetes with metabolic syndrome increases CVD risk ≈5-fold.[68] Obesity promotes CVD directly through cardiac adaptions including decreased cardiac output, increased peripheral resistance, left ventricular mass/wall thickness, and poor left ventricular systolic function.[68] Obesity adversely impacts hypertension, dyslipidemia, endothelial function, and inflammation indirectly.[68] Diet, physical activity, and behavioral therapy are recommended at all levels of BMI, with pharmacologic and surgical interventions recommended for weight management in obesity.[23]

Pharmacological Therapy

Weight-loss medications are indicated as adjuncts to diet, physical activity, and behavioral therapy for selected

patients with T2D and BMI ≥27 kg/m^2.[23] Orlistat, lorcaserin, liraglutide, naltrexone/bupropion sustained release, and phentermine/topiramate are US Food and Drug Administration (FDA)-approved for weight management with demonstrated cardiovascular safety and the additional benefit of A1c lowering.[69,70] If weight loss after 3 months is <5% or safety issues arise, the medication should be discontinued and alternative medications or treatment approaches should be considered.[23] Long-term cardiovascular event reduction has not been formally tested, but notable cardiovascular risk reduction was shown for liraglutide at lower doses among those with ASCVD or high cardiovascular risk.[71] Non-weight loss–approved medications commonly used in T2D lower weight, including pramlintide, sodium-glucose cotransporter-2 inhibitors (SGLT-2Is), metformin, and other glucagon-like peptide 1 receptor agonists (GLP-1RA).[69] Further studies are ongoing to determine the combinations of these therapies that may be most beneficial for weight loss.[69,70]

The recently published STEP (Semaglutide Treatment Effect in People with Obesity) 1,[72] STEP 2,[73] STEP 3,[74] and STEP 4[75] trials demonstrate the tremendous impact of once weekly GLP-1RA treatment with semaglutide on weight loss and cardiovascular risk factors. The STEP 2 trial specifically evaluated individuals with diabetes taking ≤3 oral hypoglycemic agents at baseline with BMI of ≥27 kg/m^2.[73] Average bodyweight reductions were 9.6%, 7.0%, and 3.4% with semaglutide 2.4 mg, 1.0 mg, and placebo, respectively, over 68 weeks combined with lifestyle intervention (counseling provided every fourth week to maintain a 500 kcal per day reduction relative to the estimated total daily energy expenditure and 150 minutes per week of physical activity).[73] Cardiovascular risk factors improved significantly on semaglutide 2.4 mg daily with reductions in A1c, glucose, very-low-density lipoprotein cholesterol, free fatty acids, triglycerides, and C-reactive protein.[73] The findings of STEP 1 and STEP 3 were consistent with STEP 2 in duration but were conducted among participants without diabetes. Both trials exhibited significant weight loss on the semaglutide 2.4 mg daily (14.9% and 16.0%, respectively), [72,74] with similar cardiovascular risk factor reduction. In STEP 1, among participants with prediabetes at baseline, 84% reverted to normoglycemia on intervention versus 48% in the control.[72] STEP 4 demonstrated the importance of long-term therapy with GLP-1 RAs by evaluating semaglutide 2.4 mg for the first 20 weeks, after which participants were randomly assigned to receive either semaglutide or placebo for the remaining 48 weeks.[75] The semaglutide 2.4 mg group had sustained weight loss over the 68 weeks, whereas the placebo group experienced weight regain and worsening of cardiovascular risk factors from weeks 21 to 68.[75] Gastrointestinal side effects were common with semaglutide, but rates of discontinuation were similar to placebo. Thus, once weekly semaglutide 2.4 mg delivers impressive weight loss and cardiovascular risk factor improvement and is FDA approved for chronic weight management in adults with BMI ≥30 kg/m^2 or BMI ≥25 kg/m^2 with a comorbid condition (ie, T2D, hypertension, hyperlipidemia).

Surgical Procedures

Growing evidence supports the use of metabolic surgery for the treatment of comorbid obesity in T2D.[23,76] The extant literature from numerous randomized controlled (nonblinded) clinical trials, matched studies, and meta-analyses demonstrate that metabolic surgery achieves superior glycemic control and reduction of cardiovascular risk factors including body weight, fasting glucose, A1c, BP, HDL, and triglycerides in patients with T2D and obesity compared with various lifestyle/medical interventions.[77–79] Improvements in CVD, CVD mortality, and all-cause mortality have been observed in nonrandomized observational studies, matched cohort studies, and meta-analyses (ranging from ≈40% to 80% risk reduction in meta-analyses) with potentially greater benefits for mortality among patients with versus without diabetes.[26,79–81] It is notable that most of the current studies were performed before the increased utilization of SGLT-2Is and GLP-1RAs with proven CVD reduction in T2D. The risk of metabolic surgery includes both short-term (<30 days) and long-term (≥30 days) complications. Short-term complications include postsurgical complications (bowel obstruction, venous thromboembolism, gastrointestinal bleeding, anastomotic leaks, wound infections, etc).[79] Long-term complications include marginal ulceration, cholelithiasis, dumping syndrome, nutritional and vitamin deficiencies, malabsorption, fistulas, etc.[79] At present, perioperative mortality ranges from 0.03% to 0.20%, which continues to improve over time.[79] Thus, a balanced discussion of the procedural and long-term risks and benefits should guide a patient-informed decision.

Metabolic surgery is recommended to treat patients who have T2D with BMI ≥40 kg/m^2 and in those with BMI 35.0 to 39.9 kg/m^2 without durable weight loss and improvement in comorbidities with nonsurgical methods, and should be considered in those with T2D and BMI of 30.0 to 34.9 kg/m^2 without similar improvements.[23] In Asian individuals, these BMI cut points are reduced by 2.5 kg/m^2.[23] In addition to these 2nd Diabetes Surgery Summit (DSS-II) recommendations, the ADA recommends that (1) metabolic surgery should be performed in high-volume centers with experienced, multidisciplinary teams; (2) long-term lifestyle support and routine monitoring of micronutrient and nutritional status must be provided; and (3) people presenting for metabolic surgery should receive comprehensive readiness and mental health assessment.[23]

Alcohol

Data from observational studies of the general population have linked light-to-moderate alcohol intake with lower risk of myocardial infarction (MI) compared with nondrinkers with no impact on stroke,[82] whereas increasing alcohol intake versus light intake is associated with a similar lower risk of MI but higher risk of stroke, HF, and fatal hypertensive disease.[83] The discrepancy for MI versus stroke may be attributable to the impact of alcohol on increasing BP but also increasing HDL.[83] Recent mendelian randomization studies suggest a causal link between alcohol consumption and cardiovascular outcomes including stroke and PAD.[84] Among individuals with T2D, light-to-moderate alcohol consumption, particularly wine consumption, has also been associated with fewer MIs compared with nondrinkers, whereas heavy alcohol consumption has been associated with higher risk.[31,32,85,86] There is a lack of evidence regarding alcohol's impact on other CVD outcomes including stroke in T2D. Recent evidence shows higher odds of hypertension in those with T2D who consume moderate or heavy amounts of alcohol.[87] These observational studies are unable to fully account for confounding and reverse causality, and randomized controlled cardiovascular outcomes trials (CVOTs) have not been performed. Small clinical trials in patients with diabetes have suggested that light-to-moderate alcohol intake may improve cardiometabolic measures such as A1c, insulin, and lipids.[88,89] In the ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care)-Cambridge study, decreasing alcohol intake by ≥2 units/week (20 mL pure alcohol) over 1 year was associated with a 44% (95% CI, 13%–64%) lower risk of CVD over 10 years versus sustained intake in individuals newly diagnosed with T2D.[90] Thus, light-to-moderate intake may have a benefit on A1c, lipids, and MI but with the concern of higher BP, thus a need for future studies on other cardiovascular outcomes.

Individuals who have underlying medical conditions that preclude alcohol use (eg, alcohol use disorders, liver disease, concomitant medications) should be advised to abstain from alcohol. Despite potentially beneficial effects of light-to-moderate alcohol intake on CVD, particularly MI, individuals who are not currently drinking should not be advised to consume alcohol for its potential health benefit. Adults with diabetes who choose to drink should be cautioned regarding the potential risks of hypoglycemia and delayed hypoglycemia, weight gain, hyperglycemia, and elevated BP that may occur with excess alcohol consumption. For women, no more than 1 drink per day, and for men, no more than 2 drinks per day is recommended (in the United States, 1 drink is equal to a 12-ounce beer, a 5-ounce glass of wine, or 1.5 ounces of distilled spirits).[20,23]

Smoking

Smoking increases the risk of coronary heart disease, HF, PAD, stroke, and cardiovascular mortality in T2D.[28] In general populations, secondhand smoke increases risk of CVD and all-cause mortality.[91] Smoking is associated with worse dyslipidemia, proinflammatory markers, and glycemic measures among adults with T2D.[92] Given the importance of tobacco as a remediable risk factor, current guidelines recommend assessing tobacco use at every health care visit and recording as a vital sign, and all adults who use tobacco should be counseled to quit, including behavioral interventions.[21] Pharmacological therapies to assist with smoking cessation include nicotine replacement therapy, bupropion, or varenicline, although data are limited specifically in T2D.[93]

Quitting smoking can be associated with weight gain.[94,95] Smoking cessation without subsequent weight gain is associated with a reduced risk of CVD and mortality among smokers with T2D.[94,95] Weight gain after smoking cessation attenuates the reduction in risk of developing CVD, but does not attenuate the beneficial effect on mortality.[94,95] Thus, weight management strategies should be discussed to maximize the health benefits of smoking cessation.[95]

Lifestyle Management in T2D Summary

Lifestyle behavior change and management is key to CVD risk reduction in T2D, but can be difficult to achieve through routine care. Important relationships also exist between glycemic control and concomitant depression, stress, and anxiety.[96,97] Thus, patient-centered, culturally appropriate recommendations through diabetes self-management education and support and medical nutrition therapy are key to meeting individualized goals for behavioral change and diabetes self-management.[20,22,33,98]

GLYCEMIC TARGETS AND CONTROL IN T2D

Lessons Learned From the Observational Studies

Higher glycemia increases the risk of CVD in T2D.[99,100] A 1-unit increase in A1c among individuals with diabetes increases the risk of macrovascular disease (MI, stroke, or PAD) by 18%, and attaining a target of <7% reduces CVD risk by 37% over 11 years.[99,101] Observational studies show the lowest mortality at A1c 6% to 6.9% with a dose-dependent increase in mortality with each 1-unit increase in A1c.[102] Fasting glucose in the prediabetes range (100–125 mg/dL) and in the diabetes range (≥126 mg/dL) moderately and dramatically increases CVD risk 3 to 4 times over 30 years, respectively.[103]

Table 2. Study Characteristics of Cardiovascular Outcome Trials Since January 1, 2014

Characteristics							A1C↓	1° Outcome	2° Outcomes				
								HR (95% CI)	HR (95% CI)				
Study	Population studied: Type 2 diabetes and one of the following:	N	Mean age, y	Baseline A1C, %	Median follow-up, y	CVD, %	A1C↓ between groups	↓ MACE *P* value Superiority	Nonfatal stroke	Nonfatal MI	CV death	Heart failure hospitalization	Renal outcome
DPP4 inhibitors													
*Saxagliptin SAVOR-TIMI53[108]	Age ≥40 y and CAD, CVA, or PVD or men ≥55 y or women ≥60 y with hypertension, dyslipidemia, or smoking	16492	65	8	2.1	78	−0.2% *P*<0.001	1.00 (0.89–1.12) *P*=0.99 3-pt MACE	1.11 (0.88–1.39)	0.95 (0.80–1.12)	1.03 (0.87–1.22)	1.27 (1.07–1.51)	1.08 (0.88–1.32)
*Alogliptin EXAMINE[109]	MI or UA hospitalization within the previous 15–90 d	5380	61	8	1.5	100	−0.36% *P*<0.001	0.96 (≤1.16) *P*=0.32 3-pt MACE	0.91 (0.55–1.50)	1.08 (0.88–1.33)	0.79 (0.60–1.04)	1.07 (0.79–1.46)	N/A
Sitagliptin TECOS[110]	Age ≥50 y with CAD, stroke, or PAD	14671	65	7.2	3	100	−0.29% *P*<0.001	0.98 (0.89–1.08) *P*=0.65 4-pt MACE	0.97* (0.79–1.19)	0.95* (0.81–1.11)	1.03 (0.89–1.19)	1.00 (0.83–1.20)	N/A
Linagliptin CARMELINA[111]	High CV risk (CAD, stroke, PVD, and urine-albumin creatinine ratio >200 mg/g), and high renal risk (↓ eGFR and micro- or macroalbuminuria)	6991	66	8	2.2	57	−0.36% *P*<0.001	1.02 (0.89–1.17) *P*=0.74 3-pt MACE	0.88 (0.63–1.23)	1.15 (0.91–1.45)	0.96 (0.81–1.14)	0.90 (0.74–1.08)	1.04 (0.89–1.22)
Linagliptin CAROLINA[112]	High CV risk and A1C of 6.5%–8.5%	6042	64	7.2	6.3	42	0%	0.98 (0.84–1.14) *P*=0.76 3-pt MACE	0.87 (0.66–1.15)	1.01 (0.80–1.28)	1.00 (0.81–1.24)	1.21 (0.92–1.59)	N/A
GLP-1 receptor antagonists													
Lixisenatide ELIXA[113]	MI or UA hospitalization within the previous 180 d	6068	60	7.6	2.1	100	−0.27% *P*<0.001	1.02 (0.89–1.17) *P*=0.81 4-pt MACE	1.12 (0.79–1.58)	1.03 (0.87–1.22)	0.98 (0.78–1.22)	0.96 (0.75–1.23)	N/A
Liraglutide LEADER[71,114]	Age ≥50 y with CAD, CVA, PAD, HF, or CKD stage ≥3 Age ≥60 y with microalbuminuria/ proteinuria, hypertension with LVH, LV dysfunction, or ABI <0.9	9,340	64	8.7	3.8	81	−0.40% (−0.45 to −0.34)	0.87 (0.78–0.97) *P*=0.01 3-pt MACE	0.89 (0.72–1.11)	0.88 (0.75–1.03)	0.78 (0.66–0.93)	0.87 (0.73–1.05)	0.78 (0.67-0.92)
Semaglutide SUSTAIN-6[115]	Age ≥50 y with CAD, CVA, PAD, HF, or CKD stage ≥ 3 Age ≥60 y with microalbuminuria/ proteinuria, hypertension with LVH, LV dysfunction, or ABI <0.9	3297	65	8.7	2.1	83	(0.5 mg): −0.7% (1.0 mg): −1.0% *P*<0.001	0.74 (0.58–0.95) *P*=0.02 3-pt MACE	0.61 (0.38–0.99)	0.74 (0.51–1.08)	0.98 (0.65–1.48)	1.11 (0.77–1.61)	0.64 (0.46–0.88)
Semaglutide Oral PIONEER-6[116]	Age ≥50 y with established CVD or CKD, or age ≥60 y with CV risk factors	3183	66	8.2	1.3	85	−0.7% (N/A)	0.79 (0.57–1.11) *P*=0.17 3-pt MACE	0.74 (0.35–1.57)	1.18 (0.73–1.90)	0.49 (0.27–0.92)	0.86 (0.48–1.55)	N/A

(*Continued*)

Table 2. Continued

Characteristics							A1C↓	1° Outcome	2° Outcomes				
								HR (95% CI)	HR (95% CI)				
Study	Population studied: Type 2 diabetes and one of the following:	N	Mean age, y	Baseline A1C, %	Median follow-up, y	CVD, %	A1C↓ between groups	↓ MACE *P* value Superiority	Nonfatal stroke	Nonfatal MI	CV death	Heart failure hospitalization	Renal outcome
Exenatide EXSCEL[117]	CAD, ischemic CVA, ≥50% carotid artery stenosis, or PAD	14752	62	8	3.2	73	−0.53% *P*<0.001	0.91 (0.83–1.00) *P*=0.06 3-pt MACE	0.85 (0.70–1.03)*	0.97 (0.85-1.10)*	0.88 (0.76–1.02)	0.94 (0.78–1.13)	0.88 (0.76–1.01)
Albiglutide HARMONY[118]	Age ≥40 y with CAD, ischemic CVA, ≥50% carotid artery stenosis/procedure, or PAD	9463	64	8.7	1.6	100	−0.52% (−0.58 to −0.45)	0.78 (0.68–0.90) *P*=0.0006 3-pt MACE	0.86 (0.66–1.14)*	0.75 (0.61–0.90)*	0.93 (0.73–1.19)	N/A	N/A
Dulaglutide REWIND[119]	Age ≥50 y with CAD, ischemic CVA, carotid or PAD, or ≥2 of the following: hypertension, dyslipidemia, smoking, or obesity	9901	66	7.3	5.4	31	−0.61% *P*<0.0001	0.88(0.68–0.90) P=0.026 3-pt MACE	0.76 (0.61–0.95)	0.96 (0.79–1.16)	0.91 (0.78–1.06)	0.93 (0.77-1.12)	0.85 (0.77–0.93)
Efpeglenatide AMPLITUDE-O[120]	Age ≥18 y with CAD, ischemic CVA or PAD, or age ≥50 y (M) or 55 y (F) with CKD (eGFR 25.0–59.9 mL·min^{-1}·1.73 m^{-2}) and ≥1 CV risk factor	4076	65	8.9	1.8	90	−1.24% (−1.17 to −1.32)	0.73 (0.58–0.92) *P*=0.007 3-pt MACE	0.80 (0.48–1.31)	0.78 (0.55–1.10)	0.72 (0.50–1.03)	0.61 (0.38–0.98)	0.68 (0.57–0.79)
Sodium-glucose cotransporter-2 inhibitors													
Empagliflozin EMPA-REG[121,122]	MI, multivessel CAD, CAD with ischemia/UA, stroke, or PAD	7020	63	8.7	3.1	100	10 mg: −0.24% (−0.40 to −0.08) 25 mg: −0.36% (−0.51 to −0.20)	0.86 (0.74–0.99) *P*=0.04 3-pt MACE	1.24 (0.92–1.67)	0.87 (0.70–1.09)	0.62 (0.49–0.77)	0.65 (0.50–0.85)	0.54 (0.40–0.75)
Canagliflozin CANVAS[123]	≥30 y with symptomatic CVD ≥50 y with ≥2 of the following: diabetes for ≥10 y, smoking, hypertension, micro-/macroalbuminuria, HDL<38.7 mg/dL	10142	63	8.2	3.6	66	−0.58% (−0.61 to −0.56)	0.86 (0.75–0.97) *P*=0.02 3-pt MACE	0.90 (0.71–1.15)	0.85 (0.69–1.05)	0.87 (0.72–1.06)	0.67 (0.52–0.87)	0.60 (0.47–0.77)
Dapagliflozin DECLARE–TIMI[124]	CAD, CVA, or PAD Men ≥55 y or women ≥60 y with hypertension, dyslipidemia, or smoking	17160	64	8.3	4.2	41	−0.42% (−0.40 to −0.45)	0.93 (0.84–1.03) *P*=0.17 3-pt MACE	1.01 (0.84–1.21)	0.89 (0.77–1.01)	0.98 (0.82-1.17)	0.73 (0.61–0.88)	0.76 (0.67–0.87)
Ertugliflozin VERTIS-CV[125]	≥40 y with atherosclerotic CVD (CAD, cerebrovascular, or PAD)	8246	64	8.2	3.5	100	≈ −0.3%	0.97 (0.85–1.11) 3-pt MACE	1.00 (0.76–1.32)	1.04 (0.86–1.27)	0.92 (0.77–1.11)	0.70 (0.54–0.90)	0.81 (0.63–1.04)
Sotagliflozin SCORED[126]	≥18 y with CKD (eGFR, 25–60 mL·min^{-1}·1.73 m^{-2}), and ≥1 major CV risk factor in ≥18 y or ≥2 minor CV risk factors in ≥55 y	10584	69	8.3	1.3	49	−0.42% (−0.47 to −0.38)	0.72 (0.63–0.83) 4-pt MACE	N/A	N/A	0.77 (0.65–0.91)	0.67 (0.55–0.82)	0.71 (0.46–1.08)

(*Continued*)

Table 2. Continued

Characteristics							A1C↓	1° Outcome	2° Outcomes				
								HR (95% CI)	HR (95% CI)				
Study	Population studied: Type 2 diabetes and one of the following:	N	Mean age, y	Baseline A1C, %	Median follow-up, y	CVD, %	A1C↓ between groups	↓ MACE *P* value Superiority	Nonfatal stroke	Nonfatal MI	CV death	Heart failure hospitalization	Renal outcome
Sotagliflozin SOLOIST-WHF[127]	18–85 y hospitalized with HF and received IV diuretics	1222	70	7.2	0.8	N/A	N/A	0.72 (0.56–0.92) 4-pt MACE	N/A	N/A	0.84 (0.58–1.22)	0.64 (0.49–0.83)	N/A
Insulin													
Insulin Degludec DEVOTE[128]	≥50 y and CAD/MI, CVA, PAD, HF, or CKD (GFR 30–59) ≥60 y with micro/ macroalbuminuria, hypertension with LVH, LV dysfunction, ABI <0.9	7637	65	8.4	2	63	0.01% *P*=0.78	0.91 (0.78–1.06) (*P*=0.21) 3-pt MACE	0.90 (0.65–1.23)	0.85 (0.68–1.06)	0.96 (0.76–1.21)	…	…
Glitazars													
Aleglitazar ALECARDIO[129]	MI or UA hospitalization	7226	61	7.8	2 terminated due to futility	100	−0.60% *P*<0.001 at 3 mo	0.96 (0.83–1.11) *P*=0.57 3-pt MACE	0.98 (0.66–1.45)	0.89 (0.74–1.07)	1.15 (0.87–1.50)	1.22 (0.94–1.59)	2.85 (2.25–3.60)
Peroxisome proliferator-activated receptor gamma agonists													
Pioglitazone TOSCA-IT[130] (Unblinded Trial, Block Randomized)	All-cause death, nonfatal MI, nonfatal stroke, or urgent coronary revascularization (futility)	3028	62	7.7	5.7	11	0.06, *P*=0.01	0.96 (0.74–1.26) *P*=0.79 4-pt MACE	0.79 (0.41–1.53)	0.87 (0.48–1.55)	…	…	1.03 (0.89–1.19)‡
Pioglitazone IRIS[131,132]	Insulin resistance without diabetes, with recent CVA	3876	64	5.8	4.8	100	…	0.76 (0.62–0.93) *P*= 0.007 2-pt MACE	0.82 (0.61–1.10)*	…	0.93 (0.73–1.17)§	…	…

ABI indicates ankle brachial index; CAD, coronary artery disease; CKD, chronic kidney disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; LV, left ventricular; LVH, left ventricular hypertrophy; MACE, major adverse cardiovascular events; MI, myocardial infarction; N/A, not available; PAD, peripheral artery disease; pt, point; PVD, peripheral vascular disease; SBP, systolic blood pressure; and UA, unstable angina.

3-Point MACE: Cardiovascular death, nonfatal MI, nonfatal stroke; 4-point MACE: Cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for UA or HF; 4-point MACE for TECOS, ELIXA: Cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for UA; 2-pt MACE for IRIS: Fatal or nonfatal stroke or MI; 2-pt MACE for SOLOIST-WHF: Deaths from cardiovascular causes and hospitalizations and urgent visits for HF.

Renal Composite Outcome: SAVOR-TIMI53 (Saxagliptin): Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL; CARMELINA (Linagliptin): First sustained end-stage renal disease, death attributable to renal failure, or sustained decrease of ≥40% in estimated glomerular filtration rate from baseline. (Participants with preexisting end-stage renal disease were excluded from the trial.) LEADER (Liraglutide): Composite of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, end-stage renal disease, or death due to renal disease; SUSTAIN-6 (Semaglutide): New or worsening nephropathy includes persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of less than 45 mL·min^{-1}·1.73 m^{-2} of body-surface area (according to the Modification of Diet in Renal Disease criteria), or the need for continuous renal-replacement therapy; EXSCEL (Exenatide): 40% eGFR decline, renal replacement, renal death, or new macroalbuminuria; EMPA-REG (Empagliflozin): Doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease; CANVAS (Canagliflozin): Sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes; DECLARE-TIMI58 (Dapagliflozin): ≥40% decrease in estimated glomerular filtration rate to <60 mL·min^{-1}·1.73 m^{-2} of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes; VERTIS-CV (Ertugliflozin): Death from renal causes, renal replacement therapy, or doubling of the serum creatinine level; SCORED (Sotagliflozin): First occurrence of a sustained decrease of ≥50% in the eGFR from baseline for ≥30 days, long-term dialysis, renal transplantation, or sustained eGFR of <15 mL·min^{-1}·1.73 m^{-2} for ≥30 days; ALECARDIO (Aleglitazar): Composite renal end point of the development of end-stage renal disease, doubling of serum creatinine, or >50% increase in creatinine leading to study drug discontinuation; AMPLITUDE-O (Efpeglenatide): Composite renal end point of incident macroalbuminuria, increase in the urinary albumin-to-creatinine ratio of ≥30% from baseline, a sustained decrease in the eGFR of ≥40% for ≥30 days, renal-replacement therapy for ≥90 days, or a sustained eGFR of <15 mL·min^{-1}·1.73 m^{-2} for ≥30 days; A1C Difference: Difference of A1C between active agent and placebo treatment groups (with Least Squares *P* value or 95% CI) at study end.

*Fatal and nonfatal MI or stroke.

†Published before January 1, 2014.

‡new or worsening nephropathy.

§Death from any cause.

Randomized Trials With Intensive Glycemic Control Using Traditional Antihyperglycemic Drugs

Earlier randomized controlled trials (RCTs) focused on CVD prevention in T2D through intensive glycemic control targeting an A1c <6% to 6.5% compared with standard therapy (A1c 7%–7.9%).[104–106] In meta-analyses, Ray et al[104] found a 17% reduction in MI and a 15% reduction in coronary heart disease with tight glycemic control, but no effect on stroke or all-cause mortality. Kelly et al[105] found a 16% reduction in nonfatal MI, no effect on cardiovascular or all-cause mortality, and twice the risk of hypoglycemia with intensive control. Boussageon et al[106] found no effect of intensive glycemic control on overall or cardiovascular mortality but a 2-fold higher risk of severe hypoglycemia and 47% increase in HF. These results suggest that any potential benefit of intensive glycemic control on CVD is modest and may be counterbalanced by increased risk of hypoglycemia and death, especially in older individuals. Most of these trials studied intensive glucose control with insulin, whereas intensive glucose control with lifestyle and newer antihyperglycemic agents is an area for further study.

CVOTs of Newer Antihyperglycemic Agents

Background

Because rosiglitazone was linked to increased risk of HF and MI, the FDA mandated that, in addition to demonstrating cardiovascular safety in phase 3 trials, newer agents should undergo a postmarketing phase 4 CVOT and show noninferiority to standard care in patients with preexisting CVD over a 2-year follow-up period.[107] Since 2014, there have been a number of CVOTs using newer antihyperglycemic agents with traditional glucose-lowering effects, but with the addition of a significant number of favorable cardiometabolic effects (Table 2).

Dipeptidyl Peptidase-4 Inhibitors

Dipeptidyl peptidase-4 (DPP4) inhibitors inhibit the DPP4 enzyme, prolonging the action of the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide leading to inhibition of glucagon release, increased insulin secretion, decreased gastric emptying, and lower glucose. DPP4 inhibitors tested in CVOTs include saxagliptin (SAVOR-TIMI53 [Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53]),[108] alogliptin (EXAMINE [Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care]),[109] sitagliptin (TECOS [Trial Evaluating Cardiovascular Outcomes With Sitagliptin]),[110] linagliptin (CARMELINA [Cardiovascular and Renal Microvascular Outcome Study With Linagliptin] and CAROLINA [Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes])[111,112] with inclusion criteria ranging from high cardiovascular risk to known CVD with median follow-up of 1.5 to 3 years. DPP4 inhibitors reduced A1c by 0.2% to 0.36% but showed no reduction in MACE (Table 2). There are concerns for increasing the risk of HF with saxagliptin but not the other DPP4 inhibitors.[133,134]

GLP-1 Receptor Agonists

GLP-1RAs stimulate insulin release, inhibit glucagon release, and slow gastric emptying to slow glucose absorption (Figure 2).[135] GLP-1RAs are administered as daily (liraglutide, lixisenatide) or once weekly (albiglutide, dulaglutide, efpeglenatide, exenatide, and semaglutide) injections. Semaglutide is also available for oral administration. Seven GLP-1RAs have completed CVOT trials: lixisenatide (ELIXA [Evaluation of Lixisenatide in Acute Coronary Syndrome]),[113] liraglutide (LEADER [Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results]),[71,114] semaglutide (SUSTAIN-6 [Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes], PIONEER-6 [Peptide Innovation for Early Diabetes Treatment 6]),[115,116] exenatide (EXSCEL [Exenatide Study of Cardiovascular Event Lowering Trial),[117] albiglutide (HARMONY [Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease]),[118] dulaglutide (REWIND [Researching Cardiovascular Events With a Weekly Incretin in Diabetes]),[136] and efpeglenatide (AMPLITUDE-O [A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Effect of Efpeglenatide on Cardiovascular Outcomes in Type 2 Diabetes Patients at High Cardiovascular Risk]).[120] Established ASCVD at baseline ranged from 31% in REWIND up to 100% in ELIXA and HARMONY. GLP-1RAs decreased A1c (0.27%–1.0%), weight (0.8–4 kg), and systolic BP (SBP; 0.8–2.6 mm Hg) over 2.1 to 3.8 years (Table 2).

Although lixisenatide, exenatide, and oral semaglutide were noninferior to standard care, liraglutide, semaglutide SQ, albiglutide, dulaglutide, and efpeglenatide showed a statistically significant 12% to 27% MACE reduction (Table 2). This reduction was driven by fewer cardiovascular deaths with liraglutide, less MI with albiglutide, and fewer strokes with injectable semaglutide and dulaglutide. In meta-analyses, GLP-1RAs reduced risk of 3-point MACE (10%–12%), cardiovascular mortality (12%–13%), all-cause mortality (12%), MI (6%–9%), and stroke (13%–14%).[137,138] There was no significant effect on hospitalizations for HF (HHF). In subgroup analyses, GLP-1RAs performed better among individuals without HF, except for albiglutide.

Adverse Effects

Gastrointestinal disturbances and increased heart rate are common GLP-1RA side effects. Major concerns regarding pancreatitis, pancreatic cancer, and medullary

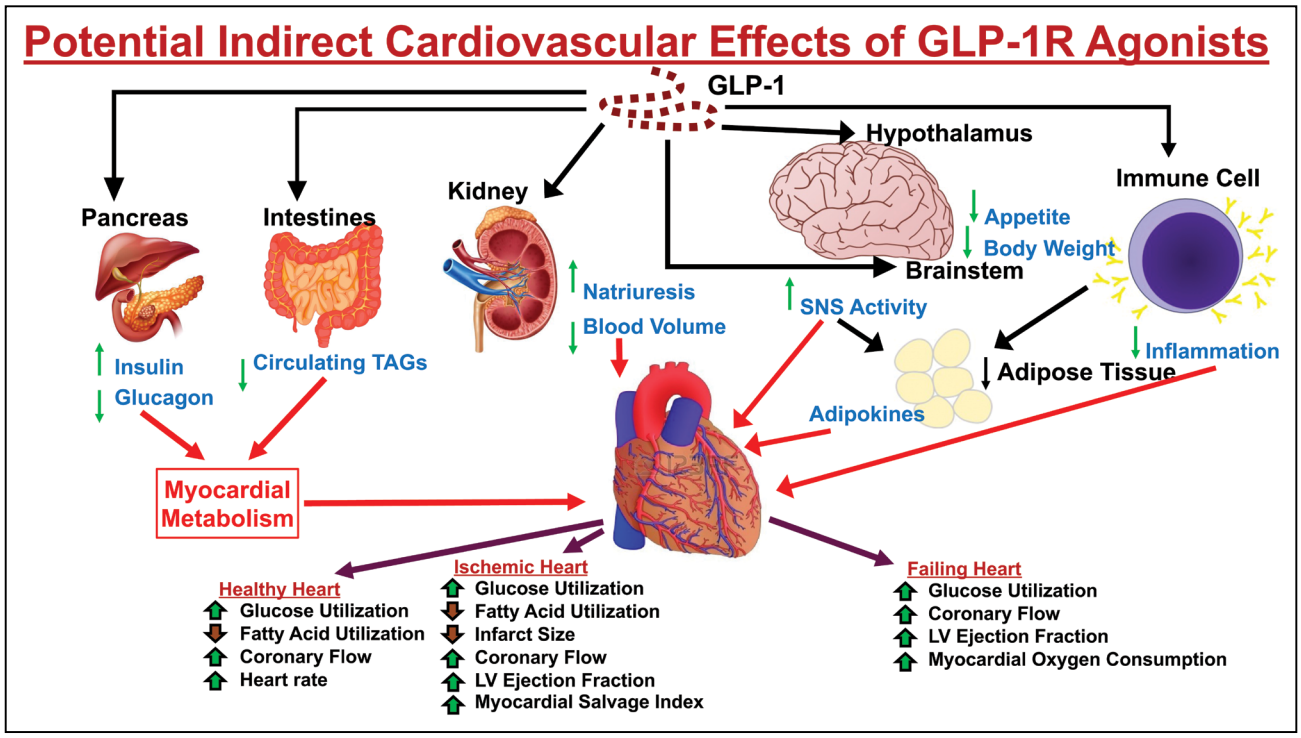

Figure 2. Proposed indirect effects of GLP-1R agonists.
GLP-1 indicates glucagon-like peptide 1; LV, left ventricular; and SNS, sympathetic nervous system.
Adapted with permission from Ussher et al.[135] © 2014 American Heart Association, Inc.

thyroid cancer have not panned out in meta-analyses of clinical trials.[139] Retinopathy occurred at a higher rate with semaglutide.[139]

Sodium-Glucose Cotransporter-2 Inhibitors

SGLT-2Is reduce filtered glucose reabsorption in the proximal renal tubule, leading to glucosuria (Figure 3).[140] SGLT-2Is tested in CVOTs: empagliflozin (EMPA-REG [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients]),[121,122] canagliflozin (CANVAS [Canagliflozin Cardiovascular Assessment Study]),[123] dapagliflozin (DECLARE–TIMI 58 [Dapagliflozin Effect on Cardiovascular Events trial]),[124] ertugliflozin (VERTIS-CV [Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes trial]),[125] and sotagliflozin (SCORED [Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk]; SOLOIST-WHF [Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure]; SGLT-1/2I).[126,127] All of the EMPA-REG and VERTIS-CV, 41% of CANVAS, 66% of DECLARE–TIMI 58, and 49% of SCORED subjects had established ASCVD at baseline. SGLT-2Is lowered A1c (0.36%–0.58%), SBP (2–3.9 mm Hg), and weight (1.0–2.8 kg) compared with placebo over 1 to 4 years (Table 2).

EMPA-REG and CANVAS both showed a significant 14% lower risk of MACE.[121,123] MACE reduction with empagliflozin was primarily driven by a significant (38%) reduction in cardiovascular death. In CANVAS, none of the individual MACE components (cardiovascular death, MI, or stroke) were significantly reduced except in the established ASCVD subgroup.[121,123] CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) established the MACE benefit of canagliflozin in those with diabetes, chronic kidney disease (CKD), and proteinuria.[141] DECLARE-TIMI 58 and VERTIS-CV did not demonstrate a significant MACE reduction (3%–7%) in overall, primary, or secondary prevention cohorts, although there was a trend toward benefit in secondary prevention in DECLARE-TIMI 58.[124] CANVAS did not show MACE benefit in the primary prevention subcohort either.[123]

The SGLT-2I trials have shown a congruently lower risk (27%–35%) of HHF.[121,123–125] In magnitude, this is the largest cardiovascular benefit of SGLT-2Is. HHF was reduced more in those with CVD but appeared independent of baseline HF. DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) trials confirmed reduction in HHF and cardiovascular death in patients with preexisting HF with or without diabetes.[142,143]

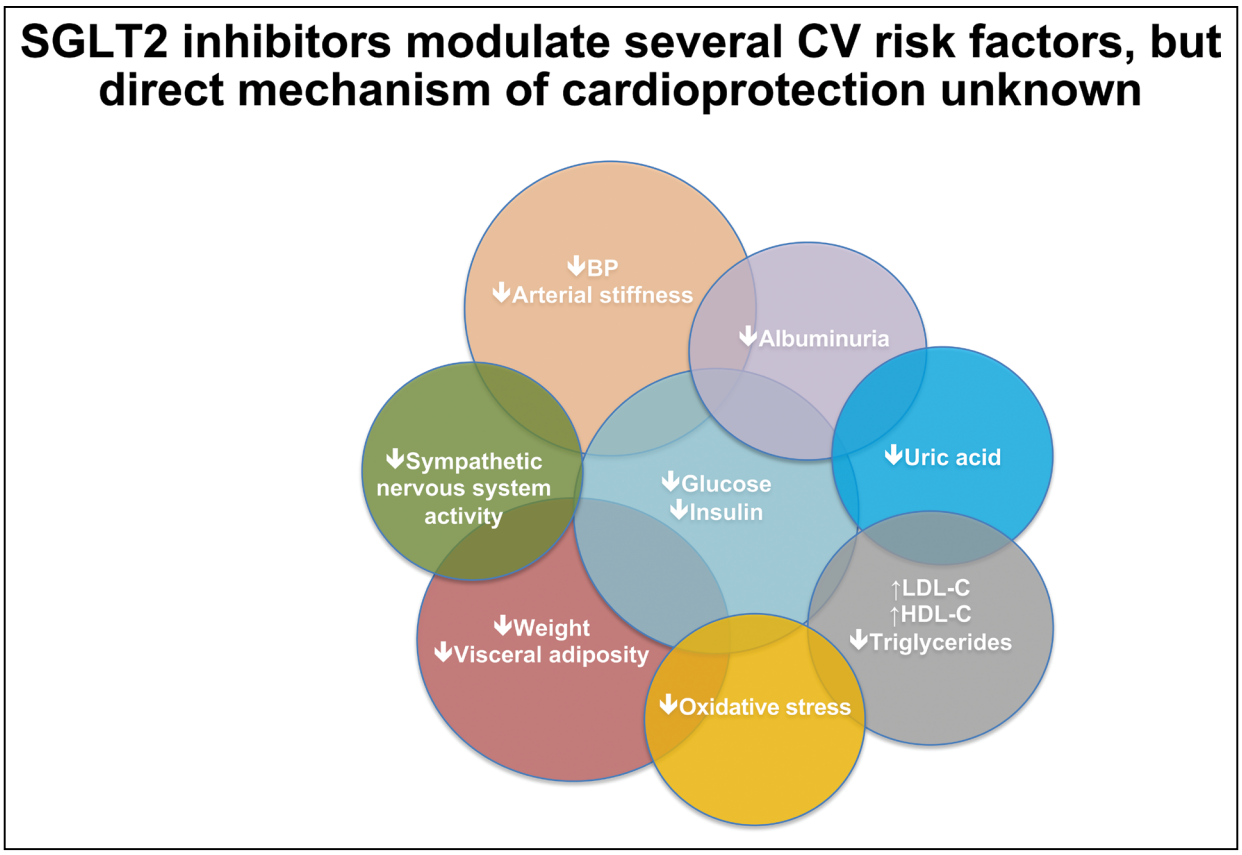

Figure 3. Potential risk factor targets of SGLT-2 inhibitors.
BP indicates blood pressure; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and SGLT-2, sodium-glucose cotransporter-2.
Adapted from Inzucchi et al.[140]

Meta-analyses of CVOTs (excluding ertugliflozin and sotagliflozin) reveal that SGLT-2Is reduced MACE (11%), cardiovascular mortality or HHF (23%), all-cause mortality (15%), MI (11%), and cardiovascular mortality (16%) with no effect on stroke.[138] The 3-point MACE, MI, and cardiovascular mortality benefits were only reduced among those with established ASCVD, whereas the HHFs were reduced independent of baseline ASCVD or HF.[138] Real-world observational studies have largely shown similar findings of reduced HHF and cardiovascular mortality, but additionally suggest lower risk of MI and stroke (Table 3).[144–155]

Adverse Effects

Higher risk of genital and urinary tract mycotic and bacterial infections exists across the SGLT-2I class because of glucosuria. There have been rare postmarketing reports of perineal necrotizing fasciitis including 55 cases from March 2013 to January 2019, with no clear causative link but requiring vigilance.[157] Polyuria-related side effects of dehydration and acute kidney injury are more likely with higher dosages and preexisting CKD and HF. Studies have shown reduced bone mineral density at the hip with SGLT-2Is, but meta-analyses of clinical trials have not shown increased hip fracture risk.[162]

Insulin Degludec, Aleglitazar, and Pioglitazone

Glitazars are dual peroxisome proliferator-activated receptor agonists that lower glucose and lipids. Glitazones improve insulin sensitivity through peroxisome proliferator-activated receptor gamma and impact lipid metabolism through peroxisome proliferator-activated receptor alpha. Insulin Degludec (DEVOTE [A Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events]),[128] Aleglitazar (ALECARDIO [The Effect of Aleglitazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus]),[129] and Pioglitazone (TOSCA-IT [Thiazolidinediones Or Sulphonylureas and Cardiovascular Accidents: Intervention Trial])[130] did not demonstrate CVD risk reduction. Pioglitazone (IRIS [Insulin Resistance Intervention After Stroke]) after ischemic stroke or transient ischemic attack in participants with insulin resistance (without diabetes) reduced the risk of fatal or

Table 3. Observational Studies of SGLT-2 Inhibitors

Study characteristics								Outcomes Hazard ratio (95% CI)				
Study	Study characteristics and design	Population studied: type-2 diabetes with and without baseline CVD defined as:	N	Baseline CVD, %	Mean follow-up time	Mean age with CVD at baseline	Mean age without CVD at baseline	Heart failure hospitalization	Stroke	Myocardial infarction	Mortality	Composite outcomes
CVD-REAL												
SGLT-2 inhibitor vs oGLD CVD–REAL[154] (United States, United Kingdom, Sweden, Norway, and Denmark)	Multinational observational study Propensity score matching	Previous history of acute MI, UA, stroke, heart failure, transient ischemic attack, coronary revascularization, occlusive PAD	306 156	13	313–387 d SGLT-2i 299–383 d oGLDs	62.7 SGLT-2i 63.5 oGLD	56.0 SGLT-2i 56.0 oGLD	0.72 (0.63–0.82) with CVD 0.61 (0.48–0.78) without CVD	N/A	N/A	0.56* (0.44–0.70) with CVD 0.56* (0.50–0.63) without CVD	0.63† (0.57–0.70) with CVD 0.56† (0.50–0.62) without CVD
SGLT-2 inhibitor vs oGLD (on-treatment) CVD–REAL[146] (United States, Sweden, Norway and Denmark)	Multinational observational study Nonparsimonious propensity score matching	Previous history of acute MI, UA, stroke, heart failure, transient ischemic attack, coronary revascularization, occlusive PAD	205 160	14	254 d SGLT-2i 232 d oGLD	57 No differentiation by baseline CVD status		N/A	0.80 (0.66–0.97)	0.78 (0.65–0.95)	N/A	N/A
SGLT-2 inhibitor vs oGLD (intent-to-treat) CVD–REAL[148] (United States, Sweden, Norway, and Denmark)	Multinational observational study Nonparsimonious propensity score matching	Previous history of acute MI, UA, stroke, heart failure, transient ischemic attack, coronary revascularization, occlusive PAD	205 160	14	339 d SGLT-2i 332 d oGLD	57 No differentiation by baseline CVD status		N/A	0.83 (0.71–0.97)	0.85 (0.72-1.00)	N/A	N/A
SGLT-2 inhibitor vs oGLDs CVD-REAL[147] (United States, Norway, Denmark, Sweden, Germany,† United Kingdom)	Retrospective multinational observational study 1:1 propensity score matched	Previous history of acute MI, UA, heart failure, atrial fibrillation, stroke, PAD	309 056	13 SGLT-2i 13.1 oGLDs	253 d SGLT-2i 233 d oGLDs	56.9 SLGT-2i 57.0 oGLDs No differentiation by baseline CVD status		0.61 (0.51–0.73)	N/A	0.49* (0.41–0.57)	N/A	0.54† (0.48–0.60)
SGLT-2 inhibitor vs oGLDs CVD-REAL Nordic[148] (Denmark, Norway, and Sweden)	Retrospective multinational observational study Propensity score matched	Previous history of MI, stroke, UA, heart failure, atrial fibrillation	91 320	24.9 SGLT-2i 24.8 oGLDs	0.9 y	61.2 SGLT-2i 61.2 oGLDs No differentiation by baseline CVD status		0.70 (0.61–0.81)	0.86 (0.72–1.04) nonfatal	0.87 (0.73–1.03) nonfatal	0.51 (0.45–0.58)* 0.53 (0.40–0.71)§ Baseline CVD 0.60 (0.42–0.85)§ No CVD: 0.55 (0.34–0.90)§	0.78 (0.69–0.87)‡ Baseline CVD 0.70 (0.59–0.83) No CVD: 0.90 (0.76–1.07)
SGLT-2 inhibitor vs oGLD (intent-to-treat) CVD-REAL 2[149] (South Korea, Japan, Singapore, Israel, Australia, and Canada)	Retrospective multinational observational study Nonparsimonious propensity score matching	Previous history of acute MI, UA, stroke, heart failure, atrial fibrillation, PAD	470 128	26.8 SGLT-2i 25.6 oGLD	374 d SGLT-2i 392 d oGLD	56.7 No differentiation by CVD status No postmatch data available		0.64 (0.50–0.82)	0.68 (0.55–0.84)	0.81 (0.74–0.88)	0.51 (0.37–0.70)*	0.60 (0.47–0.76)†

(*Continued*)

Table 3. Continued

Study characteristics								Outcomes Hazard ratio (95% CI)				
Study	Study characteristics and design	Population studied: type-2 diabetes with and without baseline CVD defined as:	N	Baseline CVD, %	Mean follow-up time	Mean age with CVD at baseline	Mean age without CVD at baseline	Heart failure hospitalization	Stroke	Myocardial infarction	Mortality	Composite outcomes
Truven Health MarketScan database												
SGLT-2 inhibitor vs sulfonylureas Truven Health MarketScan[150] (United States)	Retrospective cohort analysis Propensity score matching	Previous history of MI, angina pectoris, stroke, coronary revascularization, coronary artery disease, cerebrovascular diseases, cerebral infarction, transient ischemic attack, cerebral hemorrhage and subarachnoid hemorrhage	125 534	14.28 SGLT-2i 14.28 sulfonylureas	12 mo	54 SGLT-2i 54 sulfonylureas No differentiation by CVD status		0.48 (0.40–0.57)	0.69 (0.61–0.78)	0.70 (0.61–0.81)	N/A	0.50 (0.45–0.55)‖
SGLT-2 inhibitor vs DPP-4 Truven Health MarketScan[150] (United States)	Retrospective cohort analysis Propensity score matching	Previous history of MI, angina pectoris, stroke, coronary revascularization, coronary artery disease, cerebrovascular diseases, cerebral infarction, transient ischemic attack, cerebral hemorrhage and subarachnoid hemorrhage	133 266	12.72 SGLT-2i 14.28 sulfonylureas	12 mo	55 SGLT-2i 54 sulfonylureas No differentiation by CVD status		0.54 (0.48–0.60)	0.61 (0.50–0.73)	0.72 (0.63–0.82)	N/A	0.57 (0.52–0.62)‖
DPP-4 inhibitors vs sulfonylureas Truven Health MarketScan[144]	US retrospective observational study Propensity scoring	Previous history of acute MI, ischemic heart disease, stroke, PAD, percutaneous coronary intervention, revascularizations, bypasses, stenting, angioplasty, atherectomy, or lower extremity amputation	218 556	24.94	6 mo	63.9 DPP-4i 63.9 sulfonylureas	54.7 DPP-4i 54.8 sulfonylureas	0.95 (0.78–1.15) with CVD 0.59 (0.38–0.89) without CVD	0.87 (0.65–1.16) with CVD 0.53 (0.37–0.74) without CVD	0.84 (0.65–1.09) with CVD 0.74 (0.57–0.95) without CVD	N/A	0.87 (0.78–0.96)¶ with CVD 0.70 (0.61–0.81)¶ without CVD
Korean HIRA												
SGLT-2 inhibitor vs DPP-4i Korean HIRA[151]	South Korean nationwide population-based cohort study Propensity score matching	Previous history of acute MI, other ischemic heart disease, heart failure, cerebral infarction, cerebrovascular event, occlusive PAD, coronary revascularization	118 958	18.8 SGLT-2i 18.8 DPP-4i	318.5 d	59.7 SGLT-2i 59.7 DPP-4i	51.9 SGLT-2i 51.7 DPP-4i	0.66 (0.58–0.75)	N/A	N/A	N/A	N/A
Optum Clinformatics Datamart												
Canagliflozin vs DPP-4 inhibitor Optum Clinformatics Datamart[152] (United States)	Population-based retrospective cohort Pairwise 1:1 propensity score matched	Previous history of coronary heart disease, cerebrovascular disease, peripheral vascular disease, and heart failure	35 334	30.10 SGLT-2i 30.38 DPP-4i	0.6 y	56.5 SGLT-2i 56.5 DPP-4i No differentiation by CVD status		0.70 (0.54–0.92)	N/A	N/A	N/A	0.89 (0.68–1.17)#

(*Continued*)

Table 3. Continued

Study characteristics								Outcomes Hazard ratio (95% CI)				
Study	Study characteristics and design	Population studied: type-2 diabetes with and without baseline CVD defined as:	N	Baseline CVD, %	Mean follow-up time	Mean age with CVD at baseline	Mean age without CVD at baseline	Heart failure hospitalization	Stroke	Myocardial infarction	Mortality	Composite outcomes
Canagliflozin vs GLP-1RA Optum Clinformatics Datamart[152] (United States)	US Population-based retrospective cohort Pairwise 1:1 propensity score matched	Previous history of coronary heart disease, cerebrovascular disease, peripheral vascular disease, and heart failure	41 078	31.38 SGLT-2i 31.92 GLP-1RA	0.6 y	56.8 SGLT-2i 56.7 GLP-1RA No differentiation by CVD status		0.61 (0.47–0.78)	N/A	N/A	N/A	1.03 (0.79–1.35)#
Canagliflozin vs sulfonylurea Optum Clinformatics Datamart[152] (United States)	US Population-based retrospective cohort Pairwise 1:1 propensity score matched	Previous history of coronary heart disease, cerebrovascular disease, peripheral vascular disease, and heart failure	34 708	29.09 SGLT-2i 28.93 sulfonylurea	0.6 y	55.9 SGLT-2i 55.8 sulfonylurea No differentiation by CVD status		0.51 (0.38–0.67)	N/A	N/A	N/A	0.86 (0.65–1.13)#
Evidence for Cardiovascular Outcomes With Sodium Glucose Cotransporter 2 Inhibitors in the Real World (EASEL) Cohort												
SGLT-2 inhibitor vs oGLDs US Department of Defense Military Health System[153] (United States)	Retrospective, observational study Propensity matching	Previous history of coronary artery disease, heart failure, cerebrovascular disease, and peripheral artery disease	25 258	100	1.6 y	65.8 SGLT2i 65.9 oGLDs No differentiation by CVD status		0.57 (0.45–0.73)	0.85 (0.66–1.10)	0.81 (0.64–1.03)	0.57 (0.49–0.66)*	0.67 (0.60–0.75)‖
HealthCore Integrated Research Environment database												
SGLT-2 inhibitors vs DPP4 inhibitors HealthCore Integrated Research Environment database[154] (United States)	Retrospective observational study Propensity score matched	N/A	14 697	13.7 SGLT-2i 13.5 DPP-4i	22.9 mo SGLT2i 24 mo DPP4i	54.9 SGLT2i 55.1 DPP4i No differentiation by CVD status		0.68 (0.54–0.86)	N/A	N/A	N/A	N/A
The Health Improvement Network												
Dapagliflozin vs oGLD The Health Improvement Network[153] (United States)	Retrospective cohort study Propensity score matched	Prior history of ischemic heart disease, stroke, and heart failure	22 124	19.6	9.8 y SGLT2i 8.5 y oGLDs	58.3 SGLT2i 58.5 oGLDs (with CVD)		N/A	N/A	N/A	Adjusted incidence rate ratio: 0.50 (0.33–0.75)#	N/A

CVD indicates cardiovascular disease; CVD-REAL, Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors; DPP-4i, dipeptidyl peptidase-4 inhibitor; HIRA, Health Insurance Review and Assessment Service; MI, myocardial infarction; GLP-1RA, glucagon-like peptide 1 receptor agonist; oGLD, other glucose lowering drug; PAD, peripheral artery disease; SGLT-2, sodium-glucose co-transporter 2; SGLT-2i, sodium-glucose co-transporter 2 inhibitor; and UA, unstable angina.

*Denotes all-cause mortality.

†Denotes hospitalizations for heart failure or all-cause mortality.

‡Denotes cardiovascular mortality, nonfatal MI, nonfatal ischemic or nonfatal hemorrhagic stroke.

§Denotes cardiovascular mortality.

‖Denotes stroke and myocardial infarction.

¶Hospitalization for acute MI, hospitalization for stroke, hospitalization for UA, coronary revascularization, and hospitalizations for heart failure.

#Denotes acute MI, ischemic stroke, hemorrhagic stroke.

nonfatal stroke or myocardial infarction by 24% over 4.8 years.[131]

Regulatory Approvals, Roles, and Indications of Newer Antihyperglycemic Drugs for CVD Risk Reduction

The FDA has approved a cardiovascular death reduction label for empagliflozin and a MACE reduction label for liraglutide, semaglutide (subcutaneous), and canagliflozin in adults with T2D and established CVD and for dulaglutide in adults with T2D and established CVD or multiple CVD risk factors. In addition, dapagliflozin is approved to decrease HHF in T2D and established CVD or multiple CVD risk factors and to decrease HHF and CVD-related death in HF and reduced ejection fraction, with or without diabetes. The important question is which agent to prescribe for which patient in the pursuit of diabetes precision medicine. Some GLP-1RA trials have shown impressive improvement of MACE and atherosclerotic outcomes including MI and stroke. SGLT-2I trials have shown major reductions in HHF and renal outcomes in all trials, and cardiovascular death in the EMPA-REG trial. EMPA-REG and CANVAS, which showed a positive outcome for MACE, were more effective in individuals ≥65 years of age. Choice of diabetes therapy should be tailored per patients' risk profile and preference. In this context, the direct and indirect effects of GLP-1RA and SGLT-2Is are important because improved glycemia does not account for all the cardiovascular benefit (Figures 2 and 3).[159]

Risk of Hypoglycemia and Related Cardiovascular Events

SGLT-2Is, GLP-1RA, and DPP4 inhibitors have higher risk of hypoglycemia (24%–44%), but serious hypoglycemia (resulting in hospitalization, medical assistance, trial withdrawal, or study-defined major or serious hypoglycemia) is similar to placebo.[138] Risk increases at higher dosages in patients with CKD and HF and coadministration with insulin or sulfonylureas.[160,161] In LEADER, individuals with severe hypoglycemia were more likely to experience MACE, cardiovascular death, and all-cause death, with higher risk shortly after hypoglycemia.[162]

Glycemic Targets and Antihyperglycemic Medications in T2D Summary

The ADA guidelines recommend individualization of A1c targets using a patient-centered approach: <7% (53 mmol/mol) for most nonpregnant adults; <6.5% for young patients, long life expectancy, and no significant CVD; and less stringent targets (ie, <8%) for those with a history of severe hypoglycemia, limited life expectancy, advanced microvascular, or macrovascular complications.[163] In the ADA guidelines, metformin is first-line therapy. Among patients with established ASCVD, SGLT-2Is, or GLP-1RA with demonstrated cardiovascular benefit are recommended with preference for a SGLT-2Is in those at high risk of HF.[164] In most patients who require the greater glucose-lowering effects of an injectable medication, the ADA guidelines initially prefer GLP-1RA over insulin (Figure S1 in the Supplemental Material).[164] The American Association of Clinical Endocrinologists guidelines support an A1c goal of ≤6.5% for most patients or >6.5% if the lower target cannot be achieved without adverse outcomes or established macrovascular disease.[165] The addition of either a GLP1-RA or SGLT-2I is recommended for patients with established ASCVD.[165] The 2019 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Primary Prevention of CVD gives a class IIa recommendation for metformin as first-line therapy for T2D and a class IIb recommendation to initiate SGLT-2Is or GLP-1RAs for adults with ASCVD risk factors who require glucose lowering despite lifestyle modifications and metformin (Figure S2 in the Supplemental Material).[21] The 2019 European Society of Cardiology Guidelines/European Association for the Study of Diabetes and ACC 2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With T2D guidelines prefer GLP1-RA or SGLT-2Is as first-line therapies for individuals with high cardiovascular risk or established ASCVD (Figures S3 and S4 in the Supplemental Material).[166,167] Ongoing and future studies may further clarify the role of metformin or GLP1-RA/SGLT-2Is as first-line therapy.

BLOOD PRESSURE MANAGEMENT

Historically, studies have repeatedly demonstrated a J-curve or U-shape relationship in patients with T2D reflecting increased cardiovascular risk and negative outcomes at both low and high BP levels.[168–171] Conversely, intensive BP lowering has reduced nonfatal stroke rates and microvascular events such as nephropathy.[172] Stroke prevention may not be without consequence because higher rates of hypotension, hypokalemia, and serum creatinine elevation are noted, mainly because of the effects of aggressive antihypertensive treatment.[173] Therefore, optimal BP levels continue to be debated.[174]

Randomized Trials With Intensive BP Control and Impact of SPRINT Data

The landmark clinical trial ACCORD BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) randomized 4733 patients with T2D to intensive therapy, targeting an SBP of <120 mm Hg, or standard therapy,

Table 4. Recent Publications Comparing BP Targets and Cardiovascular Outcomes

Publication	Year	Analysis	Number of trials/patients	Key findings in patients with diabetes	Impact of findings on target BP in patients with diabetes
Ilkun et al[176]	2020	Post hoc analysis of ACCORD BP study stratified by baseline DBP and glycemic control	1/4731	Intensive SBP lowering decreased risk of CV events irrespective of baseline DBP in the setting of standard glycemic control	Favors lower boundary
Rahman et al[177]	2019	Post hoc analysis of ADVANCE study stratified by baseline SBP and CVD risk	1/10 498	Reduction in mortality, macrovascular, and microvascular events regardless of baseline SBP (evaluated down to <120 mm Hg and <70 mm Hg)	Favors lower boundary
Wang et al[178]	2019	Systematic review and meta-analysis of RCTs comparing intensive vs standard BP control in diabetic patients only	16/24 444	Intensive BP lowering resulted in significant reductions in all-cause mortality, major CV events, stroke, and CV death	Favors lower boundary
Böhm et al[179]	2019	Pooled patient data from ONTARGET and TRANSCEND studies	2/30 937	CV death, MI, stroke, and heart failure hospitalization event rates lower at SBP <140 mm Hg and DBP 80 to <90 mm Hg Low BP levels (<120 or <70 mm Hg) associated with increased CV outcomes (except stroke) and death	Favors lower boundary
Beddhu et al[180]	2018	Post hoc analysis of patient data from ACCORD BP and SPRINT studies	2/14 904	Intensive BP lowering decreased risk of CV events similarly in SPRINT (HR, 0.75) and in the ACCORD BP standard glycemia arm (HR, 0.77) Interaction between intensive SBP lowering and intensive glycemic control may have masked beneficial effects of intensive SBP lowering in ACCORD BP	Favors lower boundary
Buckley et al[181]	2018	Post hoc subgroup analysis of ACCORD and its long-term observation follow-up study	1/1284	5 y of intensive BP control reduced risk of CV death, nonfatal MI, nonfatal stroke, and unstable angina	Favors lower boundary
Brouwer et al[182]	2018	Post hoc analysis of pooled patient data from ACCORD-BP and SPRINT studies	2/14 904	Nonsignificant interaction between intensive BP lowering and type 2 diabetes, however lower event rate of unstable angina, MI, acute heart failure, stroke, and CV death	Favors lower boundary
Wan et al[182]	2018	Population-based retrospective cohort study comparing outcomes stratified by achieved SBP in diabetic patients only	1/28 014	Intensive BP lowering associated with higher CVD risk compared with <130 mm Hg (HR, 1.75) or 140 mm Hg (HR, 1.67)	Favors higher boundary
Thomopoulos et al[183]	2017	Systematic review and meta-analysis of RCTs comparing outcomes stratified by achieved SBP and DBP	81/253 125	Standard BP lowering to SBP <140 mm Hg demonstrated significantly greater relative and absolute reductions of most CV outcomes Little or no further benefit seen in lowering SBP <130 mm Hg	Favors higher boundary
Buckley et al[184]	2017	Post hoc subgroup analysis of ACCORD-BP study	2/652	Intensive BP control to <120 mm Hg significantly reduced risk of CVD death, nonfatal MI, nonfatal stroke, revascularization, or heart failure	Favors lower boundary
Ettehad et al[185]	2016	Systematic review and meta-analysis of large-scale BP-lowering trials	123/613 815	Treatment to SBP <130 mm Hg reduced risk of major CV events, coronary heart disease, stroke, and heart failure	Favors lower boundary
Brunstrom et al[168]	2016	Systematic review and meta-analysis of RCTs including ≥100 patients with diabetes treated for ≥12 mo, comparing any antihypertensive agents or different BP targets	49/73 738	In patients with baseline SBP <140 mm Hg, further treatment increased risk of CV mortality with a tendency toward increased risk of all-cause mortality with no observed benefit	Favors higher boundary
Xie et al[186]	2016	Systematic review and meta-analysis of RCTs comparing intensive vs standard BP control or different BP changes from baseline	19/44 989	Intensive treatment reduced risk for major CV events, MI, and stroke, but had no clear effects on heart failure or CV death	Favors lower boundary

ACCORD-BP indicates Action to Control Cardiovascular Risk in Diabetes Trial; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial; BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; HR, hazard ratio; MI, myocardial infarction; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; RCT, randomized controlled trial; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; and TRANSCEND, Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease.

targeting an SBP of <140 mm Hg.[173] The investigators found no significant difference in the primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes with event rates of 1.87% versus 2.09% per year in the intensive group and standard group, respectively (hazard ratio [HR] with intensive therapy, 0.88 [95% CI, 0.73–1.06]; *P*=0.20).

The results of SPRINT (Systolic Blood Pressure Intervention Trial) created a paradigm shift in BP goals and reinvigorated the deliberation of ideal BP goals. Although it is important to note that patients with diabetes were excluded, the trial was stopped prematurely because of the overwhelming evidence of benefit. Intensive SBP lowering to <120 mm Hg in high-risk patients (defined as the presence of clinical or subclinical CVD other than stroke, CKD, 10-year Framingham Risk ≥15% or age >75 years) resulted in a 25% risk reduction in MI, ACS, stroke, HF, and death attributable to CVD compared with standard BP lowering to <140 mm Hg.[175]

Recent Analyses

Antihypertensive treatment in T2D results in cardiovascular risk reduction when initiated at mean baseline BP of ≥140/90 mm Hg (Table 4). Although those without diabetes may receive continued benefit with SBP <130 mm Hg, this target, and an intensive target <120 mm Hg as well, does not appear to have robust cardioprotective effects in patients with T2D.

Subanalyses of MACE end points in diabetes therapy trials have also provided insight on the relationship between stringent BP control and outcomes. In SAVOR-TIMI 53, the adjusted risk of the composite end point of cardiovascular death, MI, or ischemic stroke showed U-shaped relationships with nadirs at SBP 130–140 mm Hg or diastolic BP 80–90 mm Hg. In addition, diastolic BP <60 mm Hg was associated with increased risk of MI compared to diastolic BP 80–90 mm Hg.[4] Similar findings were also noted in EXAMINE. Among patients who have diabetes with recent acute coronary syndromes, adjusted hazard ratios for MACE, cardiovascular death, or HF were significantly higher for SBP <130 mm Hg and diastolic BP <80 mm Hg.[175]

BP Control in T2D Summary

Although treatment algorithms are similar, there are noteworthy differences in hypertension definitions and goals between the 2017 ACC and AHA Guideline for the Prevention, Evaluation and Management of High BP in Adults[187] and the 2017 ADA Position Statement on Diabetes and Hypertension (Table 5).[188] The ADA does not promote a uniform BP target and instead risk stratifies to avoid overtreatment in frail patients with comorbidities and to decrease the potential of polypharmacy and adverse drug events. Given the significant clinical heterogeneity of patients with T2D, treatment strategies should be patient centered with shared decision-making. A multidisciplinary approach to ensure patients safely achieve BP goals should be incorporated, because the rigorous protocols and intensive follow-up utilized in RCTs are difficult to reproduce in real-world clinical practice.

LIPID ABNORMALITIES AND LIPID-LOWERING THERAPIES

Management of dyslipidemia is central to comprehensive cardiovascular risk factor control and cardiovascular risk reduction for adults with T2D. The most commonly encountered lipid abnormalities in T2D are related to the clustering of risk factors associated with the metabolic syndrome, including increased serum triglycerides, triglyceride-rich very-low-density lipoprotein, triglyceride-rich lipoproteins, small dense low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, LDL particle number, non–HDL-C, and decreased HDL-C. LDL-C is often mild-to-moderately increased. This atherogenic dyslipidemia is associated with both chronic low-level vascular inflammation and a prothrombotic state.[189] Accumulating clinical evidence suggests serum triglyceride is a predictor of ASCVD, comparable to LDL-C in populations with T2D, which both exceed the predictive power of A1c.[190]

The 2018 Cholesterol Guidelines highlight lifestyle-focused therapies as foundational to addressing lipid abnormalities in T2D in addition to consideration of pharmacotherapies. Modest regular physical activity, reducing

Table 5. Summary of Clinical Treatment Guidelines for Hypertension Treatment

Guidelines	Definition	Target blood pressure	First-line agents	Indication for dual antihypertensive therapy
ACC/AHA	130/80	<130/80	Diuretics Angiotensin-converting enzyme inhibitors* Angiotensin receptor blockers* Calcium channel blockers	>140/90
ADA	140/90	<140/90 Or <130/80 with high cardiovascular risk (existing atherosclerotic cardiovascular disease or 10-y risk score ≥15%) provided it can be safely attained	Angiotensin-converting enzyme inhibitors* Angiotensin receptor blockers * Thiazide-like diuretics Dihydropyridine calcium channel blockers	>160/100

*Preferred agents with albuminuria.

sedentary behavior, gradual weight reduction, and a healthy dietary pattern emphasizing vegetables, fruits, whole grains, legumes, healthy protein sources, and vegetable oils should be encouraged. Foods that should be limited include refined sugar, processed carbohydrates, sugar-sweetened beverages, and red meats.[191]

LDL-C Lowering With Statins

Statins are the cornerstone of lipid therapy in T2D. Consistent cardiovascular risk reduction with statins is established with reductions in MI, coronary death, coronary revascularization, and stroke. Among people with T2D, statins are beneficial irrespective of a previous history of ASCVD with those with the highest absolute cardiovascular risk likely to receive the greatest absolute benefit.[192–194]

The 2018 Cholesterol Guidelines[192] provide guidance on recommended statin therapy for primary and secondary prevention in diabetes. In patients ≤75 years of age with diabetes and clinical ASCVD, the highest intensity statin tolerated should be initiated or continued with the aim of achieving a ≥50% reduction in LDL-C. In patients >75 with diabetes and ASCVD, it is reasonable to continue high-intensity statins or the highest intensity statin tolerated after the evaluation of net clinical benefit, potential adverse effects, and significant comorbidities potentially limiting life expectancy.

For primary prevention, adults 40 to 75 years of age with diabetes should be considered for at least a moderate-intensity statin regardless of estimated ASCVD risk (COR I). Moderate-intensity statin therapy is associated with a cardiovascular risk reduction of at least 25%.[193] High-intensity statins are recommended in people with diabetes with multiple ASCVD risk factors, risk-modifying factors, or diabetes-specific risk-enhancing factors including duration of diabetes (>10 years), presence of microalbuminuria, greater than stage 2 nephropathy, evidence of retinopathy, neuropathy, or an ABI <0.9. Since the decision regarding statin intensity is affected by ASCVD risk, assessment of a 10-year estimated risk is recommended. Of note, there have been no primary prevention RCTs in diabetes specifically utilizing high-intensity statins; however, given the significant risk of those with diabetes and multiple risk factors, the 2018 Guidelines[191] give this a class IIa recommendation. In individuals with diabetes >75 already on a statin, it is reasonable to continue, and it is reasonable to initiate statin therapy after a clinician-patient discussion focused on net clinical benefit. In adults 20 to 39 years of age with diabetes, the presence of diabetes-specific risk enhancers favors the initiation of statin therapy (COR IIb).[191]

Statin use is associated with a modest increased incidence of new-onset diabetes. This is most often seen in individuals with predisposing risk factors for diabetes, metabolic syndrome, and those treated with higher intensity statins. The specific mechanisms related to statin-associated diabetes are unclear, and this risk is small relative to the cardiovascular risk reduction seen in people with diabetes or prediabetes treated with statins.[195–198] This association should not be a contraindication to statins or a reason to discontinue therapy, but it should lead to discussion in partnered care focused on strategies to either prevent diabetes or improve glycemic control.[191,199]

LDL-C Lowering With Nonstatins

An important addition to the 2018 Cholesterol Guidelines[191] is the consideration for on-statin therapies in people living with diabetes. In T2D with ASCVD and very high risk (multiple ASCVD events or 1 major event and at least 1 other high-risk condition [age >65, familial hypercholesterolemia, hypertension, tobacco use, history of congestive HF]) on maximally tolerated statins who have not achieved a 50% reduction of LDL-C or with an LDL-C >70 mg/dL adding ezetimibe is reasonable (class IIa) and is the preferred initial agent given the event reduction seen in the IMPROVE-IT trial (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), where the addition of ezetimibe reduced MIs by 24% and ischemic stroke by 39% in participants with diabetes (27% of trial participants).[200] The addition of ezetimibe to moderate-intensity statin therapy can achieve a similar LDL-C reduction as a high-intensity statin. In adults with diabetes and a 10-year ASCVD risk of ≥20%, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL-C by ≥50%.[191]

Data from the FOURIER[201] (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) and ODYSSEY Outcomes[202] (A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of Alirocumab [SAR236553/REGN727] on the Occurrence of Cardiovascular Events in Patients Who Have Recently Experienced an Acute Coronary Syndrome) trials support the consideration of PCSK9 (proprotein convertase subtilsinkexin type 9) inhibitor therapy for very high-risk individuals with ASCVD who have not achieved a 50% LDL-C reduction (or with LDL-C >70 mg/dL/non-HDL-C >100 mg/dL) with maximally tolerated statin and ezetimibe. PCSK9 inhibitors appear to be effective with an expected mean reduction of LDL-C of 60%, and safe in those with and without T2D. Available data suggest that there is no PCSK9 inhibitor–induced increased risk of new-onset diabetes or impact on glycemic control.[203] A clinician-patient discussion including cost-benefit consideration is important before initiating PCSK9 inhibitors.[191]

Bile acid sequestrants (expected to lower LDL-C by 15%–30%) can also be considered in diabetes with significant statin-associated side effects or if additional

LDL-C lowering is warranted. Clinical studies have demonstrated that colesevelam provides both lipid-lowering and glycemic benefits in adults with T2D and is FDA approved for both indications.[204]

Bempedoic acid, a prodrug that inhibits ATP citrate lyase and cholesterol synthesis upstream from hydroxymethylglutaryl coenzyme A reductase, appears to be a promising oral agent for those with statin intolerance or where modest additional LDL-C lowering is needed.[205]

Triglyceride Lowering in Diabetes

The initial approach to hypertriglyceridemia in diabetes should focus on potential secondary causes or contributory factors, including glycemic control, that should be addressed with pharmacologic and lifestyle approaches with evidenced-based cardiovascular benefit.[139,191] Modest weight loss, increased physical activity, reduction of sugar-sweetened beverages, processed carbohydrates, and reduction in alcohol use can lead to significant serum triglyceride reduction. Occult hypothyroidism and nephrosis should be excluded, and adjustment of medications that can raise triglycerides such as β-blockers, thiazide diuretics, and others should be considered.

In adults with diabetes and severe hypertriglyceridemia (fasting triglycerides >500 mg/dL), pharmacological and lifestyle therapy is warranted to prevent acute pancreatitis. In addition to the aforementioned lifestyle therapies, first-line pharmacotherapy includes fibrates or high-dose prescription omega-3 fatty acids. If a fibrate is necessary in a patient treated with concomitant statin therapy, fenofibrate is recommended rather than gemfibrozil, given the lower risk of drug interaction and myopathy.[191]

Moderate hypertriglyceridemia (fasting triglycerides 135–499 mg/dL) is considered a risk-enhancing factor,[191] and is often a manifestation of cardiometabolic risk. Moderate hypertriglyceridemia and an abnormal non–HDL-C are commonly encountered as components of diabetic dyslipidemia. In diabetes with moderate hypertriglyceridemia, statins are the recommended first-line pharmacotherapy.[191] The intensity of statin therapy should be based on both the absolute risk of ASCVD and the degree of hypertriglyceridemia because higher-intensity statins are more effective at lowering triglycerides. In patients with diabetes and ASCVD or patients with diabetes at high risk for ASCVD with serum triglycerides of 135 to 500 mg/dL despite maximally tolerated statin, and addressing contributory factors including lifestyle modification prescription icosapent ethyl at a dose of 4 g/d, as well, should be considered given the 30% additional cardiovascular risk reduction in the REDUCE-IT trial (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial).[206] Of note, the median baseline LDL-C in this trial was 75 mg/dL, and 29% of the study population had diabetes. Several RCTs have assessed the additional impact on cardiovascular events of fibrates when used in combination with statins; thus far, the data are inconclusive, although post hoc analyses have suggested potential benefit in those with residual modest hypertriglyceridemia.[207]

HDL-Raising Therapies in Diabetes

Overall, HDL-C–raising therapies, other than lifestyle and behavioral approaches, have been disappointing. Mendelian randomization data suggest that HDL-C is likely a marker of ASCVD risk versus a causative factor.[208] Low HDL-C is a common finding in individuals with diabetes and metabolic risk, in addition to dysfunctional HDL-C. Despite significantly increasing HDL-C, cholesterol ester transfer protein inhibitors have not demonstrated a reduction in cardiovascular events.[209] Niacin would not be favored in people with diabetes given the potential adverse effect on glycemic control. RCTs have not demonstrated additional cardiovascular benefit of niacin in combination with statin therapy.[209]

Lipid-Lowering Therapy in Diabetes Summary

Timely and aggressive lipid-lowering therapy is warranted for both primary and secondary prevention in diabetes as a component of comprehensive cardiovascular risk reduction. Lifestyle- and behavioral-focused approaches are recommended for all individuals with diabetes as the cornerstone to addressing dyslipidemia. Statins are the foundation of lipid therapy in diabetes given the consistent and compelling evidence supporting cardiovascular risk reduction. The 2018 Cholesterol Guidelines recommend statins as first-line therapy for both primary and secondary prevention in diabetes. In those with established ASCVD, the highest intensity statin tolerated should be initiated or continued with the aim of reducing LDL-C by at least 50% with a more individualized approach for those >75 years of age. For primary prevention in T2D, at least moderate-intensity statin should be considered based on age, absolute ASCVD risk, or the presence of risk-enhancing factors. Nonstatin therapies including ezetimibe, PCSK9 inhibitors, icosapent ethyl, bile acid resins, and fibrates should be considered after thorough evaluation of risk, LDL-C after optimal statin therapy, and presence of hypertriglyceridemia. An ongoing process of shared decision-making focused on net clinical benefit, patient preference, potential cost concerns, and medication adherence should be a consistent thread of care.[210]

ANTITHROMBOTIC THERAPY

Among the primary factors contributing to the increased cardiovascular risk in diabetes is a generalized prothrombotic state[211,212] that can be attributed to altered coagulation and platelet function and exacerbated in the setting of common comorbid conditions such as CKD (Table 6).[213–231] Although antiplatelet-based secondary

Table 6. Impact of Diabetes on Formation and Dissolution of Thrombus

Platelet activation
Increased platelet turnover
Decreased platelet cAMP
Decreased platelet cGMP
Increased thromboxane synthesis
Increase in glycoprotein IIb/IIIa receptor density on larger platelets
Increased vitronectin circulating fibrinogen and thrombin/antithrombin II complexes
Increased P-selection
Coagulation cascade activation
Increased fibrinogen
Increased von Willebrand factor and procoagulant activity
Increased fibrinopeptide A (increased thrombin activity)
Decreased activity of antithrombin III
Decreased sulfation of endogenous heparin
Chronic low-grade inflammation
Impaired fibrinolysis
Increased plasminogen activator inhibitor type 1 synthesis and activity (directly increased by insulin and insulin-like growth factor 1)
Decreased concentrations of alpha-2 antiplasmin

prevention is well established, an important advance in diabetes care over the past decade has been greater clarification of the appropriate role of antiplatelet therapy in the primary prevention of cardiovascular end points in individuals at increased risk.

The relative benefits and risks of aspirin and other primary preventive antiplatelet regimens need to be weighed carefully in at-risk patients with diabetes. The ASCEND trial (A Study of Cardiovascular Events In Diabetes) included 15 480 patients with diabetes but no overt CVD randomly assigned to aspirin 100 mg daily or placebo. At a mean follow-up of 7.4 years, there was a 1% absolute reduction in major cardiac and cerebrovascular events among these low-risk patients treated with aspirin (8.5% versus 9.6%, P=0.01), but a 1% increase in major bleeding (4.1% versus 3.2%, P=0.003) in that same group. Bleeding events were primarily gastrointestinal and other noncranial origin, with no excess in fatal bleeding.[232] Thus, in carefully selected patients with diabetes at low bleeding risk, aspirin provides a modest benefit in reducing ischemic events. In elderly patients, the CVD benefit with aspirin therapy for primary prevention is outweighed by bleeding risk, as demonstrated in the ASPREE trial (Aspirin in Reducing Events in the Elderly), which included 19 114 people ≥70 years of age (or ≥65 years in the United States and Black or Hispanic individuals), including 11% with diabetes. After a mean follow-up of 4.7 years, aspirin was found to have an insignificant effect on ischemic events but a significant increase in major hemorrhage. Overall, aspirin has a modest beneficial effect in primary prevention in nonelderly adults (50–70 years of age) with diabetes and increased cardiovascular risk based on additional clinical risk factors or imaging (see "The role of traditional and new imaging tests to assess subclinical CVD"). The risk-benefit ratio may be favorable in patients at low bleeding risk, and careful discussion and shared decision-making is appropriate before the initiation of long-term preventive therapies. The optimal aspirin dose in the setting of a demonstrable impairment in the biochemical response to aspirin is uncertain but may be improved somewhat by more frequent and higher dosing regimens,[233,234] although the safety of alternative regimens is not proven.

Newer, more potent antiplatelet agents and dosing regimens offer enhanced effects in treated patients, including those with diabetes, high on-treatment platelet reactivity, and relative clopidogrel and aspirin resistance.[235] Extending the previously documented secondary risk reduction benefit of dual antiplatelet therapy after MI among participants with diabetes,[236–238] the THEMIS trial (Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study)[239] evaluated the secondary prevention effects of dual antiplatelet therapy among 19 271 participants ≥50 years of age with diabetes and documented CAD but without a history of MI or stroke. Eligible patients were randomly assigned to ticagrelor or placebo, with low-dose aspirin included in each arm. After the initiation of the trial, the ticagrelor dose was reduced from 90 mg twice daily to 60 mg twice daily for all participants in light of excess premature ticagrelor discontinuation rates in previous trials[240] and recognition of the improved tolerability, safety, and adherence noted with this lower dose in the PEGASUS-TIMI 54 trial (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thombolysis in Myocardial Infarction 54 trial).[238] With an average follow-up of ≈40 months, the composite primary efficacy end point of freedom from cardiovascular death, MI, or stroke was better in the patients randomly assigned to ticagrelor with low-dose aspirin compared with placebo and aspirin.[240a,240b] Findings of a protective effect of potent antiplatelet regimens in this secondary preventive setting have important implications in the growing population of patients with diabetes.

The effect of antithrombin therapy with aspirin in stable but high ischemic risk patients with CAD or PAD has recently been evaluated. The COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies)[241–244] showed that adding rivaroxaban 2.5 mg twice a day to low-dose aspirin reduced ischemic events, including cardiovascular death. There was an associated cost of increase in bleeding risk, although no significant excess in fatal bleeding was

noted. The benefits were consistent in the subgroup with diabetes, suggesting that low-dose anticoagulation added to antiplatelet therapy may be another option for risk modification in high-risk patients with diabetes and provides another option for these patients with enhanced cardiovascular risk.

Antithrombotic Therapy in T2D Summary

Antiplatelet-based secondary prevention is well established in T2D. For primary prevention of CVD in T2D, the relative benefits of antithrombotic approaches need to be weighed carefully against risks using a patient-centered approach.

SCREENING FOR CARDIOVASCULAR AND RENAL COMPLICATIONS

Kidney Disease and Cardiovascular Risk in Diabetes

Diabetic nephropathy is the leading cause of CKD and end-stage renal disease in the United States.[245,246] Defined by the Kidney Disease Improving Global Outcomes Work Group as functional or structural abnormalities of the kidneys persisting for ≥3 months as manifested by decreased estimated glomerular filtration rate (eGFR) ≤60 mL·min^{-1}·1.73 m^{-2} or by evidence of kidney damage (eg, albuminuria or proteinuria),[251] prevalence among patients with diabetes is ≈20%–40%.[248–250] Concomitant CKD and diabetes impacts risk for an array of CVDs, including arrhythmias, HF, acute coronary syndrome, and stroke.[251] Cardiovascular morbidity and mortality is markedly high, and patients with diabetic kidney disease (DKD) are far more likely to die of cardiovascular complications than progress to end-stage renal disease. Although albuminuria is a risk marker of both kidney disease and CVD, it may not be present in patients with reduced eGFR.

Traditional management to reduce risk or delay advancement of kidney disease includes glycemic control, BP control, and renin-angiotensin-aldosterone system inhibition. In the ACCORD trial, a higher risk of hypoglycemia and mortality was seen in patients with baseline CKD. However, a recent meta-analysis of 27 049 participants from 4 landmark RCTs (ACCORD, ADVANCE [The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation], UKPDS [UK Prospective Diabetes Study], and VADT [Veterans Affairs Diabetes Trial]) noted a 20% relative risk reduction for kidney events (composite of end-stage kidney disease, renal death, development of an eGFR <30 mL·min^{-1}·1.73 m^{-2} or development of overt diabetic nephropathy) with more intensive glucose control over 5 years compared with less intensive.[252] Similar findings were observed in posttrial follow-up of participants in ADVANCE; intensive glucose control was associated with long-term reduction of end-stage kidney disease (defined as need for dialysis or kidney transplantation or death because of kidney disease) without evidence of any increased risk of cardiovascular events or death after 9.9 years of overall follow-up (29 versus 53 events, HR 0.54, $P<0.01$).[253] Stringent glucose control to prevent kidney failure may not be as clear. A meta-analysis by Ruospo et al[254] found that patients with intensive glycemic control had similar risks of kidney failure, defined as doubling of serum creatinine (RR=0.84 [95% CI, 0.64–1.11]; I^2=73%), and development of end-stage renal disease (RR=0.62 [95% CI, 0.34–1.12]; I^2=52%) compared with patients with less stringent treatment goals. Small clinical benefits were observed in the onset and progression of microalbuminuria.

In the CVOTs of SGLT-2Is and GLP-1RAs, secondary end points or subanalyses included renal outcomes (Table 7). When comparing drug classes, a recent meta-analysis of these trials found that GLP-1RAs primarily reduced macroalbuminuria risk, whereas SGLT-2Is reduced the risk of worsening eGFR.[138] Data from clinical trials focused on primary renal outcomes are emerging. In CREDENCE, patients with T2D and albuminuric CKD concurrently receiving renin-angiotensin-aldosterone system blockade were randomly assigned to canagliflozin 100 mg daily or placebo.[141] A 30% relative risk reduction of the primary outcome (composite of end-stage renal disease defined as dialysis, transplantation, or sustained eGFR of <15 mL·min^{-1}·1.73 m^{-2}, doubling of serum creatinine or death from renal or cardiovascular cause) was observed over 2.6 years in the canagliflozin group. Reduced risk of cardiovascular death, MI, or stroke was also noted in the canagliflozin group (HR, 0.80 [95% CI, 0.67–0.95]; P=0.01) and HHF (HR, 0.61 [95% CI, 0.47–0.80]; $P<0.001$). In the DAPA-CKD trial (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease), a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was evaluated over 2.4 years in CKD participants with or without T2D. Dapagliflozin versus placebo reduced the risk of the composite outcome by 39% overall and 36% (HR, 0.64 [95% CI, 0.52–0.79]) among participants with T2D.[255]

The most recent advances have been trials of selective nonsteroidal mineralocorticoid receptor antagonists in patients with T2D and DKD. The FIDELIO-DKD trial (Finerenone in Reducing Kidney Failure and Disease Progression in DKD Trial) evaluated kidney and cardiovascular outcomes over 2.6 years in 5734 participants with T2D and DKD on maximal renin-angiotensin-aldosterone system blockade at baseline.[256] Finerenone reduced the primary renal composite outcome (kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes) by 18%

Table 7. Renal Events in Cardiovascular Outcome Trials

Drug	Renal end points	Event rate (intervention vs placebo)	Relative risk reduction
Empagliflozin[122]	Composite of progression to urine albumin-to-creatine ratio >300 mg/g, doubling of SrCr, ESRD, or death from ESRD	12.7% vs 18.8%	39%
	Doubling of SrCr accompanied by estimated glomerular filtration rate ≤45 mL·min^{-1}·1.73m^{-2}	1.5% vs 2.6%	44%
Canagliflozin[123]	Progression of albuminuria	89.4 vs 128.7 participants with an event per 1000 patient-years	27%
	Composite of sustained 40% reduction in estimated glomerular filtration rate, kidney replacement therapy, or death from ESRD	5.5 vs 9.0 participants with the outcome per 1000 patient-years	40%
Dapagliflozin[124]	Composite of sustained decrease of 40% or more in estimated glomerular filtration rate, new ESRD, or death from renal or cardiovascular causes	4.3% vs 5.6%	24%
Liraglutide[114]	Composite of persistent macroalbuminuria, doubling of SrCr, ESRD, or death from ESRD	5.7% vs 7.2%	22%
Semaglutide[115]	Composite of persistent urine albumin-to-creatine ratio >300mg/g, creatine, doubling of SrCr of ESRD	3.8% vs 6.1%	36%

ESRD indicates end-stage renal disease; and SrCr, serum creatinine.

(HR, 0.82 [95% CI, 0.73–0.93]; *P*=0.001) and reduced the secondary cardiovascular composite outcome (death from CVD, nonfatal stroke, nonfatal MI, and HHF) by 14% (HR, 0.86 [95% CI, 0.75–0.99]; *P*=0.03) with no difference by baseline CVD status.[256,257] FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) is a completed 6400 patient trial examining a cardiovascular composite as the primary outcome with results due in late 2021. Thus, SGLT-2Is, GLP-1Ras, and nonsteroidal mineralocorticoid receptor antagonists are critical advancements in delaying the progression of CKD in T2D.

THE ROLE OF TRADITIONAL AND NEW IMAGING TESTS TO ASSESS SUBCLINICAL CVD

Diabetes has been regarded as a CAD equivalent, but not all individuals with diabetes have an equally elevated risk. The following section discusses how cardiovascular imaging to detect subclinical atherosclerosis can help risk-stratify patients with diabetes and tailor therapy.

Coronary Artery Calcification

Coronary artery calcification (CAC), a surrogate marker for atherosclerosis, is detected more commonly in metabolic syndrome (59%) and diabetes (75%) than in control subjects (53%) and is associated with duration and control of diabetes.[258–260] Twelve-year follow-up from MESA (Multi-Ethnic Study of Atherosclerosis) showed increasing CAC scores predict MI and cardiovascular events after controlling for glycemic control.[261] Sequential testing has shown faster CAC progression in diabetes.[262] The PREDICT study (Prospective Evaluation of Diabetic Ischemic Disease by Computed Tomography) found CAC doubling in diabetes increased cardiovascular risk by 32% over 4 years.[263] Accordingly, the MESA-HNR risk score that includes CAC performs better in diabetes than Framingham (net reclassification improvement 0.19, integrated discrimination improvement 0.046, *P*<0.05), and UKPDS (net reclassification improvement 0.215, integrated discrimination improvement 0.046, *P*<0.05) scores.[264]

Up to 39% of individuals have zero CAC.[265] In MESA, such individuals had a very low CVD event rate (3.7 per 1000 person-years), similar to those without diabetes and no CAC.[261] Thus, the absence of CAC can reclassify up to a third of patients with diabetes to a low-risk category, whereas higher CAC may prompt tighter risk-factor control including statin and aspirin prescription.

Coronary Artery Computed Tomography Angiography

Asymptomatic individuals can be further stratified using coronary artery computed tomography angiography (cCTA) and can further stratify asymptomatic individuals with diabetes by (1) the degree of luminal stenosis and (2) plaque morphology. The absence of luminal stenosis has been seen in 25% to 30% and obstructive CAD in 25% to 30% in cCTA studies. South Asian patients tend have even more prevalent CAD (41% versus 28%) compared with White patients with T2D.[266]

In the CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry), patients with T2D without CAD by cCTA had similar cardiovascular risk as propensity-matched patients without T2D, whereas those with obstructive CAD had higher risk at 5 years.[267] Risk increased with segment involved and segment stenosis scores.[268] cCTA has incremental risk prediction, discrimination, and reclassification advantage beyond CAC for asymptomatic individuals with diabetes.[269]

The FACTOR-64 trial (Screening for Asymptomatic Obstructive Coronary Artery Disease Among High-Risk Diabetic Patients Using CT Angiography, Following Core 64) compared a cCTA-based screening strategy in diabetes to standard care, but found no difference in all-cause death, nonfatal MI, or unstable angina (6.2% versus 7.6%; *P*=0.38) over 4 years.[270] The apparent lack of benefit may have been attributable to low event rates from risk factor control at baseline (75% statin use). It is plausible that asymptomatic but higher-risk groups with longstanding or poorly controlled diabetes, hypertension, and dyslipidemia may derive benefit from cCTA screening, but confirmatory evidence is needed. Benefits from cCTA were seen in the T2D subcohort of the PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain), but these were symptomatic patients.[271]

T2D is associated with high plaque burden.[272–274] The PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed tomographic Angiography Imaging) study of 1602 subjects showed a higher plaque volume, necrotic core volume, and faster plaque progression with T2D.[275,276] Coronary plaque also provides reclassification advantage over UKPDS and CAC scores over a 7-year follow-up.[277] Any potential benefits also need to be weighed against risks of radiation and iodinated contrast exposure.

Cardiac Magnetic Resonance Imaging

Presence of unrecognized MI detected by cardiac magnetic resonance imaging may be a stronger prognostic marker than conventional risk factors in diabetes.[278,279] In the ICELAND-MI study, unrecognized MI (17%) was more common than clinically recognized MI (10%) in individuals >65 years, and its prevalence was even higher in the T2D subgroup (21%).[280] On a 13-year follow-up, mortality of unrecognized MI in T2D was also higher, possibly from lower prescription of preventive therapy.[281] In type 1 diabetes, a cardiac magnetic resonance study found scar in 4.3%.[282] Early detection could facilitate treatment and improve outcomes, but this requires testing in clinical trials.

Stress Testing

Exercise ECG stress testing can detect silent ischemia in ≈7.6% of asymptomatic individuals with diabetes.[283,284] Detection rates with technetium-99m sestamibi single-photon emission-computed tomography myocardial perfusion are higher (22%). Although a screening strategy was ineffectual in the DIAD clinical trial (Detection of Ischemia in Asymptomatic Diabetics; 2.7% versus 3% events; *P*=0.73), the BARDOT trial (The Basel Asymptomatic High-Risk Diabetics' Outcome Trial) documented higher events in the abnormal stress test group (9.8% versus 2.9% at 2 years).[285,286] In a meta-analysis, a normal single-photon emission-computed tomography study predicted an annual event rate of 1.6% with and <1% without T2D.[287] Absence of ischemia and late gadolinium enhancement on stress perfusion cardiac magnetic resonance can also effectively stratify patients with diabetes to low risk (1.4% and 0.5% event rates, respectively).[288]

Cardiac Positron Emission Tomography

Reduced coronary flow reserve in T2D (1.58 versus 1.87; *P*=0.0001) as measured by positron emission tomography can predict a 4.9-fold higher risk of cardiac death.[289] Patients with T2D without epicardial stenosis but with a coronary flow reserve <1.6 have cardiac event rates (2.8%) similar to those with stenosis (2.9%), suggesting prognostic implications of microvascular dysfunction. In MESA, higher fasting glucose was associated with lower hyperemic myocardial blood flow.[290]

CVD Screening in T2D Summary

Many imaging tests can facilitate risk stratification in asymptomatic patients with T2D, but there are limited data to support routine screening. CAC appears to provide the most actionable triggers for lipid-lowering and antiplatelet therapy. The 2018 Cholesterol Guidelines and the 2019 ACC/AHA Guideline on the Primary Prevention of CVD recommend moderate-intensity statin prescription for adults 40 to 75 years of age with diabetes without further risk stratification.[21,191] The National Lipid Association's scientific statement on CAC scoring recommends escalation to high-intensity statin for CAC >100.[291] CAC is also deemed reasonable in 30- to 39-year-old adults with long-standing diabetes and >75-year-old adults if it would facilitate statin prescription. Aspirin is also considered reasonable by the National Lipid Association and the Society of Cardiovascular Computed Tomography for CAC >100.[292] Ischemia testing in asymptomatic individuals with diabetes is not currently recommended.

CLINICAL IMPLICATIONS OF RECENT CVOTS

The leading cause of mortality in diabetes remains CVD; thus, strategies to reduce CVD are paramount. The majority of CVOTs for GLP-1RAs and SGLT-2Is have shown significant reduction in cardiovascular outcomes: (1) GLP-1RAs having greater ASCVD benefits, and (2) SGLT-2Is have shown greater reduction in HHF and renal outcomes among those with established ASCVD and high cardiovascular risk. FIDELIO-DKD showed a reduction in CVD among individuals with T2D and DKD with a selective nonsteroidal mineralocorticoid receptor antagonist as a secondary out-

come with the results pending for the larger primary outcome trial FIGARO-DKD.[256,257] The findings are impressive, given that the trials occurred in an era of comprehensive ASCVD risk management with effective therapies for lipid, BP, and antithrombotic management. There remains an opportunity to increase prescribing and utilization of these medications among cardiologists for their CVD benefit, because they are currently mostly prescribed by internists and endocrinologists.[293,294] Thus, approaches to increase utilization of collaborative approaches, in particular among patients with ASCVD and T2D, is important, leading some to call for a new cardiometabolic medicine specialty to improve prevention and treatment of cardiometabolic diseases at the interface of cardiology, endocrinology, and general medicine.[295]

Even with the large amount of high-quality evidence, important areas for research remain. MACE, MI, and cardiovascular mortality reduction with GLP-1RA and SGLT-2Is is firmly established for individuals with diabetes and ASCVD. Consistent beneficial impacts in the primary prevention of ASCVD among those with T2D, although desired, remain to be established.[138] Second, differences in therapy response across racial and ethnic groups deserve further evaluation. For example, empagliflozin was associated with a 32% lower ASCVD risk in Asian populations and 48% higher ASCVD risk in Black populations compared with placebo, whereas canagliflozin was associated with a 8% higher ASCVD risk in Asian populations and a 55% lower ASCVD risk in Black populations.[121,123] Recent analyses also indicate potential lower use of GLP-1RA and SGLT-2Is in racial and ethnic minority groups and lower socioeconomic status groups.[296,297] Third, there are no head-to-head comparison trials between newer antihyperglycemic medications and their impact on ASCVD outcomes. Last, long-term safety of the newer agents remains under investigation.

CONCLUSION

Although efficacious therapies are available to improve cardiovascular risk factors, in the United States and across the world, comprehensive management of various cardiovascular risk factors in T2D remains poor.[298,299] In the United States, <20% of adults with T2D without known CVD meet control targets for a combination of A1c, BP, LDL-C, and nonsmoking status and that drops to <10% if including BMI <30 kg/m^2 target.[298] Among those with known ASCVD, the realities are worse with only 6.8% meeting the combined target and 2.7% with inclusion of BMI <30 kg/m^2 target.[298] Similar challenges exist throughout the world to varying degrees, as is seen in the EUROASPIRE V survey, where large proportions of people at high cardiovascular risk had unhealthy lifestyles and inadequate control of BP, lipids, and diabetes.[299] Explanations for the discordance between effective therapies and poor control include medical factors (ie, clinical inertia, monotherapy, patient adherence, cost, lack of guideline-based treatment), but these all occur in the environmental context of a patient.

Clinical care and treatment accounts for 10% to 20% of the modifiable contributors to healthy outcomes.[300] The other 80% to 90% are the SDoH, which includes health-related behaviors, socioeconomic factors, environmental factors, and racism, which have been recognized to have a profound impact on CVD and T2D and their outcomes by the AHA and ADA.[301–303] If we are to continue to advance the management of cardiovascular risk factors, we must also address the SDoH in the delivery of health care.[304,305] Concurrent interventions to (1) directly address the SDoH condition (ie, approaches to improve food insecurity have shown reductions in A1c)[306] and (2) address the root causes of SDoH through policy changes are critical.[307] Racism is increasingly recognized as an upstream SDoH that drives midstream SDoH and downstream health outcomes.[301–303] A reinvigorated focus on efforts to address and improve racism is 1 pillar on which to intervene to eliminate the disparities in cardiovascular risk factors and cardiovascular death in our work to advance health equity.[68,302,303]

Multifaceted efforts are needed to prevent CVD in patients with diabetes. Data from 4 EUROASPIRE surveys since the 1990s showed worsening of lifestyle factors, obesity and diabetes prevalence, and control among individuals with coronary heart disease or high CVD risk.[308] In response, the European Society of Cardiology developed the EUROACTION plan aimed at improving preventive care for these individuals in clinical practice. After 1 year, participants assigned to the EUROACTION intervention program were less likely to smoke, more likely to have improved their dietary habits and be prescribed angiotensin-converting enzyme inhibitors and statins.[309] In the United States, the AHA and ADA have partnered in a groundbreaking program, "Know Diabetes by Heart." Know Diabetes by Heart works with patients, communities, professionals, and health systems to reduce cardiovascular deaths, heart attacks, and strokes in people living with T2D by raising awareness of the link between diabetes and CVD, empowering patients, and supporting health care professionals in patient engagement and prevention of CVD. The Target:T2D ambulatory program, part of Know Diabetes by Heart, is a quality improvement initiative for outpatient care of T2D and cardiovascular risk factors. The initiative brings together resources, regional support, education, and recognition to target clinical improvement. These strategies recognize the impor-

tance of multifaceted approaches to CVD prevention and treatment in T2D.

Overall Summary

Diabetes is a major public health problem. CVD is the leading cause of death and disability in diabetes. A large number of RCTs have demonstrated that the risk of cardiovascular events can be significantly reduced by incorporating evidence-based therapies for control/modification of multiple cardiometabolic abnormalities in patients with T2D. We recommend a comprehensive approach to management of all cardiovascular risk factors in patients with T2D, including glycemia, BP, lipid abnormalities, thrombotic risk, obesity, and smoking, using lifestyle and pharmacological approaches with proven benefit using a patient-centered approach. A patient-centered approach in this context means reframing our clinical encounters to think about patients as people who live in families, communities, and societies that must be considered in their cardiovascular risk management. Further research exploring the role of combined lifestyle, pharmacological, and SDoH intervention approaches remain an area of further investigation. An example of such an approach would study the impact of an SGLT-2I in the setting of a specific dietary approach (ie, Mediterranean, Ketogenic, and DASH) that also uses a produce-provision prescription to ensure access to healthy food choices. Cardiovascular risk management from global risk assessment through individual- and population-level interventions to increase the control of cardiovascular risk factors in T2D are critical to the AHA mission to be a relentless force of longer and healthier lives.

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Deepak L. Bhatt	Brigham and Women's Hospital, Harvard Medical School	Research funding: Abbott†; Afimmune†; Amarin†; Amgen†; AstraZeneca†; Bayer†; Boehringer Ingelheim†; Bristol-Myers Squibb†; Cardax†; CellProthera†; Cereno Scientific†; Chiesi†; CSL Behring†; Eisai†; Ethicon†; Ferring Pharmaceuticals†; Forest Laboratories†; Fractyl†; Garmin†; HLS Therapeutics†; Idorsia†; Ironwood†; Ischemix†; Janssen†; Lexicon†; Lilly†; Medtronic†; MyoKardia†; NirvaMed†; Novartis†; Novo Nordisk†; Owkin†; Pfizer†; PhaseBio†; PLx Pharma†; Regeneron†; Roche†; Sanofi†; Stasys†; Synaptic†; The Medicines Company†; 89Bio†; Site Co-Investigator: Abbott†; Biotronik†; Boston Scientific†; CSI†; St. Jude Medical (now Abbott)†; Philips†; Svelte†; Unfunded research: FlowCo*; Merck*, Takeda*; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott)†; Boston Scientific (Chair, PEITHO trial)†; Cleveland Clinic (including for the ExCEED trial, funded by Edwards)†; Contego Medical (Chair, PERFORMANCE 2); Duke Clinical Research Institute†; Mayo Clinic†; Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo)†; Novartis†; Population Health Research Institute†	None	American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee)†; Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation)†; Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring)†; Belvoir Publications (Editor in Chief, Harvard Heart Letter)†; Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees)†; Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals)†; Ferring Pharmaceuticals†; HMP Global (Editor in Chief, *Journal of Invasive Cardiology*) †; *Journal of the American College of Cardiology* (Guest Editor, Associate Editor)†; K2P (Co-Chair, interdisciplinary curriculum)†; Level Ex, Medtelligence/ReachMD (CME steering committees)†; MJH Life Sciences†; Piper Sandler†; Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer)†; Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*†; Society of Cardiovascular Patient Care (Secretary/Treasurer)†; WebMD (CME steering committees)†	None	Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease)†	Advisory Board: Boehringer Ingelheim†; Cardax†; CellProthera†; Cereno Scientific†; Elsevier Practice Update Cardiology†; Janssen†; Level Ex†; Medscape Cardiology†; MyoKardia†; NirvaMed†; Novo Nordisk†; PhaseBio†; PLx Pharma†; Regado Biosciences†; Stasys†; Board of Directors: Boston VA Research Institute†; Society of Cardiovascular Patient Care†; TobeSoft†; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee†	Trustee: American College of Cardiology†
Deborah A. Chyun	University of Connecticut	None	None	None	None	None	None	None
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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

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Michael J. Blaha	Johns Hopkins University School of Medicine	Novo Nordisk*	None	Novo Nordisk*	None	None	Novo Nordisk*; Kaliedo*; Amgen*; Sanofi/ Regeneron*; Bayer*	None
Michael D. Miedema	Minneapolis Heart Institute and Minneapolis Heart Institute Foundation	None	None	None	None	None	None	None
Judith Wylie-Rosett	Albert Einstein College of Medicine	None	None	None	None	None	None	None

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*Significant.

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