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REVIEW

Diabetes: how to manage cardiovascular risk in secondary prevention patients

Sarah L Anderson[1], Joel C Marrs[2,3]

[1]Clinic Care Options, Reston, VA, USA; [2]Ambulatory Pharmacy Clinical Coordinator, Billings Clinic, Billings, MT, USA; [3]Visiting Clinical Associate Professor at the University of Colorado School of Medicine, Department of Pediatrics, Child Health Associate/Physician Assistant Program, Aurora, CO, USA

Abstract

Atherosclerotic cardiovascular disease (ASCVD) commonly affects people with type 2 diabetes (T2D). Historically, traditional cardiovascular (CV) risk-lowering therapies in patients with T2D and ASCVD have included antiplatelet agents, blood pressure-lowering therapies, lipid-lowering therapies and healthy lifestyle modifications. In the past decade, multiple antihyperglycaemic agents have emerged as CV risk-lowering therapies in this population as well. This article provides a narrative review on the current non-glycaemic and glycaemic treatment options for CV risk reduction in patients with T2D and ASCVD. The FDA requirement that all new antihyperglycaemic agents undergo cardiovascular outcomes trials has demonstrated increasing evidence to support the role of glucagon-like peptide 1 (GLP1) receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors as first-line agents for both glycaemic control and CV risk reduction in this population.

Keywords: atherosclerotic cardiovascular disease, cardiovascular disease, diabetes, GLP1 receptor agonists, SGLT2 inhibitors, type 2 diabetes.

Citation

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Introduction

It is well established that individuals with type 2 diabetes (T2D) are at an increased risk for cardiovascular disease (CVD) compared to individuals without T2D. Further, CVD has been shown to be the cause of over half of the deaths seen in patients with T2D.[1] Based on the known associated increased risk of CVD in patients with T2D, there is a need to focus both on the primary and the secondary prevention of CVD. The primary focus is to reduce the risk of atherosclerotic cardiovascular disease (ASCVD), which is defined as coronary heart disease, cerebrovascular disease or peripheral arterial disease. ASCVD is the leading cause of morbidity and mortality for individuals with diabetes.[2] There are many cardiovascular (CV) risk factors that are targets in both the primary and secondary prevention of ASCVD. Attention should be given to key factors or conditions that, when improved or controlled, have demonstrated lower rates of ASCVD, including ischaemic events such as myocardial infarctions, strokes and CV death, blood pressure, cholesterol, and unhealthy lifestyle habits.

The role of antihyperglycaemic medications in reducing the risk of ASCVD has evolved over the last decade. Because the primary contributor to the development of ASCVD has been noted to be atherosclerosis, the role of antihyperglycaemic medications in reducing ASCVD risk has not been a major focus of CV risk reduction trials. Rather, the role of these agents has primarily focused on improving glycaemic control and reducing the risk of microvascular events. It was not until the requirement over the last decade that the CV safety of new antihyperglycaemic agents be evaluated that their role in reducing ASCVD and macrovascular events became known. In the next section, we will discuss the recommended approaches to lower ASCVD in patients with T2D, followed by a focused review of the role of antihyperglycaemic medications in reducing ASCVD.

Landscape of therapeutic approaches to reduce CV risk in patients with T2D and ASCVD

For many years, the approach to lower ASCVD risk in T2D patients has been targeted at traditional risk-lowering modalities, including antiplatelet therapy, antihypertensive therapy, lipid-lowering therapy, and lifestyle modifications. We will review the evidence and recommendations for the role of each traditional approach to lower CV risk.

Antiplatelet therapy

Aspirin has been proven to be an effective medication to lower CV morbidity and mortality in patients who are at high risk for a CV event and those with established ASCVD. The evidence to support the role of antiplatelet therapy in the primary prevention of ASCVD in patients with and without T2D is less robust.[3] The Antithrombotic Trialists' Collaboration most recent evaluation of antiplatelet trials for primary prevention found that aspirin reduced the risk of serious vascular events by 12% (relative risk (RR) 0.88, 95% CI 0.82–0.94).[3] The most recent is the ASCEND (A Study of Cardiovascular Events iN Diabetes) trial evaluated the benefit of aspirin 100 mg or placebo in 15,840 patients aged 40 years and older with T2D without evidence of ASCVD.[4] The findings of this study showed a 12% reduction (8.5% *versus* 9.6%, p=0.01) in the primary efficacy endpoint (CV death, myocardial infarction (MI) or stroke) but a significant increased rate of bleeding in patients treated with aspirin (4.2% *versus* 3.2%, p=0.003).[4] The American Diabetes Association (ADA) currently recommends aspirin as a secondary prevention approach in patients with diabetes and a history of ASCVD.[5] The ADA further recommends considering aspirin as a primary prevention strategy in patients with diabetes aged 50 years and older who are at increased CV risk as long as the patient is not at an increased risk of bleeding.[5]

Antihypertensive therapy

Hypertension is a major risk factor for both ASCVD and microvascular complications. Many clinical trials have demonstrated that reducing blood pressure (BP) to less than 140/90 mmHg reduces CV events, which justifies treating patients with T2D to at least this goal BP. Additionally, in patients with T2D and established ASCVD, lowering BP to less than 130/80 mmHg has demonstrated further CV event lowering in multiple meta-analyses.[6,7] The choice of antihypertensive medication should be driven by compelling indications for the individual patient. Evidence supports the role of initiating antihypertensive therapy with either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker in patients with T2D and established ASCVD.[8–10] If necessary, additional antihypertensive therapy should be added to maintain BP control and should be determined by compelling indications, guideline recommendations and patient preference/tolerability.

Lipid-lowering therapy

Lipid-lowering therapy with statins in patients with established ASCVD must be the first-line approach to lower the risk of a future CV event. Evidence in patients with T2D and ASCVD further supports this approach. The ADA and the American Heart Association/American College of Cardiology (AHA/ACC) recommend a high-intensity statin therapy for patients with diabetes and established ASCVD.[5,11] This recommendation is based on the Cholesterol Treatment Trialists' Collaboration evaluation of 26 statin trials and specifically reviewing the data for high-intensity *versus* moderate-intensity statins. This meta-analysis demonstrated greater CV event lowering with high-intensity statins *versus* moderate-intensity statins in patients with established ASCVD with or without T2D.[12] Clinical trial evidence also supports the addition of ezetimibe and/or a PCKS9 inhibitor to maximally tolerated statin therapy in patients with established ASCVD regardless of diabetes diagnosis if they are above the low-density lipoprotein cholesterol (LDL-C) threshold of 70 mg/dL.[13–15]

Lifestyle modifications

There is substantial evidence to support the role of positive lifestyle modifications, in addition to medications, for specific risk factors or conditions to reduce the risk of CV events. With regards to improving BP, the evidence-based approach is to recommend the Dietary Approaches to Stop Hypertension pattern of eating, including reducing sodium intake, increasing potassium intake, moderating or eliminating alcohol consumption, increasing physical activity, and achieving weight loss if overweight or obese.[16] Patients who are overweight or obese should implement dietary, behavioural and physical activity approaches to achieve ≥5% weight loss.[16] Additionally, approaches to help improve cholesterol such as reducing consumption of saturated and trans fats, increasing dietary consumption of omega-3 fatty acids, increasing fibre, and increasing intake of plant stanols/sterols are recommended. These recommendations are supported by the ADA and the ACC/AHA to reduce the risk of CVD in patients with diabetes and ASCVD. Related to physical activity, the ACC/AHA and ADA specifically recommend a target of 150 minutes per week of moderate-intensity activity for both primary and secondary prevention patients with diabetes.[17,18]

The recommendations listed earlier describe traditional risk factor modification with use of antiplatelet agents, blood pressure-lowering therapies, lipid-lowering therapies and lifestyle modifications. In the STENO-2 trial, the combination of these approaches in patients with T2D demonstrated a lower rate of vascular complications and CV death.[19] The remainder of this review focuses on the emerging role of antihyperglycaemic agents as modes of CV risk reduction in patients with T2D and ASCVD.

Methods

To inform this Review, a literature search limited to the English language was performed using PubMed, Google Scholar and Cochrane Library databases from 1996 to September 2021 with the following keywords and phrases (searched alone and in iterative combinations): "diabetes", "antihyperglycemic", "cardiovascular risk reduction" and "secondary prevention". The search strategy included clinical trials, observational studies, meta-analyses, guidelines, reviews and cross-references of the relevant articles. The information collected from the search was used in the creation of this Review.

Mechanism of glucose-lowering therapies in the role of CV risk reduction in patients with established ASCVD

There are several postulated hypotheses to explain how agents within the different antihyperglycaemic classes work to reduce CV risk. In general, the reduction of glycosylated haemoglobin (A1C) and weight observed in cardiovascular outcomes trials (CVOTs) is modest; therefore, the CV benefit of antihyperglycaemic agents is likely independent of improved glycaemic control and weight loss. Certain antihyperglycaemic agents have demonstrated beneficial effects on lipid parameters in CVOTs; however, the degree of improvements in lipids has been modest and the mean follow-up time brief. This indicates that improvements in lipid parameters are also not likely to be driving CV outcomes. The mechanisms of CV risk reduction for each class of antihyperglycaemic agent are unique and likely unrelated to reductions in A1C and weight and unrelated to improvements in lipid parameters.

Older therapeutic options

Metformin

The possible mechanism underlying the role of metformin in CV risk reduction in patients with established ASCVD is several-fold. Experimental data have demonstrated that metformin reduces inflammation, exerts beneficial effects on lipids, exhibits antithrombotic and anti-atherosclerotic activity, and improves both the gut microbiome and endothelial cell function.[20] In patients with T2D and coronary artery disease, there is evidence to support that metformin exerts a cardioprotective effect by altering cardiac metabolism, which in turn improves cardiac function.[21]

Thiazolidinediones

Rosiglitazone and pioglitazone have different roles in patients with T2D and ASCVD. Whilst rosiglitazone has demonstrated an increased risk of myocardial infarction in patients with T2D and ASCVD, pioglitazone has demonstrated favourable effects in this population.[22] Investigators of the PROactive Study, which evaluated pioglitazone in patients with T2D and ASCVD, hypothesized that the CV benefit demonstrated with the use of pioglitazone was due to an improved metabolic profile. Patients treated with pioglitazone in this study had improved glucose values, high-density lipoprotein cholesterol (HDL-C), triglycerides and BP at the end of the study.[23] However, these were all modest improvements that were observed over a period of less than 3 years, which is likely not enough time for these modestly improved metabolic parameters to have exerted a protective CV effect. Preclinical data of thiazolidinediones suggested that these agents have anti-inflammatory properties (e.g. reducing C-reactive protein) and beneficial vascular effects; however, it is still largely unknown what mechanism underlies the ability of thiazolidinediones to reduce CV risk.[24,25]

Insulin

Despite its widespread use in patients with type 1 diabetes and T2D, the mechanism of CV risk reduction with the use of insulin is largely unknown and the CV benefit unproven. Experimental data suggest that insulin may have antithrombotic and anti-atherosclerotic effects, but the CV effects of insulin are primarily neutral.[25] Because insulin is a life-saving medication for patients with type 1 diabetes, new insulins do not have to undergo the same CVOTs that other new antihyperglycaemic agents do. Because of this, there is less CV outcomes data with insulin products.

Newer therapeutic options

DPP4 inhibitors

Like metformin and thiazolidinediones, dipeptidyl peptidase 4 (DPP4) inhibitors have demonstrated beneficial effects on metabolic parameters (e.g. weight, BP, lipids), reduced inflammation and oxidative stress, and improved endothelial function. However, despite these beneficial effects, most CVOTs evaluating DPP4 inhibitors have not demonstrated a superior benefit of these agents in reducing major adverse cardiovascular events (MACE).[26] This means that, despite the exertion of beneficial effects on surrogate markers for CVD, the effects of DPP4 inhibitors do not translate into reductions in hard clinical endpoints (e.g. CV death). In fact, CVOTs of DPP4 inhibitors have demonstrated that, in patients with CVD or multiple CVD risk factors, use of DPP4 inhibitors may increase the risk of or exacerbate hear failure (HF) with the strongest association with saxagliptin.[25,27]

GLP1 receptor agonists

Glucagon-like peptide 1 (GLP1) receptor agonists exert many beneficial effects on the CV and renal systems. These agents alter renal natriuresis and diuresis by releasing atrial natriuretic peptide and affecting the renal proximal tubule cells. This not only promotes renal protection but also contributes to positive effects on the CV system. Natriuresis, in combination with improved endothelial function and vasodilation, decreases preload, lowers BP and decreases inflammation.[26] Weight loss is also an effect of GLP1 receptor agonist and, whilst weight loss alone does not account for the CV benefits seen in many GLP1 receptor agonist CVOTs, weight loss in combination with improved BP and renal outcomes contributes to CV risk reduction.[26]

SGLT2 inhibitors

Similar to GLP1 receptor agonists, the beneficial CV effects of sodium–glucose co-transporter 2 (SGLT2) inhibitors are likely due to their effects on haemodynamics. Data from an exploratory analysis of the EMPA-REG OUTCOME trial demonstrated that indicators of plasma volume status – haemoglobin, haematocrit and albumin levels – were important markers associated with CV mortality reduction.[28] Presence of these markers may indicate improved oxygenation and normalization of erythropoietin production. SGLT2 inhibitors beneficially affect cardiac preload and afterload

by promoting natriuresis and diuresis and reducing arterial stiffness, respectively. SGLT2 inhibitors may also improve cardiac myocyte energetics. These agents may improve cardiac mitochondrial energy output via decreased concentrations of sodium and calcium via inhibition of the cardiac sodium/hydrogen exchangers and increased mitochondrial calcium concentrations. Related to this, SGLT2 inhibitors increase free fatty acid oxidation and ketogenesis, shifting to a more efficient use of fatty acids and ketones by the CV system.[28] SGLT2 inhibitors increase uric acid secretion via co-inhibition of glucose and uric acid reabsorption. The reduction in uric acid levels has been associated with reduced CV (and renal) events.[26] All these effects, combined with weight loss and improved or at least protected renal function, work together to improve CV function and reduce the risk of CV events.

Glucose-lowering therapies and major CVOTs

Concerns about the CV safety of antihyperglycaemic agents, driven in large part by negative CV data associated with the use of rosiglitazone, prompted the US Food and Drug Administration (FDA) to issue draft guidance in 2008 that required large CVOTs for all new antihyperglycaemic therapies (with the exception of insulin).[29,30] Between 2008 and the most recent CVOT Summit, named 'Cardiovascular and Renal Outcomes 2020', there have been 17 published CVOTs amongst the DPP4 inhibitor, GLP1 receptor agonist and SGLT2 inhibitor classes. These studies along with CVOTs evaluating pioglitazone are outlined in Table 1.[23,27,31–50]

FDA-approved indications for antihyperglycaemic medications in patients with established ASCVD and T2D

The landscape of clinical trials demonstrating the CV risk-lowering ability of antihyperglycaemic medications over the last decade had expanded dramatically. Through this process, there are multiple antihyperglycaemic medications that now have an FDA-approved indication to lower CV risk in patients with T2D and ASCVD. Three SGLT2 inhibitors have FDA indications to lower CV risk in patients with T2D and ASCVD.[51] Canagliflozin is indicated to reduce the risk of myocardial infarction, stroke and CV death in adults with T2D and ASCVD. Dapagliflozin is indicated to reduce the risk of heart failure hospitalizations in adults with T2D and ASVCD. Empagliflozin is indicated to reduce the risk of CV death in adults with T2D and ASCVD. Three GLP1 receptor agonists have FDA indications to

Table 1. Glucose lowering therapies and major cardiovascular outcome trials.[23, 27, 31–50]

Trial (drug studied)	*n*	Patient population	Follow-up, mean (wk)	Primary outcome	Other outcomes
DPP4 inhibitors					
EXAMINE[31] (Alogliptin)	5380	T2D uncontrolled with recent (15–90 days) MI or UA requiring hospitalization	78	MACE (CV death, MI, stroke): 11.3% (Alo) *versus* 11.8% (P); $p<0.001$ for non-inferiority	MACE (CV death, MI, stroke, RUA): HR, 0.95 (<1.14); CV death: HR, 0.79 (95% CI 0.60–1.04); non-fatal MI: HR, 1.08 (95% CI 0.88–1.33); non-fatal stroke: HR, 0.91 (95% CI 0.55–1.50)
SAVOR-TIMI 33[27] (Saxagliptin)	16,490	T2D uncontrolled with ASCVD or age ≥55 years (male) or ≥60 years (female) with ≥1 CVD risk factors	109	MACE (CV death, MI, stroke): 7.3% (Sa) *versus* 7.2% (P); $p<0.001$ for non-inferiority; $p=0.99$ for superiority	MACE (CV death, MI, stroke, HUA, HF, coronary revascularization): HR, 1.02 (0.94–1.11); CV death: HR, 1.03 (95% CI 0.87–1.22); HHF: HR, 1.27 (95% CI 1.07–1.51); non-fatal MI: HR, 0.95 (95% CI 0.80–1.04); non-fatal stroke: HR, 1.11 (95% CI 0.88–1.39)
TECOS[32] (Sitagliptin)	14,671	T2D uncontrolled with ASCVD and age ≥50 years	156	MACE (CV death, MI, stroke, HUA): 11.4% (Si) *versus* 11.6% (P); $p<0.001$ for non-inferiority; $p=0.65$ for superiority	MACE (CV death, MI, stroke): HR, 0.99 (0.89-1.10); CV death: HR, 1.04 (95% CI 0.87–1.24); HHF: HR, 0.98 (95% CI 0.81–1.19); MI: HR, 0.96 (95% CI 0.81–1.13); stroke: HR, 0.93 (95% CI 0.75–1.16)

(Continued)

Table 1. ***(Continued)***

Trial (drug studied)	*n*	Patient population	Follow-up, mean (wk)	Primary outcome	Other outcomes
CARMELINA[33] (Linagliptin)	6979	T2D uncontrolled with ASCVD and UACR >200 mg/g or CKD with albuminuria	114	MACE (CV death, MI, stroke): 12.4% (Lin) *versus* 12.1% (P); $p<0.001$ for non-inferiority; $p=0.74$ for superiority	Kidney composite (ESRD, death from kidney failure, decrease eGFR ≥ 40%): HR, 0.99 (0.81–1.14); CV death: HR, 0.96 (95% CI 0.87–1.24); HHF: HR, 0.90 (95% CI 0.74–1.08); non-fatal MI: HR, 1.15 (95% CI 0.91–1.45); non-fatal stroke: HR, 0.88 (95% CI 0.63–1.23)
CAROLINA[34] (Linagliptin)	6033	T2D uncontrolled with ASCVD or CKD or age ≥70 years or ≥2 CVD risk factors	328	MACE (CV death, MI, stroke): 11.8% (Lin) *versus* 12.0% (P); $p<0.001$ for non-inferiority; $p=0.76$ for superiority	MACE (CV death, MI, stroke, HUA): HR, 0.99 (0.86–1.14); CV death: HR, 1.00 (95% CI 0.81–1.24); HHF: HR, 1.21 (95% CI 0.92–1.59); non-fatal MI: HR, 1.01 (95% CI 0.82–1.29); non-fatal stroke: HR, 0.86 (95% CI 0.66–1.12)
GLP-1 RAs					
LEADER[35] (Liraglutide)	9340	T2D uncontrolled age ≥50 years with ASCVD or ≥ 60 years ≥1 CVD risk factors	198	MACE (CV death, MI, stroke): 13.0% (Lir) *versus* 14.9% (P); $p=0.01$ for superiority	MACE (CV death, MI, stroke, HUA, coronary revascularization): HR, 0.88 (0.81–1.96); CV death: HR, 0.78 (95% CI 0.66–0.93); HHF: HR, 0.87 (95% CI 0.73–1.05); non-fatal MI: HR, 0.88 (95% CI 0.75–1.03); non-fatal stroke: HR, 0.89 (95% CI 0.72–1.11)
SUSTAIN-6[36] (Semaglutide)	3297	T2D uncontrolled age ≥50 years with ASCVD or CKD or age ≥60 years or ≥1 CVD risk factors	109	MACE (CV death, MI, stroke): 6.6% (Se) *versus* 8.9% (P); $p=0.02$ for superiority	MACE (CV death, MI, stroke, HUA, coronary revascularization, HHF): HR, 0.74 (0.62–0.89); CV death: HR, 0.98 (95% CI 0.65–1.48); HHF: HR, 1.11 (95% CI 0.77–1.61); non-fatal MI: HR, 0.74 (95% CI 0.51–1.08); non-fatal stroke: HR, 0.61 (95% CI 0.38–0.99)
HARMONY[37] OUTCOMES (Albiglutide)	9463	T2D uncontrolled age ≥40 years with ASCVD	83	MACE (CV death, MI, stroke): 7.0% (Alb) *versus* 9.0% (P); $p=0.0006$ for superiority	MACE (CV death, MI, stroke, RUA): HR, 0.78 (0.69–0.90); CV death: HR, 0.93 (95% CI 0.73–1.19); MI: HR, 0.75 (95% CI 0.61–0.90); stroke: HR, 0.86 (95% CI 0.66–1.14)
REWIND[38] (Dulaglutide)	9901	T2D uncontrolled age ≥50 years with ASCVD or ≥1 CVD risk factors	281	MACE (CV death, MI, stroke): 12.0% (Du) *versus* 13.4% (P); $p=0.026$ for superiority	CV death: HR, 0.91 (95% CI 0.78–1.06); HHF: HR, 0.93 (95% CI 0.77–1.12); non-fatal MI: HR, 0.96 (95% CI 0.79–1.16); non-fatal stroke: HR, 0.76 (95% CI 0.61–0.95)

(Continued)

Table 1. ***(Continued)***

Trial (drug studied)	*n*	Patient population	Follow-up, mean (wk)	Primary outcome	Other outcomes
ELIXA[39] (Lixisenatide)	6068	T2D uncontrolled age ≥30 years with ACS in last 15–180 days	109	MACE (CV death, MI, stroke, UA): 13.4% (Lix) *versus* 13.2% (P); *p*=0.81	CV death: HR, 0.98 (95% CI 0.78–1.22); HHF: HR, 0.96 (95% CI 0.75–1.23); non-fatal MI: HR, 1.03 (95% CI 0.87–1.22); non-fatal stroke: HR, 1.12 (95% CI 0.79–1.58)
ESXCEL[40] (Exenatide)	14,752	T2D uncontrolled with ASCVD (*N*=10,782) or CVD risk factors (*N*=3970)	166	MACE (CV death, MI, stroke): 11.4% (Ex) *versus* 12.2% (P); *p*=0.06 for superiority	CV death: HR, 0.88 (95% CI 0.76–1.02); HHF: HR, 0.94 (95% CI 0.78–1.13); MI: HR, 0/97 (95% CI 0.85–1.10); stroke: HR, 0.85 (95% CI 0.70–1.03)
PIONEER 6[41] (Semaglutide)	3183	T2D uncontrolled age ≥50 years with ASCVD or CKD or age ≥60 years with ≥2 CVD risk factors	68	MACE (CV death, MI, stroke): 3.8% (Sem) *versus* 4.8% (P); *p*<0.001 for non-inferiority; *p*=0.17 for superiority	CV death: HR, 0.49 (95% CI 0.27–0.92); HHF: HR, 0.86 (95% CI 0.48–1.55); non-fatal MI: HR, 1.18 (95% CI 0.73–1.90); non-fatal stroke: HR, 0.74 (95% CI 0.35–1.57)
SGLT2 Inhibitors					
EMPA-REG[42] OUTCOME (Empagliflozin)	7020	T2D uncontrolled with CVD	161	MACE (CV death, MI, stroke): 10.5% (Em) *versus* 12.1% (P); *p*=0.004 for superiority	CV death: 3.7% (Em) *versus* 5.9% (P); *p*<0.001; HHF: 2.7% (Em) *versus* 4.1% (P); *p*=0.002; death from any cause: 5.7% (Em) *versus* 8.3% (P); *p*<0.001
CANVAS[43] (Canagliflozin)	10,142	T2D uncontrolled with ASCVD or age ≥50 years with ≥2 CVD risk factors	188	MACE (CV death, MI, stroke): HR, 0.86 (95% CI 0.75–0.97); *p*=0.02 for superiority	CV death: HR, 0.87 (95% CI 0.72–1.06); HHF: HR, 0.67 (95% CI 0.52–0.87); non-fatal MI: HR, 0.85 (95% CI 0.69–1.05); non-fatal stroke: HR, 0.90 (95% CI 0.71–1.15)
DECLARE-TIMI 58[44] (Dapagliflozin)	17,160	T2D uncontrolled with ASCVD (*N*=6974) or multiple risk factors for ASCVD (*N*=10,186)	218	MACE (CV death, MI, stroke): 8.8% (D) *versus* 9.4% (P); *p*=0.17	CV death or HHF: 4.9% (D) *versus* 5.8% (P); *p*=0.005; CV death: HR, 0.98 (95% CI 0.82–1.17); HHF: HR, 0.73 (95% CI 0.61–0.88), MI: HR, 0.89 (95% CI 0.77–1.01); ischemic stroke: HR, 1.01 (95% CI 0.84–1.21)
VERTIS-CV[45] (Ertugliflozin)	8246	T2D uncontrolled with ASCVD	182	MACE (CV death, MI, stroke): 11.9% (Er) *versus* 11.9% (P); *p*<0.001 for non-inferiority	CV death: 1.8% (Er) *versus* 1.9% (P); *p*=0.39 (ITT); non-fatal MI: 1.7% (Er) *versus* 1.6% (P); *p*=0.66; non-fatal stroke: 0.8% (Er) *versus* 0.8% *p*=0.006 (ITT)
SCORED[46] (Sotagliflozin)	10,584	T2D uncontrolled with CKD and additional CV risk	69	MACE (CV death, MI, stroke): HR, 0.74 (0.63–0.88); *p*<0.001	CV death: HR, 0.90 (95% CI 0.73–1.12); *p*=0.35; HHF: HR, 0.67 (95% CI 0.55–0.82); *p*<0.001

(Continued)

Table 1. ***(Continued)***

Trial (drug studied)	*n*	Patient population	Follow-up, mean (wk)	Primary outcome	Other outcomes
Thiazolidinediones					
IRIS[47] (Pioglitazone)	3876	Recent ischemic stroke or TIA and insulin resistance	250	Fatal or non-fatal stroke or MI: 9.0 (Pi) *versus* 11.8% (P); p=0.007	New DM: 3.8% (Pi) *versus* 7.7% (P); p<0.001; all-cause mortality: 7.0% (Pi) *versus* 7.5% (P); p=0.52; mean weight change: +2.6 kg (Pi) *versus* −0.5 kg (P); p<0.001
J-SPIRIT[48] (Pioglitazone)	120	Symptomatic ischemic stroke or TIA and IGT or new DM	146	Recurrence of ischemic stroke: 4.8% (Pi) *versus* 10.5% (P); p=0.49	Any stroke: 6.3% (Pi) *versus* 12.3% (P); p=0.5; any stroke, TIA, and all-cause mortality: 7.9% (Pi) *versus* 17.5% (P); p=0.35
Kaku et al.[49] (Pioglitazone)	587	Japanese patients with T2D without a recent history of CV events	180	Cumulative incidence of macrovascular events: 3.56% (Pi) *versus* 4.49% (P); p=0.5512	Death, acute MI or stroke: 2.4% (Pi) *versus* 2.4% (P)
PROactive[23] (Pioglitazone)	5238	Uncontrolled T2D and evidence of macrovascular disease	150	All-cause mortality, non-fatal MI, stroke, ACS, intervention in coronary or leg arteries, above-the-ankle amputation: 19.7% (Pi) *versus* 21.7% (P); p=0.095	All-cause mortality, non-fatal MI, stroke: 11.6% (Pi) *versus* 13.4% (P); p=0.027; HHF: 6% (Pi) *versus* 4% (P); p=0.007; any report of HF: 11% (Pi) *versus* 8% (P); p<0.0001
PROFIT-J[50] (Pioglitazone)	522	Uncontrolled T2D at high risk of stroke	96	Time to first occurrence of all-cause mortality, non-fatal cerebral infarction or non-fatal MI: HR, 1.053 (p=0.9114)	Time to first occurrence of all-cause mortality, non-fatal cerebral infarction, non-fatal MI, TIA, angina pectoris, PCI/CABG or ACS: HR, 0.995 (p=0.9898)

A, active; ACS, acute coronary syndrome; Alb, albiglutide; Alo, alogliptin; ASCVD, atherosclerotic cardiovascular disease; C, canagliflozin; CABG, coronary artery bypass grafting; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; D, dapagliflozin; DM, diabetes mellitus; DPP4, dipeptidyl peptidase 4; Du, dulaglutide; Em, empagliflozin; Er, ertugliflozin; Ex, exenatide; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio; HUA, hospitalization for unstable angina; IGT, impaired glucose tolerance; ITT, intention to treat; Lin, linagliptin; Lir, liraglutide; Lix, lixisenatide; MACE, major cardiovascular event; mg, milligram; MI, myocardial infarction; NS, non-significant; P, placebo; PCI, percutaneous coronary intervention; Pi, pioglitazone; RUA, revascularization for unstable angina; Sa, saxagliptin; Se, semaglutide; Si, sitagliptin; T2D, type 2 diabetes; TIA, transient ischemic attack; UACR, urine-albumin creatinine ratio; wk, weeks.

lower CV risk in patients with T2D and ASCVD.[51] Dulaglutide is indicated to reduce MACE in adults with T2D and ASCVD. Both liraglutide and semaglutide subcutaneous formulations are indicated to reduce risk of MI, cerebral vascular accident, or CV death in adults with T2D and ASCVD. Based on these indications, guidelines recommend the use of a SGLT2 inhibitor or a GLP1 receptor agonist with beneficial CV evidence to lower CV events in patients with T2D and established ASCVD.

Current guideline recommendations

The 2022 ADA Standards for Medical Care in Diabetes provides guidance on the role of antihyperglycaemic medications in patients with T2D and ASCVD.[52] These guidelines recommend the initiation of an SGLT2 inhibitor or a GLP1 receptor agonist with proven CVD benefit in patients with T2D and established ASCVD.[52] If a patient is unable to tolerate one of these medication classes, then the other should be tried if the patient has established ASCVD.

The American Association of Clinical Endocrinology (AACE)/ American College of Endocrinology (ACE) 2020 guidelines and the European Society of Cardiology (ESC)/European Association for the Study of Diabetes (EASD) 2019 guidelines have specific guidance on the choice of antihyperglycaemic medication for patients with T2D and established ASCVD.[53,54] Similar to

the ADA, both guidelines recommend the initiation of an SGLT2 inhibitor or a GLP1 receptor agonist with proven efficacy in patients T2D and established ASCVD.[53,54] The key component of AACE, ADA and ESC/EASD recommendations is to select a medication within one of the classes with known benefit to lower CV risk in patients with T2D and ASCVD.

The ACC published an Expert Consensus Decision Pathway (ECDP) on the role of novel therapies for CV risk reduction in patients with T2D in 2020. The ECDP specifically recommends the initiation of an SGLT2 inhibitor or a GLP1 receptor agonist with proven CV benefit in adult patients with T2D and ASCVD based on patient-specific factors and comorbidities.[51] The ECDP further goes on to describe opportunities where an SGLT2 inhibitor or GLP1 receptor agonist should be considered in a patient with T2D and ASCVD. The medication initiation could occur at the time of diagnosing clinical ASCVD in a patient with T2D or at the time of diagnosing T2D in a patient with established ASCVD.

Ongoing/future trials

One CVOT is currently in progress and is due to be completed in 2024. SURPASS-CVOT is a CVOT study of tirzepatide, a novel dual gastric inhibitory polypeptide and GLP1 receptor agonist. SURPASS-CVOT will compare CV outcomes of tirzepatide with dulaglutide, and this represents a new type of CVOT trial design to include a comparator agent.[55]

A retrospective analysis of US claims database data has demonstrated positive CV effects of the addition of an SGLT2 inhibitor compared with the addition of a sulfonylurea to background GLP1 receptor agonist therapy. In a propensity score-matched cohort, those receiving a GLP1 receptor agonist who had an SGLT2 inhibitor added had a 24% decrease (95% CI 0.59–0.98) in the composite CV endpoint of myocardial infarction, stroke and all-cause mortality compared to those who had a sulfonylurea added to their regimen. The study authors postulate that the observed effect was due to the complementary mechanisms of action of the two drug classes.[56] These data should be confirmed with prospective, randomized, controlled clinical trials.

Beyond T2D CVOTs, there has been an increase in HF and renal outcome trials of newer antihyperglycaemic agents. The 7th CVOT Summit, which occurred in November 2021, had a focused review on FIGARO-DKD, EMPA-KIDNEY, DELIVER and EMPEROR-Preserved, none of which are CVOTs in patients with established ASCVD. In the FIGARO-DKD trial, there was a lower CV composite endpoint (CV death, non-fatal MI, non-fatal stroke or HF hospitalization) with finerenone compared to placebo in patients with T2D and chronic kidney disease with albuminuria, which was driven by a lower rate of HF hospitalization.[57] The other pivotal clinical trials focus on renal safety and efficacy of these studied antihyperglycaemic agents as well as on their role in patients with HF. This indicates that there are few new antihyperglycaemic agents in the development pipeline and, instead, pharmaceutical manufacturers are focusing on evaluating the HF and renal outcomes of their existing agents. Given that multiple agents in the GLP1 receptor agonist and SGLT2 inhibitor classes have demonstrated superiority at reducing MACE in patients with T2D, the challenge now is to determine which agents produce renal and/or HF benefits in patients with (and without) T2D.

Conclusion

Patients with T2D and established ASCVD are at a high risk for a subsequent CV event if not maximized on guideline-directed therapy to lower their risk. The therapies to lower CV risk include non-glycaemic modifying approaches (antiplatelet therapy, lipid-lowering therapy, antihypertensive therapy) and glycaemic modifying approaches. This review highlighted the emerging evidence supporting the initiation of GLP1 receptor agonists and SGLT2 inhibitors in patients with T2D and ASCVD to further lower their risk of a future CV event. Key to this benefit is utilizing agents within the GLP1 receptor agonist and SGLT2 inhibitor classes that have demonstrated benefit. Additionally, recent trials have focused on the benefits of these medication classes on renal and HF outcomes, likely cementing their place in guidelines as first-line choices for patients with T2D and ASCVD, HF, and/or renal dysfunction.

Key practice points

- Patients with type 2 diabetes (T2D) and established atherosclerotic cardiovascular disease (ASCVD) should be treated with guideline-directed therapies to reduce future cardiovascular (CV) risk.
- Guideline-directed therapies to reduce CV risk in patients with T2D and ASCVD include antiplatelet agents, lipid-lowering agents, antihypertensive agents, and certain antihyperglycaemic agents.
- Since 2008, the US FDA requires all new antihyperglycaemic agents to undergo cardiovascular outcomes trials testing to ensure CV safety.
- Numerous agents in the GLP1 receptor agonist and SGLT2 inhibitor classes have demonstrated superior efficacy in reducing risk of CV outcomes in patients with T2D and ASCVD or at high CV risk.
- The focus has shifted from cardiovascular outcomes trials to evaluating renal and heart failure outcomes with agents in the GLP1 receptor agonist and SGLT2 inhibitor classes.
- Improved renal function has a direct link to ASCVD risk reduction.

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Correspondence: Sarah Anderson, 12001 Sunrise Valley Dr, Suite 300, Reston, VA 20191. Email: sanderson@clinicaloptions.com

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