




REVIEW

# Rationale for the Early Use of Sodium-Glucose Cotransporter-2 Inhibitors in Patients with Type 2 Diabetes

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## ABSTRACT

Diabetes-related complications including cardiovascular disease, heart failure (HF), chronic kidney disease, retinopathy, and neuropathy are associated with a high burden of disease. Early initiation of glucose-lowering therapy in patients with type 2 diabetes to achieve glycemic control is important for reduction of not only microvascular risk but also of CV (cardiovascular) risk. Clinical studies have indicated that early achievement of glycemic targets is likely to have the greatest effect on preventing microvascular and macrovascular complications. In addition to improvements in glycemic control and CV risk factors, CV outcomes trials (CVOTs) of empagliflozin (EMPA-REG OUTCOME), canagliflozin (CANVAS), and dapagliflozin (DECLARE-TIMI 58) showed significant glucose-independent reductions in the risk of major adverse CV events and/or hospitalization for HF, as well as reductions in the risk of kidney disease progression, versus placebo. These CVOTs and a renal outcomes study of canagliflozin (CREDENCE) support the early initiation of sodium-glucose cotransporter (SGLT)-2 inhibitors to potentially

provide the most benefit toward glycemic control and CV and renal risk. Thus, current treatment recommendations include the early addition of SGLT-2 inhibitor therapy, not only in patients with established CVD, HF, and/or CKD but also in the general population of patients with T2D.

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**Keywords:** Canagliflozin; Cardiovascular effects; Dapagliflozin; Early treatment; Empagliflozin; Ertugliflozin; Glycemic control; Renal effects; Sodium-glucose cotransporter-2 inhibitors; Type 2 diabetes

## PLAIN LANGUAGE SUMMARY

People with type 2 diabetes (T2D) are at risk of developing complications, including macrovascular [cardiovascular disease (CVD), strokes, and heart failure (HF)] and microvascular [chronic kidney disease (CKD) and damage to the eyes and nerves] conditions. Reduction of blood sugar (glucose) levels (glycemic control) can prevent or halt these complications. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a class of glucose-lowering drugs that improve glycemic control, reduce CV (cardiovascular) risk factors such as being overweight and having high blood pressure, and have a low risk of hypoglycemia (low blood sugar levels).

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Health care providers who treat people with T2D sometimes add SGLT-2 inhibitors after initial treatment with metformin alone. Recently, clinical trials and real-world studies in patients with T2D have shown that SGLT-2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) reduced the risk of CV events, CV death, and hospitalization for HF and reduced worsening of kidney disease. Although the reduction in CV events with SGLT-2 inhibitor treatment was greatest for patients who already had CVD, the risk was also reduced in those without CVD. Reductions in death from CV causes or hospitalization for HF and kidney events were similar for patients with or without CVD. Some updated treatment guidelines for T2D, therefore, recommend early use of SGLT-2 inhibitors in patients with T2D, not only those with established CVD. This review describes the reasons for starting early treatment with SGLT-2 inhibitors when the potential benefit may be greatest, providing protection against CV events, hospitalization for HF, and progression of CKD.

## INTRODUCTION

The burden of diabetes in the United States is considerable and growing. An estimated 30.3 million Americans had diabetes in 2015 (9.4% of the population) [1], and projections suggest a prevalence of ~ 55 million by 2030 [2], with ~ 90–95% of these individuals having type 2 diabetes (T2D) [1].

A high proportion of diabetes-related disease burden and cost can be attributed to comorbidities and complications [3], including congestive heart failure (HF), atherosclerotic cardiovascular disease (CVD), peripheral vascular disease, chronic kidney disease (CKD), neuropathy, and retinopathy [1, 3]. Although the rate of diabetes-related complications is decreasing, the increasing prevalence of T2D means the number of individuals who develop diabetes-related illnesses remains substantial [4]. There is, therefore, an urgent need to reduce T2D-associated morbidity and mortality

through the effective management of glycemia, CV risk factors, and other risk factors of chronic disease.

Early intervention to achieve glycemic control and reduce CV and renal risk is important, because a high proportion of patients with T2D already have risk factors before diagnosis [5]. In the National Health and Nutrition Examination Survey (NHANES), 61.9% of patients with undiagnosed T2D had hypertension, 82.6% had hypercholesterolemia, 56.8% had obesity, and an additional 29.5% were overweight [5]. Current American Diabetes Association (ADA) and American Association of Clinical Endocrinologists/American College of Endocrinology (AAACE/ACE) guidelines recommend regular assessment of CV risk factors in patients with diabetes and treatment of any modifiable risk factors outside the normal range [6, 7]. Both guidelines also emphasize the importance of patient-centered care, in which treatment is tailored to patients' individual preferences and needs, including effects on CV outcomes, risk factors, glycemic control, body weight, and renal function [7, 8].

Agents from two classes of glucose-lowering therapies, sodium-glucose cotransporter (SGLT)-2 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs), have been shown to significantly reduce the incidence of CV events in patients with T2D. In large-scale CV outcomes trials (CVOTs), the SGLT-2 inhibitors empagliflozin, canagliflozin, and dapagliflozin [9–11], and the GLP-1RAs liraglutide, semaglutide, dulaglutide, and albiglutide [12–15], significantly reduced the risk of CV events. In addition, although the GLP-1RA exenatide once weekly did not show superiority to placebo in the overall population of the Exenatide Study of Cardiovascular Event Lowering (EXSCCEL) CVOT [16], a follow-up analysis showed CV events were significantly reduced in patients with established CVD [17]. While most CVOTs showed reduction of CV events in patients with CVD at baseline [11–14, 17, 18], some also demonstrated this in patients without established CVD [9, 10, 15].

This review describes the rationale for early initiation of SGLT-2 inhibitors, when the potential to modify outcomes may be greatest,

to provide protection against CV events and prevent the development of HF, CKD, and microvascular complications.

This article is based on previously conducted studies and does not include any new studies with human participants or animals performed by the author.

## RATIONALE FOR EARLY RISK MANAGEMENT

Evidence from clinical trials indicates that early intervention and achievement of glycemic control reduces the long-term risk of microvascular and macrovascular complications in T2D. Two landmark studies, the UK Prospective Diabetes Study (UKPDS) in patients with newly diagnosed T2D and the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) study in patients with a mean T2D duration of ~ 8 years at baseline, demonstrated that intensive glycemic control [treatment with a sulfonylurea or insulin, or metformin for patients with body weight > 120% of ideal, in the UKPDS and treatment to a glycated hemoglobin A1c (HbA1c) level of < 6.5% in ADVANCE] not only reduced the occurrence of microvascular complications but also significantly reduced the long-term incidence of macrovascular events, including myocardial infarction (MI) [19, 20].

In the Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria (Steno-2) study (median diabetes duration of 4–6 years at baseline), intensive multifactorial treatment that targeted several CV risk factors was associated with significant reductions in the risk of mortality (45%;  $p = 0.005$ ), CV events (45%;  $p < 0.001$ ), and microvascular complications (range, 33%–48%) compared with conventional therapy over 21.2 years of follow-up [21]. However, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [22] and the Veterans Affairs Diabetes Trial (VADT) [23], in which the duration of diabetes at baseline was longer (median of 10 years and mean of 11.5 years, respectively), the results are less clear. Although these

studies showed no significant effect of intensive glycemic control on CV complications [22, 23], the intensive therapy arm of the ACCORD study was stopped early (after 3.5 years) because of a significant increase in mortality [22]. This was despite a significantly reduced risk of nonfatal MI with intensive therapy [22].

The ADA, American Heart Association (AHA), and American College of Cardiology (ACC) reviewed these apparently contradictory data and determined that the differences were at least partly due to patient characteristics [24]. Patients most likely to have reduced CVD risk with intensive glycemic control were those with a shorter T2D duration who had not yet developed atherosclerosis, whereas, in older or frail patients, those with a long duration of T2D or patients with advanced atherosclerotic disease, the risks associated with intensive glycemic control may exceed its benefits [24]. In a post hoc analysis of ACCORD, the greatest risk of mortality with intensive therapy appeared to be among patients who continued to have an HbA1c level of > 7.0% [25], highlighting the need for personalized medicine and individualized treatment goals, as recommended by treatment guidelines [6, 7]. These findings were supported by a subsequent analysis of VADT, which found that intensive glycemic control reduced the risk of CV events in patients with a T2D duration of < 15 years, but was associated with increased risk in those with a disease duration of  $\geq 15$  years and was potentially harmful in those with a disease duration of  $\geq 20$  years [26].

A 10-year post-trial follow-up of UKPDS found a significant reduction in the risk of CV events in patients with newly diagnosed T2D who had received intensive glycemic control, but only after enough time had passed to demonstrate an effect on these outcomes [19]. This study demonstrated a legacy effect of early intensive therapy because the difference in the CV event rate 10 years post-trial was apparent even though there was no longer a difference in HbA1c levels between the intensive and conventional therapy groups [19].

A similar legacy effect was seen in patients with type 1 diabetes who had received intensive or conventional therapy for 6.5 years in the

Diabetes Control and Complications Trial (DCCT) [27]. Thirty-year post-trial follow-up data showed that, among young patients who had not yet developed CVD, early intensive diabetes therapy significantly reduced the later risk of a CV event by 30% compared with conventional therapy ( $p = 0.016$ ) [27].

Real-world evidence has also shown a legacy effect of early intensive glycemic control in patients with T2D. The Diabetes & Aging Study found that, after 13 years' follow-up, patients who achieved an HbA1c of  $< 6.5\%$  during the first year after diagnosis had a lower risk of microvascular and macrovascular complications than those with HbA1c  $\geq 6.5\%$  and a lower mortality risk than those with HbA1c  $\geq 7.0\%$  during the first year [28].

Early use of combination therapy in patients with newly diagnosed T2D has also been shown to reduce the progression of atherosclerosis, in addition to improving glycemic control, compared with conventional therapy [29, 30]. In the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT) study, first-line treatment with exenatide, pioglitazone, and metformin was associated with a greater reduction in HbA1c and more patients achieving glycemic targets after 2 years compared with initial treatment with metformin and sequential addition of a sulfonylurea and insulin glargine [29]. The greater reduction in HbA1c was maintained at 6 years, and the early combination therapy group also had significantly reduced carotid intimal media thickness compared with the conventional therapy group [30].

These studies demonstrate that early achievement of glycemic targets has the greatest effect on macrovascular complications, with a legacy effect even if intensive glycemic control is not maintained. However, it also raises the question whether continued intensive therapy would provide much earlier benefits beyond the legacy effect.

## MECHANISM OF GLYCEMIC CONTROL OF SGLT-2 INHIBITORS

SGLT-2 inhibitors act by insulin-independent mechanisms to improve glycemic control and

CV risk factors in patients with T2D. SGLT-2 inhibitors reduce reabsorption of glucose from the proximal tubule of the kidneys, which in turn increases glucosuria [31]. Because inhibition of SGLT-2 also reduces sodium reabsorption, SGLT-2 inhibitors have a natriuretic effect, which may partially explain the observed reduction in blood pressure (BP) [32]. These reductions in BP are not accompanied by increases in heart rate, indicating a lack of reflex sympathetic nervous system activation [33]. The natriuretic effects of SGLT-2 inhibitors, which may lead to reductions in plasma volume and cardiac preload, also occur without activation of the renin–angiotensin–aldosterone system [34]. Although the specific effects of SGLT-2 inhibitors on intrarenal hemodynamics are unclear, changes in tubuloglomerular feedback may be involved in neurohormonal stimulation and fluid and electrolyte homeostasis, and the net effect of SGLT-2 inhibition in the diabetic kidney appears to be protective and associated with preservation of renal function [34].

SGLT-2 inhibitors are also associated with increased lipolysis, with an early shift in substrate utilization from carbohydrates to fats [32]. Coupled with increased glucosuria and other as yet unknown mechanisms, such as a reduction in sympathetic nervous system activity [35], the net effect of SGLT-2 inhibitor treatment is a reduction in both body weight and fat mass [32]. Studies have also shown decreases in hepatic fat [36, 37] and fibrosis [37–39] with SGLT-2 inhibitors in patients with T2D and nonalcoholic fatty liver disease, and reduced epicardial fat accumulation in patients with T2D [40]. Reductions in body weight and BP (independent of glucosuria) have also been observed with SGLT-2 inhibitor therapy in patients with T2D and CKD [estimated glomerular filtration rate (eGFR) 30–59 mL/min/1.73 m<sup>2</sup>] in whom there is reduced glucosuria compared to patients with normal or mildly impaired renal function [41].

Because the SGLT-2 inhibitor mechanism of action is independent of insulin, and differs from those of other classes of glucose-lowering therapy, which typically affect beta-cell function, hepatic glucose production, or glucose uptake by the muscles, SGLT-2 inhibitors can

potentially act synergistically with other agents [32]. Unlike other glucose-lowering therapy classes, efficacy with SGLT-2 inhibitors does not decline with worsening beta-cell function [32]. Furthermore, SGLT-2 inhibitors are associated with a low risk of hypoglycemia [31].

## CARDIOVASCULAR AND RENAL EFFECTS OF SGLT-2 INHIBITORS

### Randomized Controlled Trials

The effects of SGLT-2 inhibitors on CV outcomes have been assessed in several randomized, placebo-controlled trials [9–11] and in real-world studies [42–44]. In addition, ertugliflozin is currently being investigated in a large-scale CVOT [Evaluation of Ertugliflozin Efficacy and Safety CV Outcomes Trial (VERTIS-CV); NCT01986881] [45], with study completion expected in September 2019.

In the completed CVOTs, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) included patients with established CVD (> 99% of patients) and almost no patients (< 1%) with multiple CVD risk factors [11], while the Canagliflozin Cardiovascular Assessment Study (CANVAS) [9] and the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) study [10] also included patients with multiple CVD risk factors (34% and 59% of patients, respectively).

In these studies, empagliflozin and canagliflozin were associated with a 14% reduction in the risk of major adverse CV events (MACE) compared with placebo [9, 11]. The risk of MACE was not significantly lower with dapagliflozin versus placebo; however, dapagliflozin significantly reduced the risk of the coprimary composite end point of CV death or hospitalization for HF by 17% [10].

SGLT-2 inhibitors were also associated with reductions in the risks of HF and mortality outcomes compared with placebo in these studies [9–11]. In EMPA-REG, significant reductions in the risk of CV mortality (38%), all-cause mortality (32%), and hospitalization for HF (35%) were observed with empagliflozin

compared with placebo [11]. Although the risk of the individual end point of hospitalization for HF was lower with canagliflozin versus placebo in CANVAS, these results were not considered statistically significant because hypothesis testing was not performed based on a prespecified hierarchy of secondary end points [9, 10]. However, in DECLARE, dapagliflozin had dual primary outcomes and, although it did not demonstrate the superiority of MACE reduction, the reduction in hospitalization for HF and CV Mortality was statistically significant [10].

Differences in study design, including exclusion of patients with a creatinine clearance of < 60 mL/min and inclusion of a large proportion of patients without established CVD, may have affected the findings in DECLARE [10]. A prespecified analysis of patients with prior MI in DECLARE found significant reductions in the risk of MACE, as well as CV mortality or hospitalization for HF [46]. A meta-analysis of CANVAS, DECLARE, and EMPA-REG found that, while the risk of MACE was reduced by 11% in the overall population, the reduction was primarily in the subgroup with established CVD, and there was no significantly reduced risk in the subgroup without CVD [47]. However, the risks of CV death or hospitalization for HF and renal outcomes were reduced in both the subgroup without established CVD and the subgroup with established CVD, as well as the overall population.

While all SGLT-2 inhibitor CVOTs showed a reduction in the risk of renal outcomes with SGLT-2 inhibitors versus that with placebo [10, 18, 48, 49], in CANVAS and DECLARE, it was also seen in patients without CVD at baseline [10, 48]. Canagliflozin was associated with a reduction in the risk of albuminuria progression by 27% overall and by 31% in the subgroup without CVD [48]. Despite the DECLARE population having a mean eGFR of 85.2 mL/min/1.73 m<sup>2</sup> and 48% of patients having eGFR ≥ 90 mL/min/1.73 m<sup>2</sup> at baseline, dapagliflozin was associated with a reduction in the risk of the composite outcome of 40% decrease in eGFR, end-stage renal disease (ESRD), or death from renal causes by 47% overall and by 49% in the subgroup without CVD [10].

Reductions in individual components of this end point (eGFR reduction of  $\geq 40\%$  to  $< 60$  mL/min/1.73 m<sup>2</sup> and ESRD) were also observed with dapagliflozin ( $p < 0.05$  vs. placebo) [50]. In addition, dapagliflozin, given with or without saxagliptin, was found to significantly reduce albuminuria in a study in patients with T2D, moderate-to-severe CKD, and micro- or macroalbuminuria [51]. The impact of the SGLT-2 inhibitor class on the kidney was further shown in Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), a dedicated renal outcomes trial comparing canagliflozin with placebo given in addition to the standard of care in patients with T2D and CKD (eGFR  $\geq 30$  to  $< 90$  mL/min/1.73 m<sup>2</sup> and albuminuria) [52]. Canagliflozin reduced the relative risk of the primary composite end point of ESRD, doubling the serum creatinine level, or of renal or CV death by 30% ( $p = 0.00001$ ); relative risks of the individual components of ESRD and doubled serum creatinine were also significantly reduced [53]. Significant reductions were also seen in the relative risks of the secondary end points of CV death or hospitalization for HF (31% reduction); CV death, MI, or stroke (20%); hospitalization for HF (39%); and ESRD, doubled serum creatinine, or renal death (34%) [53].

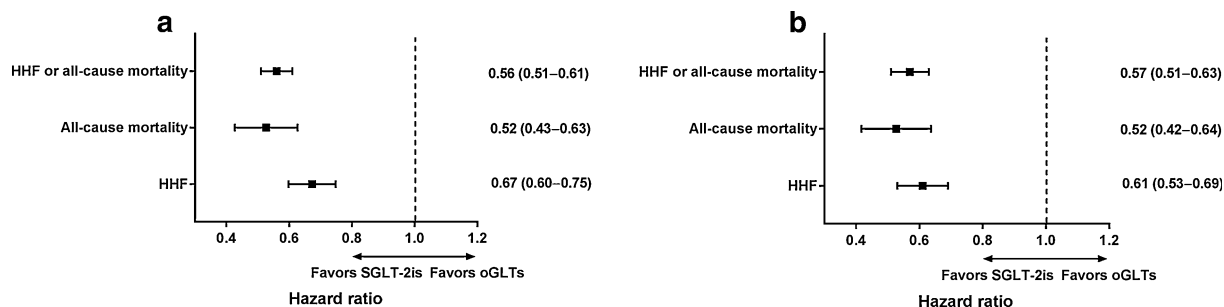
### Real-World Evidence

Although randomized controlled trials are necessary to demonstrate the efficacy of different treatments, their highly selected patient populations (especially the population with established CVD) can limit the generalizability of results to clinical practice populations [54, 55]. Given the low number of CV events among patients without established CVD, these studies would need to include much larger numbers of patients to be sufficiently powered to confirm improved CV outcomes in this subgroup. Conducting real-world observational studies allows the study of outcomes in large patient populations, and may also provide supplemental evidence of treatment efficacy that potentially

increases the applicability of treatment recommendations to clinical practice [54, 55].

The Comparative Effectiveness of CV Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) study compared CV outcomes in  $> 300,000$  propensity-matched patients with T2D who newly initiated SGLT-2 inhibitors or another form of glucose-lowering therapy in the United States, United Kingdom, Denmark, Germany, Norway, and Sweden [42]. In this study, in which 13% of patients had established CVD and  $< 3\%$  had CKD, SGLT-2 inhibitor therapy was associated with significantly lower risks of all-cause mortality, hospitalization for HF, and the composite outcome of all-cause mortality or hospitalization for HF compared with other glucose-lowering therapies (Fig. 1) [42]. These findings were consistent across the unadjusted intent-to-treat analysis (Fig. 1a) and the on-treatment analysis after adjustment for age, sex, frailty, hypertension, obesity/body mass index, duration of T2D, use of antihypertensive agents, and history of HF, MI, and atrial fibrillation (Fig. 1b) [42]. In an analysis of the Nordic subgroup of CVD-REAL participants (in Norway, Denmark, and Sweden), there were significant decreases in risks of CV mortality (by 47%) and major CV events (by 22%) with SGLT-2 inhibitors versus those with other glucose-lowering therapies ( $p < 0.0001$ ) [43]. Similarly, in the CVD-REAL 2 study of  $> 400,000$  propensity-matched patients with T2D in the Asia-Pacific region, Middle East, and North America, who newly initiated an SGLT-2 inhibitor or other glucose-lowering therapy, in which  $\sim 27\%$  had established CVD and  $< 2\%$  had CKD, SGLT-2 inhibitors were associated with a reduced risk of all-cause mortality, hospitalization for HF, the composite of all-cause mortality or hospitalization for HF, MI, and stroke, compared with other glucose-lowering therapies ( $p \leq 0.001$  for all) [44]. Of note, the risk of these outcomes was reduced not only in patients with established CVD but also in those without CVD at baseline [44].

A real-world meta-analysis of four US databases (OBSERVE-4D) assessed hospitalization for HF outcomes among  $> 700,000$  patients with T2D who newly initiated canagliflozin, other SGLT-2 inhibitors, or other non-SGLT-2



**Fig. 1** Cardiovascular outcomes in real-world patients receiving SGLT-2is or oGLTs in the CVD-REAL study [42]. **a** Unadjusted intent-to-treat analysis. **b** On-treatment analysis adjusted for history of heart failure; age; sex; frailty; history of myocardial infarction; history of atrial fibrillation; hypertension; obesity/body mass index; duration of type 2 diabetes; and use of angiotensin-converting

enzyme inhibitors or angiotensin receptor blockers, alpha- or beta-blockers, calcium-channel blockers, loop diuretics, or thiazide diuretics. Error bars 95% confidence interval. *HHF* hospitalization for heart failure, *SGLT-2is* sodium-glucose cotransporter-2 inhibitors, *oGLTs* other glucose-lowering therapies

inhibitor therapy, 30% of whom had established CVD [56]. In OBSERVE-4D, there was a significant reduction in the risk of hospitalization for HF in the overall population with newly initiated canagliflozin versus non-SGLT-2 inhibitor therapy (by 61%) and with newly initiated other SGLT-2 inhibitors versus non-SGLT-2 inhibitor therapy (by 57%); these reductions were similar to those observed in the subgroup with established CVD [56]. However, no difference was observed with canagliflozin versus other SGLT-2 inhibitors [56].

Initial results from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) study also showed that empagliflozin and other SGLT-2 inhibitors reduced hospitalization for HF in patients with and without established CVD compared with dipeptidyl peptidase-4 (DPP-4) inhibitors [57]. Analysis of propensity score-matched patient pairs found that empagliflozin reduced the risk of hospitalization for HF as the primary discharge diagnosis and as any discharge diagnosis by 50% and 49%, respectively, compared with sitagliptin, although the number of events was low [57]. Compared with all DPP-4 inhibitors, empagliflozin reduced the risk of HF as the primary or any-position discharge diagnosis by 51% and 44%, respectively [57]. Similarly, comparison of the two drug classes indicated that, compared with DPP-4 inhibitors, SGLT-2 inhibitors were

associated with 58% and 30% reductions in the risk of primary and any-position hospital discharge diagnosis of HF, respectively [57].

## MECHANISMS OF CV AND RENAL PROTECTION WITH SGLT-2 INHIBITORS

As described in the section “Mechanism of glycemic control of SGLT-2 inhibitors”, the effects of glycemic control on CV outcomes can take years to manifest [19]; therefore, the observed effects of SGLT-2 inhibitors in the CVOTs and the CVD-REAL study are likely to result from mechanisms beyond glycemic control [33]. The cardioprotective and renoprotective effects of SGLT-2 inhibitors in patients with T2D are likely multifactorial and encompass additive effects on glycemia and CV risk factors (including BP and body weight) [58, 59]; there are potentially other pathophysiologic mechanisms of atherosclerosis (Table 1) [58]. The effect of SGLT-2 inhibitors on renal function also plays an important role in CV risk reduction.

There is emerging evidence that, in addition to their effects on CV risk factors, SGLT-2 inhibitors may have other direct effects on CV function. Because of their natriuretic and diuretic effects, SGLT-2 inhibitors reduce plasma volume and therefore lower cardiac

**Table 1** Change from baseline in cardiovascular risk factors with SGLT-2 inhibitors [58]

Cardiovascular risk factor	Change from baseline (95% CI) <sup>a</sup>
Blood pressure (mm Hg)	
Systolic	− 2.46 (− 2.86, − 2.06)
Diastolic	− 1.46 (− 1.82, − 1.09)
Lipid levels (mg/dL)	
Total cholesterol	0.77 (0.33, 1.21)
HDL cholesterol	3.89 (3.23, 4.56)
Triglycerides	− 2.08 (− 2.51, − 1.64)
Lipid levels, mmol/L	
Total cholesterol	0.02 (0.01, 0.03)
HDL cholesterol	0.10 (0.08, 0.12)
Triglycerides	− 0.02 (− 0.03, − 0.02)
Glycemic measures	
Fasting blood glucose (mg/dL)	− 2.40 (− 2.68, − 2.11)
Fasting blood glucose (mmol/L)	− 0.13 (− 0.15, − 0.12)
HbA1c (%)	− 2.48 (− 2.73, − 2.24)
Adiposity indicators	
Body weight (kg)	− 1.88 (− 2.11, − 1.66)
Waist circumference (cm)	− 2.89 (− 4.32, − 1.46)
Indicators of renal function	
eGFR (mL/min/1.73 m <sup>2</sup> )	− 0.98 (− 1.69, − 0.27)
Urea (mmol/L)	0.99 (0.35, 1.64)

Data are from a meta-analysis of 43 controlled trials (14 trials with canagliflozin, 22 with dapagliflozin, 4 with empagliflozin, 2 with remogliflozin, and 1 with ipragliflozin) with a treatment duration range of 4–208 weeks. *HbA1c* glycated hemoglobin A1c, *CI* confidence interval, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *SGLT* sodium-glucose cotransporter

<sup>a</sup> Blood pressure data are from the overall meta-analysis; all other data are the results of the leave-one-out sensitivity analysis. Results of the leave-one-out sensitivity analyses were similar to those of the primary analysis across all studies and parameters

preload [34]. Unloading the heart by this mechanism may explain why SGLT-2 inhibitors have beneficial effects on left ventricular diastolic function, as well as on left ventricular mass [60, 61]. The reduction in plasma volume with SGLT-2 inhibitors does not appear to be associated with a reflex increase in sympathetic activity [60]. Whether SGLT-2 inhibitors suppress abnormal sympathetic activity, thereby providing patients with diabetes some protection against arrhythmias in the acute setting, is currently being investigated [62].

Another potential mechanism of benefit for SGLT-2 inhibitors in CVD is through mediation of improvements in endothelial function [63, 64]. The Dapagliflozin Effectiveness on Vascular Endothelial Function and Glycemic Control in T2DM (DEFENCE) study found that treatment with dapagliflozin for 16 weeks significantly improved flow-mediated dilation in the brachial artery compared with metformin [64]. Patients in this study had early T2D (mean duration, ~ 6 years) and good glycemic control (mean A1C, < 7%) [64].

SGLT-2 inhibitor therapy is also associated with an increase in ketone bodies, which results in the cardiac uptake and oxidation of  $\beta$ -hydroxybutyrate rather than fatty acids [65]. This may promote increased hepatic synthesis of ketones (including  $\beta$ -hydroxybutyrate) that can be used as an alternative cardiac fuel, potentially providing a more efficient energy source than either glucose or fatty acids [66].

The beneficial effects of SGLT-2 inhibitors in HF outcomes may result from their ability to inhibit sodium–hydrogen exchangers in the heart and kidneys, which could potentially increase the natriuretic effects of other agents routinely administered to patients with HF (e.g., diuretics and mineralocorticoid receptor antagonists) [67]. This may attenuate cardiomyocyte injury and prevent the onset of left ventricular hypertrophy and ultimately HF [67].

Preliminary studies suggest SGLT-2 inhibitors reduce epicardial fat [68], and may also exhibit antifibrotic effects in myocardial and pericardial cells [69–72]. In a study of postinfarction rats, dapagliflozin administration led to decreases in myofibroblast infiltration and collagen deposition that were independent of the



glucose-lowering effects [70]. At the cellular level, other mechanisms are likely also involved in the renoprotective and cardioprotective effects of SGLT-2 inhibitors, including anti-inflammatory and anti-oxidative effects [73], although further research is required to elucidate these mechanisms.

## SAFETY CONSIDERATIONS FOR SGLT-2 INHIBITOR THERAPY

SGLT-2 inhibitors are generally well tolerated and do not increase the risk of hypoglycemia when used with metformin, GLP-1RAs, DPP-4 inhibitors, or thiazolidinediones [74, 75]. The most common adverse events with SGLT-2 inhibitors are genital mycotic infections [74, 76–79]. These occur in up to 10% of patients and in both men and women, although the incidence is lower among circumcised men [76, 78]. Genital mycotic infections are usually of mild to moderate intensity and can be mitigated through hygiene and the occasional use of antifungal agents. However, an alternative to SGLT-2 inhibitor therapy may be preferable for patients with a history of multiple yeast infections.

Volume depletion-related adverse events, including hypotension and dizziness, have also been reported with SGLT-2 inhibitor therapy [76–79]. Volume depletion occurs more frequently among patients who are older, have a longer duration of T2D, and have  $eGFR < 60 \text{ mL/min/1.73 m}^2$ , and those receiving a concomitant diuretic, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker therapy [76–79]. Before starting treatment with SGLT-2 inhibitors, volume status should be assessed and hypovolemia corrected. Increasing fluid intake and reducing or discontinuing diuretic treatment can reduce the risk of volume depletion-related events.

Serious, but rare, adverse events associated with SGLT-2 inhibitor therapy include diabetic ketoacidosis (DKA), amputations, fractures, and Fournier's gangrene [76–79]. The risk of such events can be reduced by assessing patients for risk factors before starting treatment with SGLT-2 inhibitors, and monitoring for, and

educating patients about, the signs and symptoms of these events during treatment.

DKA primarily occurs in patients who are insulin-deficient, and is generally not seen in those with earlier stage T2D [80]. Patients taking SGLT-2 inhibitors who develop DKA may have normal or less elevated than anticipated blood glucose levels because of the reduced threshold for glucose excretion with this drug class [80]. Patients should be evaluated for predisposing factors for DKA before starting treatment with an SGLT-2 inhibitor [76–80]. To reduce the risk of DKA, SGLT-2 inhibitor therapy should be temporarily discontinued 1–2 days before elective surgery, and before extreme physical activity such as marathon running, and stopped immediately in patients with sepsis or undergoing emergency surgery [80]. In addition, excessive alcohol consumption and ketogenic or very low carbohydrate diets should be avoided [80].

An increased risk of lower limb amputations was seen with canagliflozin in the CANVAS program but not with other SGLT-2 inhibitors in CVOTs [9–11]. However, while amputations were more frequent with canagliflozin versus placebo in the CANVAS program, this was not observed in the CREDENCE trial [9, 53]. Amputations were more common among patients with a prior history of amputations and among those with severe vascular disease or neuropathy [76, 81]. SGLT-2 inhibitor therapy should be avoided in patients considered to be at increased risk of lower limb amputation, and discontinued in patients who develop ulcers and infections of the lower limbs [76].

Fractures were previously a concern with SGLT-2 inhibitor therapy, but long-term data do not suggest an increased risk [82]. However, factors that may increase a patient's risk for fracture should be considered when prescribing an SGLT-2 inhibitor therapy [76].

Fournier's gangrene is a rare but potentially life-threatening complication of SGLT-2 inhibitor therapy. This adverse event should be managed with broad-spectrum antibacterial agents and surgical debridement as necessary; SGLT-2 inhibitor therapy should be discontinued [76–79].

Although serious adverse events have been reported with SGLT-2 inhibitor therapy, the risk should be weighed against the potential benefits of reduced CV and renal complications. Furthermore, the risk of adverse events is likely to be lower among patients with earlier-stage T2D than that reported in clinical trials and real-world studies, because those data were obtained from across the patient population, including older patients and those with longer duration or greater severity of T2D [80].

## PLACE OF SGLT-2 INHIBITORS IN EARLY DIABETES THERAPY

Current ADA guidelines recommend monotherapy with metformin in combination with lifestyle management as first-line therapy from the time of T2D diagnosis to achieve glycemic control [8]. AACE/ACE guidelines also recommend that pharmacologic treatment be started together with lifestyle management following diagnosis [7]. Patients with an HbA1c < 7.5% at diagnosis should receive monotherapy, with metformin being the preferred first-line treatment, although other agents can also be used [7]. For patients whose HbA1c is  $\geq$  7.5% at diagnosis, AACE/ACE guidelines recommend starting on dual therapy with metformin and another class of glucose-lowering therapy, with GLP-1RAs and SGLT-2 inhibitors preferred [7]. For patients with HbA1c > 1.5% above goal at diagnosis, the ADA and European Association for the Study of Diabetes (EASD) guidelines recommend first-line treatment with a dual combination [8, 83]. The ADA and EASD recommend an SGLT-2 inhibitor as the first post-metformin treatment in patients with established CVD, congestive HF, or CKD [8, 83]. The ACC/AHA primary prevention guidelines also recommend SGLT-2 inhibitor or GLP-1RA therapy after first-line metformin to reduce CV risk in patients with T2D and additional CV risk factors [84].

The AACE/ACE and ADA guidelines recommend that patients should be initially assessed every 3 months, and additional glucose-lowering treatments should be added as needed at each assessment to meet glycemic targets [7, 8].

For add-on therapy in patients without CVD, the ADA guidelines state that treatment choice should be guided by patient needs, including avoidance of adverse effects (e.g., hypoglycemia and body weight gain), cost considerations, or other needs [8], while the AACE/ACE guidelines recommend a hierarchy of use for add-on glucose-lowering therapy based on safety and efficacy and consideration of the properties of each agent for individual patients [7]. The AACE/ACE guidelines also recommend that GLP-1RAs or SGLT-2 inhibitors with proven CV benefits should be prescribed to patients with CVD regardless of glucose level [7]. The ADA/EASD consensus statement not only recommends SGLT-2 inhibitors in patients with HF or a high risk of HF but also recommends that their use be considered in patients with CKD (with or without CVD) to prevent or reduce progression of CKD [83], although there is some debate regarding the quality of evidence for these recommendations. In patients with T2D and overweight or obesity (without CVD or CKD), glucose-lowering therapy should include add-on therapy with an SGLT-2 inhibitor (in those with an adequate eGFR) or a GLP-1RA with good weight loss efficacy, in addition to lifestyle management, nonsurgical energy restriction, and consideration of weight loss medications and metabolic surgery [83].

Each of the SGLT-2 inhibitors approved in the United States is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with T2D [76–79]; empagliflozin has an additional indication for reducing the risk of CV death [77] and canagliflozin is indicated to reduce the risk of MACE [76] in patients with both T2D and established CVD.

A PubMed search conducted in July 2019 identified 15 studies in which SGLT-2 inhibitors were used early in the course of T2D [64, 85–97]. Ten studies evaluated dapagliflozin [64, 85–89, 91, 93, 94, 98], two studied canagliflozin [90, 97], two assessed empagliflozin [92, 96], and one evaluated ertugliflozin [95]. Seven studies investigated SGLT-2 inhibitors as monotherapy [85–90, 98], while, in eight studies, SGLT-2 inhibitors were given in combination with metformin (Table 2) [64, 91–97].

**Table 2** Studies in which sodium-glucose cotransporter-2 inhibitors have been used in combination with MET in patients with early-stage type 2 diabetes

Author, year [ref]	Design	Patients	Treatment arms	n	Duration, weeks	Mean change in HbA1c at end of treatment			
Henry et al., 2012 [91]	Study 1: randomized, double-blind	Treatment-naive (mean duration of diabetes: 2 years)	MET + PBO	201	24	– 1.35%			
			DAPA 5 mg/day + PBO	203		– 1.19%			
			DAPA 5 mg/day + MET	194		– 2.05%*			
			MET + PBO	208		– 1.44%			
	Study 2: randomized, double-blind		DAPA 10 mg/day + PBO	219		– 1.45%			
			DAPA 10 mg/day + MET	211		– 1.98%*			
			EMPA 12.5 mg BID + MET 1000 mg BID	169	24	– 2.08% <sup>†‡</sup>			
			EMPA 12.5 mg BID + MET 500 mg BID	165		– 1.93% <sup>‡\$</sup>			
Hadjadj et al., 2016 [96]	Randomized, double-blind	Drug-naive	EMPA 5 mg BID + MET 1000 mg BID	167		– 2.07% <sup>†‡</sup>			
			EMPA 5 mg BID + MET 500 mg BID	161		– 1.98% <sup>‡\$</sup>			
			EMPA 25 mg OD	164		– 1.36%			
			EMPA 10 mg OD	169		– 1.35%			
			MET 1000 mg BID	164		– 1.75%			
			MET 500 mg BID	168		– 1.18%			
			Muscelli et al., 2016 [92]	Open-label	Treatment-naive On stable MET monotherapy ≥ 1500 mg for ≥ 3 months	EMPA 25 mg/day + MET	32	4	NR <sup>†</sup>
						EMPA 25 mg/day + MET	34		NR <sup>†</sup>

Table 2 continued

Author, year [ref]	Design	Patients	Treatment arms	n	Duration, weeks	Mean change in HbA1c at end of treatment
Rosenstock et al., 2016 [97]	Randomized, double-blind	Drug-naïve mean duration of diabetes 3 years)	CANA 100 mg/day + MET CANA 300 mg/day + MET CANA 100 mg/day CANA 300 mg/day MET	237 237 237 238 237	26	– 1.77% <sup>§\ \ </sup> – 1.78% <sup>§\ \ </sup> – 1.37% – 1.42% – 1.30%
Shigiyama et al., 2017 [64]	Randomized, open-label	On stable MET ≥ 750 mg ± another oral glucose-lowering therapy for ≥ 12 weeks (mean duration of diabetes: ~ 6 years)	DAPA 5 mg/day + MET 750 mg/day MET 1500 mg/day	37 37	16	– 0.2%** – 0.4%**
Handelsman et al., 2018 [93]	Randomized, double-blind	On stable MET ≥ 1500 mg for ≥ 8 weeks and no other glucose-lowering therapy for > 2 weeks	DAPA 10 mg/day + SAXA 5 mg/day + MET SITA 100 mg/day + MET	232	52	– 1.29%
Mathieu et al., 2018 [94]	Open-label	On stable MET monotherapy ≥ 1500 mg for ≥ 8 weeks (mean duration of diabetes: 7 years)	DAPA 10 mg/day + MET SAXA 5 mg/day + MET	482 349	16	– 0.81% – 1.6% – 1.3%

Table 2 continued

Author, year [ref]	Design	Patients	Treatment arms	n	Duration, weeks	Mean change in HbA1c at end of treatment
Pratley et al., 2018 [95]	Randomized, double-blind	On stable MET monotherapy ≥ 1500 mg for ≥ 8 weeks	ERTU 5 mg/day + MET	250	52	− 1.0%
			ERTU 15 mg/day + MET	248		− 0.9%
			SITA 100 mg/day + MET	247		− 0.8%
			ERTU 5 mg/day + SITA 100 mg/day + MET	243		− 1.4%
Kong et al., 2019 [98]	Randomized, open-label, crossover	Treatment-naive	ERTU 15 mg/day + SITA 100 mg/day + MET	244		− 1.4%
			DAPA 10 mg/day	22	8 per treatment	− 0.5% <sup>††</sup>
			MET 1000 mg/day titrated to ≤ 2000 mg/day	22		− 0.5% <sup>**</sup>

*HbA1c*: glycated hemoglobin A1c, *BID* twice daily, *CANA* canagliflozin, *DAPA* dapagliflozin, *EMPA* empagliflozin, *ERTU* ertugliflozin, *MET* metformin, *NR* not reported, *OD* once daily, *PBO* placebo, *SAXA* saxagliptin, *SITA* sitagliptin  
<sup>\*</sup>*p* < 0.0001 versus MET + PBO; <sup>†</sup>*p* = 0.006 versus MET; <sup>‡</sup>*p* < 0.001 versus corresponding daily EMPA dose; <sup>§</sup>*p* ≤ 0.001 versus MET; <sup>¶</sup>*p* < 0.0001 versus baseline; <sup>||</sup>*p* = 0.001 versus corresponding CANA dose; <sup>\*\*</sup>*p* ≤ 0.001 versus baseline; <sup>††</sup>*p* < 0.05 versus baseline

The studies that evaluated the combination of an SGLT-2 inhibitor plus metformin demonstrated a significant difference in HbA1c reduction compared with the same dose of metformin as monotherapy [64, 91, 96, 97] or compared with baseline [92]; the magnitude of the HbA1c reduction varied depending on study duration and background therapy at the start of treatment. Two studies have also demonstrated that the magnitude of the change in HbA1c with an SGLT-2 inhibitor, with or without metformin, was similar in treatment-naive patients as in patients who had already received metformin [92] or insulin with metformin, pioglitazone, or rosiglitazone [86]. In a study of patients with T2D receiving stable metformin therapy, early addition of dapagliflozin plus saxagliptin was associated with a significantly greater reduction in HbA1c after 26 weeks compared with addition of sitagliptin ( $p = 0.0008$ ); the between-group difference in HbA1c reduction increased at 52 weeks [93]. Similarly, in the 52-week Evaluation of Ertugliflozin Efficacy and Safety Factorial (VERTIS FACTORIAL) study, significantly greater HbA1c reductions were observed with the combination of ertugliflozin plus sitagliptin as add-on therapy to metformin versus those with either agent individually after 26 weeks of treatment ( $p < 0.001$ ), with sustained HbA1c reductions at 52 weeks [95].

In addition to being the guideline-recommended approach, early combination therapy in T2D makes clinical sense for several reasons [99]. First, a meta-analysis of clinical trials has demonstrated that the early use of combination therapy significantly increases the likelihood of achieving the glycemic target of HbA1c  $< 7\%$  compared with metformin monotherapy [100]. Combining drugs with different mechanisms of action will have an additive effect on glycemic control while using lower doses of each drug, thereby reducing the potential for adverse events [99].

Second, the number of therapy choices to include in combination treatment is greatest early in the course of the disease when patients are relatively young and before they have developed significant comorbidities, including renal impairment, which may preclude the use

of certain drugs. SGLT-2 inhibitors can be used without dose reduction in patients with mild-to-moderate renal impairment [74], but, from current evidence, they are not recommended in patients with advanced kidney disease (eGFR  $< 45$  mL/min/1.73 m<sup>2</sup> for canagliflozin, dapagliflozin and empagliflozin and  $< 60$  mL/min/1.73 m<sup>2</sup> for ertugliflozin) and are contraindicated in patients with severe renal impairment (eGFR  $< 30$  mL/min/1.73 m<sup>2</sup>) [76–79]. Another reason for using SGLT-2 inhibitors early in the course of T2D is the likelihood of response to treatment, perhaps because renal function is generally better. A multivariate logistic regression analysis found that, in clinical practice, shorter T2D duration was a significant predictor of response to dapagliflozin [101]. Even among older patients (mean age at diagnosis, 57 years), early intensive glycemic control has shown benefit, with reduced risk of mortality and microvascular and macrovascular complications among those with HbA1c  $< 6.5\%$  during the first year after treatment [28]. These findings underscore the potential role of SGLT-2 inhibitors in early therapy.

## CONCLUSIONS

Current US treatment guidelines for T2D recommend early intensification of glucose-lowering therapy to meet glycemic targets, which usually requires the use of combination therapy [7, 8]. Most patients with T2D have CV risk factors, such as hypertension, hypercholesterolemia, and overweight/obesity at diagnosis, so meeting and maintaining glycemic targets early in the course of T2D is the most effective way to reduce the long-term risk of complications.

SGLT-2 inhibitors appear to be an effective option for early treatment of T2D because of their favorable tolerability profile and low potential for hypoglycemia; their beneficial effects on CV risk factors, such as BP and body weight; and the evidence of benefit in terms of CV and renal risk reduction seen in CVOTs to date. In patients with T2D and established CVD or CKD, and those with multiple CV risk factors, SGLT-2 inhibitor therapy should be considered.

Initiating early treatment with SGLT-2 inhibitors in patients without significant diabetes-related complications is likely to provide the most benefit with regard to glycemic control and prevention of CV and renal events in patients without established CVD or CKD.

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