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American Journal of Cardiovascular Drugs

ISSN 1175-3277

Am J Cardiovasc Drugs
DOI 10.1007/s40256-020-00397-y

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https://doi.org/10.1007/s40256-020-00397-y

REVIEW ARTICLE

Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors for Cardiovascular Disease Prevention

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Abstract
Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). Because of these associated risks, managing diabetes and CVD, including heart failure (HF), has become a joint effort to reduce the risk of adverse outcomes. Although many patients with T2DM are receiving preventive therapies for CVD, their residual risk remains high for atherosclerotic CVD (ASCVD). Recent data regarding the use of antidiabetic medications to prevent negative cardiovascular outcomes has revealed a positive association with reduced major adverse cardiovascular events (MACE). One class of medications, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, are at the forefront of the cardiovascular outcomes prevention discussion. The clinical data presented in this review indicate the potential cardiovascular benefits of SGLT-2 inhibitors in patients with CVD and its potential value as a treatment option in preventing CVD in various patient populations.

Key Points

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus.

The clinical data presented in this review indicate the potential cardiovascular benefits of sodium-glucose cotransporter-2 (SGLT-2) inhibitors in patients with CVD and its potential value as a treatment option in preventing CVD in various patient populations.

1 Introduction

Countless patients with type 2 diabetes mellitus (T2DM) are at increased risk of major adverse cardiovascular events (MACE) from coexistent atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and/or renal disease [1]. Managing T2DM often requires the use of multiple antidiabetic agents, which can introduce challenges such as pill burden and an increased incidence of adverse events [2]. To maintain glycemic control in patients with T2DM, treatment intensification may be necessary, and practitioners must consider therapy options that simultaneously have clinical benefits on comorbid cardiovascular conditions [2]. This is important since data from numerous pathological and epidemiological studies have indicated that diabetes is an independent risk factor and precursor for cardiovascular disease (CVD), with approximately 65% of deaths in patients with diabetes attributed to CVD [3]. Furthermore, patients with diabetes who develop CVD often have a worse morbidity and mortality prognosis than patients who have CVD without diabetes [3]. Such considerations have strongly encouraged the American Diabetes Association (ADA) to highlight antidiabetic therapy that not only targets glycated hemoglobin (HbA1c) lowering but also aids in the reduction of blood pressure (BP) and weight, with added benefits for HF and renal disease protection to reduce the risk of

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Published online: 11 February 2020

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CVD complications in patients with T2DM [4]. Numerous clinical studies have demonstrated that the sodium-glucose cotransporter-2 (SGLT-2) inhibitor drug class can provide these benefits [4].

The US FDA requires cardiovascular outcomes trials (CVOTs) for all new antidiabetic agents to ensure no excess cardiovascular risk is posed to patients with T2DM [5]. These CVOTs have provided data suggesting that some antidiabetic medications have benefits outside of their glucose-lowering ability. The EMPA-REG OUTCOME CVOT was the first among SGLT-2 inhibitors to report cardiovascular benefit, showing reductions in both cardiovascular death and risk of death from any cause. Other CVOTs then revealed decreased rates of hospitalization for heart failure (HHF), which is a unique benefit of the SGLT-2 inhibitor medication class.

Clinical studies in patients with T2DM and a history of ASCVD taking SGLT-2 inhibitor therapy have shown reduced rates of MACE [4]. Recently, when studied in patients with T2DM, empagliflozin (Jardiance®) demonstrated a reduction in cardiovascular outcomes, including cardiovascular mortality and HHF, and canagliflozin (Invokana®) displayed a decrease in HHF. However, to date, dapagliflozin (Farxiga®) is the only SGLT-2 inhibitor to show a reduction in cardiovascular death and in worsening of HF (WHF) in patients both with and without T2DM. The exact mechanism of this reduction in cardiovascular outcomes, including mortality and HHF, is not completely understood, and many ongoing studies are exploring these effects and their causes. Table 1 outlines the SGLT-2 inhibitor agents, their current FDA-approved indications, and potential indications under investigation. In this review, we evaluate the clinical studies of SGLT-2 inhibitors as related to CVD and assess the clinical efficacy and safety of using SGLT-2 inhibitors for the prevention of CVD in patients with T2DM.

2 Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors

2.1 Mechanism of Action

Introduced to the US market in 2013, SGLT-2 inhibitors demonstrate significant glycemic control by inhibiting the SGLT-2 cotransporter in the proximal tubule responsible for approximately 90% of the glomerular filtered glucose [6]. Inhibition of the SGLT-2 cotransporter prevents renal glucose resorption, promoting glucosuria and resulting in a reduction in hyperglycemia [1, 6]. This insulin-independent mechanism results in reductions in fasting plasma glucose and HbA1c in patients with T2DM [2]. SGLT-2 inhibitors are a unique antidiabetic therapy in that they are not directed at restoring, preserving, or working with pancreatic β-cell function and, therefore, maintain their potency as diabetes progresses and β-cell function decreases [7]. SGLT-2 inhibitors also modestly lower BP and reduce cardiac preload, cardiac afterload, and arterial stiffness through osmotic diuresis. Furthermore, through the inhibition of the SGLT-2 cotransporter, SGLT-2 inhibitors can lead to moderate weight loss through glucosuria (calorific loss), with about 60–100 g of glucose excreted in urine per day [8].

Additionally, regression of left ventricular (LV) hypertrophy (LVH) and decrease in global longitudinal strain (GLS) of the LV of the heart are two mechanisms currently being studied as potential methods for the demonstrated cardiovascular benefit. Currently, four medications in the SGLT-2 inhibitor drug class are approved by the FDA for use within the USA: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin (Steglatro™).

2.2 Clinical Data

2.2.1 Empagliflozin

Empagliflozin was initially approved by the FDA in August 2014 to improve glycemic control in patients with T2DM as an adjunct to diet and exercise. However, results from a key clinical study, EMPA-REG OUTCOME, published in November 2015, revolutionized the use of empagliflozin and SGLT-2 inhibitors as a class beyond this indication. After positive results from the EMPA-REG OUTCOME study, the FDA granted approval for an additional indication: to reduce the risk of cardiovascular death in patients with T2DM and established CVD. The EMPA-REG OUTCOME study was conducted over 3.1 years and evaluated the efficacy of empagliflozin on cardiovascular morbidity and mortality from nonfatal myocardial infarction (MI) (excluding silent MI) or nonfatal stroke in subjects with T2DM. A total of 7028 subjects with established CVD were randomized (1:1:1) to receive standard antidiabetic therapy plus either empagliflozin 10 mg once daily, empagliflozin 25 mg once daily, or matching placebo. The study demonstrated a reduction in composite death from cardiovascular causes of 14% ($P < 0.001$), with an absolute rate of 10.5% in the empagliflozin group versus 12.1% in the placebo group (hazard ratio [HR] 0.86; 95% confidence interval [CI] 0.74–0.99). However, the reduction of MI with empagliflozin (4.8%) versus placebo (5.4%) was not statistically significant [9]. In an intent-to-treat approach analysis of the EMPA-REG OUTCOME study, Zinman et al. [10] found no significant difference in the occurrence of fatal stroke between the empagliflozin and placebo groups (0.3% and 0.5%, respectively; HR 0.72; 95% CI 0.33–1.55; $P = 0.40$), with no statistical significance with the composite of stroke or transient ischemic attack (TIA) (HR 1.05; 95% CI 0.82–1.35; $P = 0.87$) between

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Table 1 Current and potential indications of sodium-glucose cotransporter-2 inhibitors

SGLT-2 inhibitor (trade name)	Approved indications	Date indication approved	Potential indications under investigation	Other benefits	Risks
Empagliflozin (Jardiance®)	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	August 2014	T1DM	Reduced BP	Genital mycotic infections
			CKD	Weight loss	UTIs
			HFpEF	Reduced LDL	Increased urination
			HFrEF	Reduced albuminuria	Dehydration
			Children + adolescent s with T2DM		Hypotension
					Ketoacidosis
	To reduce the risk of CV death in adult patients with T2DM and established CVD	December 2016			
Canagliflozin (Invokana®)	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	March 2013	Obesity	Reduced BP	Genital mycotic infections
			T1DM	Weight loss	UTIs
			Children + adolescents with T2DM	Reduced LDL	Increased urination
			Diabetic nephropathy	Reduced albuminuria	Dehydration Hypotension Ketoacidosis
	To reduce the risk of MACE in adults with T2DM and established CVD	October 2018			Risk of bone fractures Lower limb amputations Increased serum potassium
	Treat DKD and reduce the risk of HHF in patients with T2DM and DKD	September 2019			
Dapagliflozin (Farxiga®)	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	January 2014	T1DM	Reduced BP	Genital mycotic infections
			CKD and CV/renal death	Weight loss Reduced LDL	UTIs Increased urination
			HFpEF	Reduced albuminuria	Dehydration
			HFrEF		Hypotension
			CV death or HHF		Ketoacidosis
			Weight loss		
Ertugliflozin (Steglatro®)	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	December 2017	CVD	Reduced BP	Genital mycotic infections
			CV outcomes	Weight loss	UTIs
			Cardiac function	Reduced LDL	Increased urination
			HF	Reduced albuminuria	Dehydration Hypotension
					Ketoacidosis Headache
Sotagliflozin (Zynquista®)	Not yet approved in USA		CV morbidity and mortality benefit	Reduced BP Weight loss	Genital mycotic infections UTIs
			CKD	Reduced LDL	Increased urination
			Worsening HF	Reduced albuminuria	Dehydration Hypotension Ketoacidosis Nausea/vomiting Stomach pain

BP blood pressure, *CKD* chronic kidney disease, *CV* cardiovascular, *CVD* CV disease, *DKD* diabetic kidney disease, *HF* heart failure, *HFpEF* HF with preserved ejection fraction, *HFrEF* HF with reduced ejection fraction, *HHF* hospitalization for HF, *LDL* low-density lipoprotein, *MACE* major adverse CV events, *SGLT-2* sodium-glucose cotransporter-2, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus, *UTI* urinary tract infection

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the two groups. The EMPA-REG OUTCOME study also illustrated that subjects in the empagliflozin group had a 35% reduction in HHF ($P < 0.002$) compared with placebo [11]. Furthermore, even though most of the subjects enrolled in the EMPA-REG OUTCOME study did not have a diagnosis of HF at baseline, benefits with the addition of empagliflozin was seen in subjects both with and without baseline HF [9].

In a post hoc analysis of the EMPA-REG OUTCOME study, Verma et al. [12] analyzed a subgroup of subjects with T2DM and a history of coronary artery bypass graft (CABG) and found that, in subjects with a history of CABG, empagliflozin was associated with a 48% reduction in the risk for cardiovascular death (HR 0.52; 95% CI 0.32–0.84). However, no difference was observed in relation to the risk of MI or stroke in subjects with a history of CABG. Consistent with the data collected on the total study population in the EMPA-REG OUTCOME trial, there was a 50% risk reduction of HHF in the empagliflozin group in subjects with a history of CABG at baseline compared with placebo (HR 0.50; 95% CI 0.32–0.77) [12]. These findings indicate that the use of empagliflozin for secondary prevention may help in the reduction of cardiovascular events, more particularly death from cardiovascular causes or HHF in patients with CABG.

Similarly, Wanner et al. [13] evaluated the efficacy of empagliflozin on clinical outcomes for CVD (cardiovascular death, HHF, all-cause hospitalization, and all-cause mortality) and chronic kidney disease (CKD) in subjects with T2DM from the EMPA-REG OUTCOME study. A total of 7020 subjects were enrolled, of whom 32% had prevalent kidney disease defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 and/or macroalbuminuria at baseline, 26% had eGFR < 60 mL/min/1.73 m^2, and 29% had microalbuminuria with a urine albumin-to-creatinine ratio of 30–300 mg/g at baseline [13]. In these subjects, the risk of cardiovascular death was reduced by 29% in the empagliflozin arm compared with placebo (HR 0.71; 95% CI 0.52–0.98), all-cause mortality risk was reduced by 24% (HR 0.76; 95% CI 0.59–0.99), the risk of HHF was reduced by 39% (HR 0.61; 95% CI 0.42–0.87), and the risk of all-cause hospitalization was reduced by 19% (HR 0.81; 95% CI 0.72–0.92) [13]. Overall, this study demonstrated the clinical potential of empagliflozin in subjects with prevalent kidney disease and established CVD.

Numerous clinical studies are currently underway to determine the efficacy of empagliflozin in patients with CKD and/or HF. One ongoing phase III study (EMPA-KIDNEY) began enrollment in July 2018 and is expected to be complete in the second quarter of 2022. This study is further evaluating the efficacy of empagliflozin in approximately 5000 patients with CKD. In the study, empagliflozin is being compared with placebo for either the first occurrence of or progression to kidney disease (defined as end-stage renal disease [ESRD] requiring dialysis or kidney transplant with eGFR < 10 mL/min/1.23 m^2, death due to kidney disease, or a continued decline in eGFR by ≥ 40%) or cardiovascular death in adult patients with or without T2DM [14].

Four large phase III clinical studies have investigated or are currently investigating empagliflozin in patients with HF. EMPERIAL-reduced, which evaluated the efficacy of empagliflozin 10 mg compared with placebo for 12 weeks in 312 patients with HF with reduced ejection fraction (EF) (HFrEF) (EF ≤ 40%) in relation to exercise capacity, has been completed, and the results are expected to be released within the next year [15]. EMPERIAL-preserved has also completed enrollment; similar to EMPERIAL-reduced, it evaluated the effects of empagliflozin 10 mg daily on exercise ability but in 315 patients with preserved HF (EF > 40%) [16]. Two additional ongoing clinical studies that are expected to complete in 2020, EMPEROR-Preserved and EMPEROR-Reduced, are examining empagliflozin 10 mg once daily compared with placebo in patients with or without diabetes who have HF. EMPEROR-Preserved is evaluating the efficacy and safety of empagliflozin in 5750 patients with New York Heart Association (NYHA) class II–IV HF with preserved EF (HFpEF) with EF > 40% and elevated N-terminal-pro b-type natriuretic peptide (NT-proBNP) to the first occurrence of cardiovascular event such as cardiovascular death or HHF [17]. EMPEROR-Reduced is studying empagliflozin 10 mg once daily versus placebo to a similar outcome but in 3600 patients with HFrEF with EF ≤ 40% and elevated NT-proBNP [18].

2.2.2 Canagliflozin

Canagliflozin was approved by the FDA in March 2013 to improve glycemic control in adult patients with T2DM as an adjunct to diet and exercise [19]. On 30 October 2018, the FDA approved an additional indication for canagliflozin to reduce the risk of MACE (cardiovascular death, nonfatal MI, and nonfatal stroke) in adults with T2DM and established CVD after the results of the CANVAS (Canagliflozin Cardiovascular Assessment Study) program were released. Clinically meaningful findings from this program demonstrated statistically significant benefits from using canagliflozin in patients with T2DM and established CVD. In addition, results from the CREDENCE study released in early 2019 led the FDA to grant another significant indication for canagliflozin: reducing the doubling of serum creatinine and reducing the risk of ESRD, cardiovascular death, and HHF in patients with T2DM and diabetic nephropathy with albuminuria of > 300 mg/day [19].

The CANVAS program encompasses the CANVAS trial, initiated in 2009, and the CANVAS-R trial, started in 2014. This program was created to evaluate the safety and efficacy of canagliflozin on composite cardiovascular death,

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nonfatal MI, or nonfatal stroke in patients with T2DM and HbA1c ≥ 7%. Combining these two large randomized studies provided data for over 188.2 weeks from 10,142 patients with T2DM and high cardiovascular risk, of whom 72.2% had a history of ASCVD and 14.1% had a history of HF at baseline [20].

In the CANVAS trial, 4330 patients were randomized (1:1:1) to receive canagliflozin 100 mg once daily, canagliflozin 300 mg once daily, or matching placebo. In the CANVAS-R trial, 5812 patients were randomized (1:1) to receive canagliflozin 100 mg once daily with optional uptitration to 300 mg once daily (in patients who tolerated 100 mg daily and required additional glycemic control) or matching placebo. The analysis of the two studies combined evinced a mean difference of − 0.58% in HbA1c, − 1.60 kg for body weight, − 3.93 mmHg in systolic BP (SBP), and − 1.39 mmHg in diastolic BP (DBP) ($P < 0.001$ for all) when comparing canagliflozin and placebo. Regarding cardiovascular outcomes, canagliflozin resulted in a statistically significant reduction in the composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke compared with placebo, with an event occurring in 26.9 versus 31.5 patients per 1000 patient-years, respectively (HR 0.86; $P < 0.001$ for noninferiority and $P = 0.02$ for superiority). In subjects with established CVD, canagliflozin also demonstrated a decrease in the composite outcome of cardiovascular death, nonfatal MI, and nonfatal stroke by 18% compared with placebo, with an event occurring in 34.1 versus 41.3 patients per 1000 patient-years, respectively [20].

Within the CANVAS study, 19% of the population presented with a prior stroke or TIA at baseline. Throughout the study, 309 subjects had a stroke, of whom 123 had a prior stroke or TIA. The rate of this occurrence of stroke in the canagliflozin group was 7.93 patients per 1000 patient-years compared with 9.62 patients per 1000 patient-years in the placebo group (HR 0.87; 95% CI 0.69–1.09). Further analysis identified a significant reduction in hemorrhagic stroke (HR 0.43; 95% CI 0.20–0.89) but no reduction in the occurrence of ischemic stroke (HR 0.95; 95% CI 0.74–1.22) [21]. Additionally, significance was not met for the study's secondary outcome of death from any cause (HR 0.87; 95% CI 0.74–1.01) and death from cardiovascular causes (HR 0.87; 95% CI 0.72–1.06) [20].

Furthermore, when compared with placebo, canagliflozin was associated with a statistically significant lower risk for HHF in subjects with a history of HF at baseline (HR 0.61; 95% CI 0.46–0.80), with an absolute risk difference of − 106.97 per 1000 patient-years in subjects with a baseline diagnosis of HF compared with − 8.36 per 1000 patient-years for subjects without an HF diagnosis ($P < 0.003$) [22]. Additionally, this decrease in HHF risk was not dose related (100 mg vs. placebo: HR 0.82; 95% CI 0.65–1.03; and 300 mg vs. placebo: HR 0.82; 95% CI 0.65–1.03). These preliminary findings from the CANVAS trial provided a strong foundation on the related benefits of canagliflozin in patients with HF.

The CANVAS program also evaluated the effects of canagliflozin on albuminuria and eGFR because of the association of impaired kidney function and an increased risk for CVD. Data from numerous clinical studies indicated that patients with CKD are more likely to die from CVD than from developing kidney failure. Therefore, using therapy that has dual benefits on CVD and renal function may be beneficial in patients with CKD [23]. In the CANVAS studies, data from 2039 subjects with an eGFR < 60 mL/min/1.73 m^2 demonstrated a decrease in the progression of albuminuria in the canagliflozin arms (event rate of 89.4 patients per 1000 patient-years) compared with the placebo arm (event rate of 128.7 patients per 1000 patient-years) (HR 0.73; 95% CI 0.67–0.79). In addition, albuminuria regressed in subjects receiving canagliflozin, with 293.4 patients per 1000 patient-years compared with 187.5 per 1000 patient-years with placebo (HR 1.70; 95% CI 1.51–1.91) [20].

Similarly, the beneficial effects of canagliflozin on kidney function was also observed in the CREDENCE study. A total of 4401 subjects with T2DM, CKD, and albuminuria were randomized (1:1) to receive either canagliflozin 100 mg daily or matching placebo [24]. This study reported that the primary composite outcome of ESRD, doubling of serum creatinine, or death from renal or CVD was 30% lower in those receiving canagliflozin (event rate 43.2 per 1000 patient-years) than in those receiving placebo (event rate 61.2 per 1000 patient-years; HR 0.10; 95% CI 0.59–0.82; $P = 0.00001$). In addition, the relative risk for the primary composite outcome was 34% lower in those receiving canagliflozin than in those receiving placebo (HR 0.66; 95% CI 0.53–0.81; $P < 0.001$), with a 32% decrease in relative risk of ESRD (HR 0.68; 95% CI 0.54–0.86; $P = 0.002$). In relation to cardiovascular effects, subjects in the canagliflozin arm had a lower risk of cardiovascular death, MI, or stroke (HR 0.80; 95% CI 0.67–0.95; $P = 0.01$), as well as HHF, compared with placebo (HR 0.61; 95% CI 0.47–0.80; $P < 0.001$) [24]. These positive findings meant canagliflozin gained FDA approval for a new indication in patients with T2DM and diabetic nephropathy with albuminuria of > 300 mg/day to help decrease the risk of ESRD, cardiovascular death, HHF, and doubling of serum creatinine [19].

2.2.3 Dapagliflozin

Dapagliflozin was first approved by the FDA in January 2014 as an adjunct to diet and exercise to improve glycemic control in adults with T2DM [25]. One of the most important clinical studies demonstrating the benefits of dapagliflozin for the prevention of CVD was the DECLARE-TIMI 58 study, which was completed in September 2018. This study

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evaluated dapagliflozin 10 mg once daily or placebo (randomized 1:1) in patients with T2DM who either had preexisting ASCVD or were at risk for ASCVD and were followed for a median of 4.2 years. The study included 17,160 patients and had a primary safety outcome of composite MACE (cardiovascular death, MI, or ischemic stroke) and primary efficacy outcomes of MACE and the composite of cardiovascular death or HHF. Of the 17,160 patients who completed the run-in phase of the study, 40.6% had established ASCVD and 59.4% had multiple risk factors for ASCVD at baseline. The trial demonstrated that dapagliflozin lowered HbA1c compared with placebo with an average least-squares (LS) mean absolute difference of 0.42% (95% CI 0.40–0.45). Additionally, the LS mean difference between the groups in weight reduction was 1.8 kg, favoring dapagliflozin (95% CI 1.7–2.0), and the difference in the reduction was 2.7 mmHg in SBP and 0.7 mmHg in DBP (95% CI 2.4–3.0 and 95% CI 0.6–0.9, respectively), both of which were lower in the dapagliflozin group [1].

Originally designed with MACE as the primary safety outcome, the DECLARE-TIMI 58 study responded to the information released from the EMPA-REG OUTCOME trial by amending the protocol to include both MACE and cardiovascular death or HHF as the two primary efficacy outcomes before the data and safety monitoring committee reviewed the data on MACE. The DECLARE-TIMI 58 study illustrated a lower rate of HHF with dapagliflozin, resulting in noninferiority compared with placebo for the primary efficacy outcome of lower rate of cardiovascular death or HHF (4.9 vs. 5.8%, respectively; $P=0.005$). However, no difference in rate of cardiovascular death was confirmed for dapagliflozin versus placebo (2.9% for both). Of the patients who had established ASCVD at baseline (40.6% of the total study population), those taking dapagliflozin and placebo experienced similar rates of cardiovascular death or HHF (7.8 and 9.3%, respectively; P = 0.99). Similarly, a subgroup of patients with multiple risk factors for ASCVD showed no difference in the rates of cardiovascular death or HHF between those taking dapagliflozin or placebo (2.8 and 3.4%, respectively; P = 0.99). The DECLARE-TIMI 58 study also found that the difference between the dapagliflozin and placebo groups for MACE was not statistically significant, with MACE occurring in 8.8% in the dapagliflozin group versus 9.4% in the placebo group (0.6%; $P=0.17$). Additionally, the rate of MACE in the subgroup of patients with established ASCVD was similar (13.9 and 15.3% with dapagliflozin and placebo, respectively; $P=0.25$), as it was in patients with multiple risk factors for ASCVD (5.3 and 5.2%; $P=0.25$) [1].

A subanalysis of the DECLARE-TIMI 58 study looked at 3584 patients with T2DM who had a previous MI [4]. While no reduction in MACE was shown for patients without a previous MI (7.1 vs. 7.1%; $P=-0.97$), in patients with T2DM with a history of MI, dapagliflozin compared with placebo reduced the absolute risk of MACE by 2.6% (15.2 vs. 17.8%; $P=0.039$) and reduced the absolute risk for cardiovascular death/HHF by 1.9% (8.6 vs. 10.5%; $P=0.046$) [4].

Before the DECLARE-TIMI 58 study, data on the effects of SGLT-2 inhibitors in patients without baseline ASCVD were not robust, and this study provided insight into the effects in this population. While subjects in the dapagliflozin group did not show decreased MACE compared with subjects in the placebo group, dapagliflozin proved noninferior for the primary safety outcome of MACE. The results of this trial showed that, regardless of history of ASCVD or HF, dapagliflozin prevented cardiovascular events, particularly HHF, because of the lower rate of cardiovascular death or HHF in patients receiving dapagliflozin versus placebo [1].

The DAPA-HF study examined dapagliflozin 5 or 10 mg once daily versus placebo in 4744 patients (with or without T2DM) with chronic NYHA class II–IV HFrEF and elevated NT-proBNP levels [26]. The study population had an average age of 66 years, 68% had NYHA class II HF at baseline, and the average LVEF was 31%. In addition, 42% of the patients enrolled had diabetes, 35% were obese, and 74% had hypertension at baseline. The DAPA-HF study was completed in July 2019 and met its primary composite endpoint by demonstrating a statistically significant reduction in the composite of cardiovascular death or WHF by 26% ($P<0.0001$) when added to standard of care [27]. The primary outcome occurred in 16.3% of patients in the dapagliflozin group compared with 21.2% of patients in the placebo group ($P<0.00001$). In the dapagliflozin arm, 10.0% of patients experienced a first episode of WHF and 9.6% died from cardiovascular causes compared with 13.7 and 11.5% in the placebo group, respectively ($P<0.00004$ and $P=0.029$). Furthermore, when evaluating each component of the primary composite endpoint individually, dapagliflozin resulted in a 30% reduction in the risk of WHF ($P<0.0001$) and an 18% reduction in the risk of cardiovascular death ($P=0.0294$) [28]. This was the first study to publish results on the use of SGLT-2 inhibitors in patients with HF without diabetes and showed benefit by reducing death and hospitalization in patients with HF regardless of their baseline glycemic status.

The DAPA-LVH study was conducted in 66 patients at a single center in Scotland and was completed in April 2019, but the results were not yet available at the time of this publication. This study was conducted to determine whether dapagliflozin 10 mg once daily could regress LVH in patients with T2DM and LVH who were normotensive [7, 29]. Regression of LVH has been thought to be a mechanism for reducing risk for cardiovascular events and death in patients with T2DM, as it is present in up to 70% of these patients. The study included 64 patients with SBP < 145 mmHg, DBP < 90 mmHg, and HbA1c of 6.5–9.9% [7].

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The DAPACARD study, completed in March 2019, attempted to identify the mechanism for decreased cardiovascular events with the use SGLT-2 inhibitors, specifically dapagliflozin. This phase IV study included 52 patients with T2DM and evaluated cardiac substrate uptake, myocardial efficiency, and myocardial contractile work over 6 weeks through positron emission tomography and magnetic resonance imaging scans [30]. At the time of this publication, the results were not yet available.

More information regarding the impact of dapagliflozin on CVD prevention should be revealed as the study results are released from current ongoing clinical trials, including DEFINE-HF and DAPA-CKD, which have completed subject recruitment [31, 32]. The DEFINE-HF study enrolled 263 patients with NYHA class II–III HFrEF and elevated NT-proBNP or BNP and is evaluating the mean difference in NT-proBNP and quality of life between patients receiving dapagliflozin or placebo [31, 33]. The DAPA-CKD study is evaluating the effects of dapagliflozin 5 or 10 mg once daily on the progression of CKD or cardiovascular/renal death when added to standard of care in approximately 4000 patients with CKD and increased albuminuria versus placebo [32].

In addition to these currently active studies, numerous studies are still recruiting, including ELUCIDATE, PRESERVED-HF, DELIVER, and DETERMINE-preserved, all of which are examining the effect of dapagliflozin on cardiovascular events [33–35]. The ELUCIDATE study (target completion date July 2020) is a phase IV study of dapagliflozin 10 mg versus placebo that will measure cardiac GLS from baseline to week 24 in 90 patients with T2DM and normal LVEF [33]. The PRESERVED-HF study (target completion date September 2019) is a phase IV study evaluating the effects of dapagliflozin 10 mg once daily versus placebo on the change in NT-proBNP from baseline to 12 weeks in patients with NYHA class II–IV HFpEF with an elevated NT-proBNP presenting with at least one additional risk factor [34]. The DELIVER study (target completion date June 2021) is a phase III study evaluating the reduction in the composite of cardiovascular death or HHF/urgent HF visits with dapagliflozin 10 mg once daily versus placebo in 4700 patients with NYHA class II–IV HFpEF who have elevated NT-proBNP levels at baseline [35]. The DETERMINE-preserved study (target completion date July 2020) plans to enroll 400 patients with elevated NT-proBNP levels and evidence of structural heart disease to evaluate dapagliflozin 10 mg versus placebo on the change from baseline in 6-min walking distance test at week 16 [36].

2.2.4 Ertugliflozin

Ertugliflozin was first approved by the FDA in December 2017 as an adjunct to diet and exercise to improve glycemic control in adults with T2DM [37]. The major CVOT for ertugliflozin is the VERTIS-CV study, which was initiated in November 2013 and completed in December 2019. This study's primary objective is to demonstrate noninferiority of ertugliflozin versus placebo in regards to MACE (the time to first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke), and the secondary objectives are to establish superiority of ertugliflozin versus placebo on time to the composite endpoint of cardiovascular death or HHF, time to cardiovascular death, and time to the composite endpoint of renal death, dialysis/transplant, or doubling of serum creatinine from baseline [38]. Subjects in the VERTIS-CV study are aged ≥ 40 years and have T2DM and established ASCVD involving the coronary, cerebrovascular, and/or peripheral arterial systems at baseline; they were randomized (1:1:1) to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo once daily [39]. Of the 8252 patients enrolled, 76.3% had coronary artery disease, 23.1% had cerebrovascular disease, and 18.8% had peripheral arterial disease (not mutually exclusive) before screening. Furthermore, almost 48% of the subjects had a previous MI, 21% had a prior stroke, 57.3% had a previous coronary revascularization, and 8.2% had a previous peripheral revascularization. Lastly, within the study population, 23.1% of patients had a baseline diagnosis of HF, with most having a diagnosis of HFpEF (80.6%) compared with 19.4% presenting with HFrEF [39]. This is important because it is the highest percentage of patients presenting with baseline HF out of all SGLT-2 inhibitor CVOTs.

A smaller phase II study (MK-8835-042) evaluating ertugliflozin in patients with T2DM and hypertension assessed the change from baseline in average 24-h SBP to day 28. This 4-week study, which was completed in 2011, included 194 patients with inadequate glycemic and BP control who were taking at least one oral diabetes medication and up to two medications for BP control. Patients were randomized (1:1:1:1:1) to either ertugliflozin 1 mg, ertugliflozin 5 mg, ertugliflozin 10 mg, hydrochlorothiazide (HCTZ) 12.5 mg, or placebo [40]. The study showed significant decreases in 24-h mean SBP for all doses of ertugliflozin, with −2.71 mmHg for ertugliflozin 1 mg, −3.73 mmHg for ertugliflozin 5 mg, and −3.42 mmHg for ertugliflozin 25 mg, and −2.95 mmHg for HCTZ compared with 0.26 for placebo ($P = 0.034$, $P = 0.010$, $P = 0.012$, and $P = 0.024$, respectively) [40, 41].

The ERADICATE-HF study, the ERTU-GLS study, and the EMMED-HF study are currently looking at various components of the effects of ertugliflozin on CVD. The ERADICATE-HF study is a phase II study evaluating the change in proximal sodium reabsorption, effective renal plasma flow, GFR, SBP, DBP, and heart rate in patients with T2DM with NYHA class II–III HF with an LVEF ≥ 20% and elevated BNP levels. The purpose of this study is to try to explain the

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mechanisms by which SGLT-2 inhibitors modify cardiorenal effects on fluid volume and neurohormonal activation in patients with T2DM and HF [42]. The study is testing the hypothesis that ertugliflozin increases proximal tubular natriuresis, resulting in a reduction in plasma volume, without inducing significant renal vasoconstriction or activation of the sympathetic nervous system. The ERADICATE-HF study is expected to be completed in March 2021.

The ERTU-GLS study is currently recruiting patients with T2DM with stage B HF (structural heart disease but no current or prior symptoms of HF) in Korea and plans to enroll 120 patients. The rationale of this study is to evaluate the effects of ertugliflozin on cardiac function by measuring GLS and other hemodynamic factors using echocardiogram [43]. This study is expected to be completed in October 2020.

The EMMED-HF is a phase IV study that plans to include 52 patients with T2DM and HFpEF and evaluate peak oxygen uptake (VO_2) as the primary outcome measure to determine whether ertugliflozin alters cardiac metabolism by improving VO_2 compared with placebo over 12 weeks. This study is expected to be completed in June 2021 [44].

2.2.5 Sotagliflozin

Sotagliflozin (Zynquista®) is a dual sodium-glucose cotransporter-1 (SGLT-1) and SGLT-2 inhibitor that does not yet hold any FDA-approved indications in the USA. However, numerous studies examining sotagliflozin and CVD are currently recruiting patients, including SOLOIST-WHF, SCORED, and the "Safety, Tolerability and Pharmacodynamic Activity of Sotagliflozin in Hemodynamically Stable Patients with Worsening Heart Failure" study [45–47].

The SOLOIST-WHF study (target completion date January 2021) aims to demonstrate that sotagliflozin reduces cardiovascular morbidity and mortality with a composite of cardiovascular death or HHF compared with placebo in patients with T2DM and HFrEF after admission for WHF [46]. This study plans to enroll approximately 4000 patients with T2DM and a history of HFrEF (LVEF < 40%) who were recently admitted to the hospital or had an urgent HF visit for WHF. The SCORED study (target completion date March 2022) plans to evaluate approximately 10,500 patients to ensure sotagliflozin does not increase the time to first MACE (cardiovascular death, nonfatal MI, and nonfatal stroke) and reduces the time to cardiovascular death or HHF. The SCORED study is evaluating patients with T2DM and CKD who are aged ≥ 18 years with at least one major cardiovascular risk factor or ≥ 55 years with at least two minor cardiovascular risk factors [47].

Lastly, the "Safety, Tolerability and Pharmacodynamic Activity of Sotagliflozin in Hemodynamically Stable Patients with WHF" study (target completion date November 2020) is evaluating approximately 81 patients who were admitted to a hospital or visited an emergency department/HF clinic for congestive HF requiring intravenous diuretics and presented with at least two clinical signs and symptoms of cardiac congestion. This study is assessing the safety and tolerability of sotagliflozin and its effects on plasma volume changes, erythropoiesis, and NT-proBNP levels [48].

3 Discussion

Similar to the glucagon-like peptide-1 receptor agonists (GLP-1 RAs), a blood sugar-lowering therapy, SGLT-2 inhibitors have been gaining more attention, not only for their glycemic benefits but also for the favorable effects on cardiovascular outcomes that were observed in multiple randomized CVOTs. As a result, for the first time in history, the ADA guidelines recommend the use of an antidiabetic agent based on the patient's cardiovascular comorbidities. In the 2018 ADA guidelines, in addition to liraglutide (GLP-1 RA), SGLT-2 inhibitors are recommended as a first-choice add-on treatment in patients with T2DM and established ASCVD who do not achieve adequate glycemic control with metformin monotherapy [11]. Similarly, the 2019 American College of Cardiology/American Heart Association guidelines recommended the use of an SGLT-2 inhibitor in addition to metformin for adults with T2DM and ASCVD risk factors [49].

Clinical studies have consistently demonstrated the significant effects of SGLT-2 inhibitors on the relative risk reduction of HHF and progression of renal disease. Their effects on the reduction of MACE, such as MI, stroke, or cardiovascular death, have been modest for many of the agents within this class, but statistical significance in this outcome was observed in the CANVAS trial. These results are similar to those obtained in trials of GLP-1 RAs, where an overall 12% reduction in MACE and a 9% reduction in HHF was noted in patients with T2DM taking these agents [50]. Nevertheless, within the SGLT-2 CVOTs, reduction in MACE was more prevalent in patients who had established ASCVD than in patients without ASCVD. On the other hand, the reduction in HHF was found to be a class effect and observed in all patients regardless of prior HF diagnosis.

The cardiovascular benefits of SGLT-2 inhibitors may be due to the glycemic control attained by these agents in patients with diabetes, suggesting that achieving adequate glycemic control may have a greater effect in the reduction of microvascular complications than in macrovascular complications. However, many other proposed mechanisms are being explored that could potentially aid in the cardiovascular outcome reduction seen with these agents. The inhibition of SGLT-2 cotransporters in the proximal renal tubule also mediates the excretion of uric acid through the glucose

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transporter 9, which may have some association with cardiovascular benefits since increased uric acid levels have been linked to HF and cardiovascular complications [51]. Furthermore, in addition to their glycemic effects, SGLT-2 inhibitors are also responsible for a natriuretic and osmotic diuresis effect that may play a role in BP reduction through volume contraction, leading to a decrease in afterload and reduction in cardiac preload and arterial stiffness [51]. These potential mechanisms are all being further studied in numerous clinical studies across the various SGLT-2 inhibitors mentioned in this review.

In relation to the possible adverse effects (AEs) of SGLT-2 inhibitors, as a drug class they are well-tolerated in patients with T2DM. All agents carry an increased risk for genital mycotic infections and diabetic ketoacidosis (DKA). Although the risk for these AEs is increased, the prevalence is low and can often be reduced with thorough patient education on risks and prevention methods. Since the risk of genital mycotic infection is a result of the drug's mechanism of action and the increase in urinary glucose excretion, patients can be educated to maintain adequate personal hygiene to reduce the occurrence of this AE [52]. In addition, patient education on the signs and symptoms associated with DKA for patients taking SGLT-2 inhibitors is crucial because patients are often euglycemic in DKA on these agents. This is because SGLT-2 inhibitors can increase the intrinsic ketogenesis by increasing secretion of glucagon, lowering insulin concentration, and promoting lipolysis [53]. Nevertheless, providing proper education on possible symptoms of DKA, such as fatigue, shortness of breath, abdominal pain, nausea, and vomiting, with the possible steps to take if a patient experiences these symptoms, can greatly help decrease its severity [54]. The CANVAS study for canagliflozin also showed an increased risk of amputation and fracture, but this risk was not observed in the CREDENCE study or in any other clinical study evaluating SGLT-2 inhibitors.

4 Conclusions

The robust data from these large clinical studies of SGLT-2 inhibitors have provided evidence that these agents, unlike other glucose-lowering agents, have a positive benefit in a spectrum of patients with T2DM with and without established CVD, including HF. So far, published data on these agents have also shown significant benefits on cardiovascular outcomes in patients without T2DM. In addition, major clinical studies are currently ongoing and will hopefully provide more insight and rigorous data to further support the efficacy of these agents in patients with CVD.

Funding No external funding was used in the preparation of this manuscript.

Compliance with Ethical Standards

Conflicts of Interest Jessica Reid, Khyatiben Rana, Stephanie Niman, Mae Sheikh-Ali, Todd Lewis, Rushab R. Choksi, and Rebecca F. Goldfaden have no potential conflicts of interest that might be relevant to the contents of this manuscript.

References

1. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347–57.
2. Leiter LA, Cefalu WT, de Bruin TWA, Gause-Nilsoon I, Sugg J, Parikh SK. Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. J Am Geriatr Soc. 2014;62(7):1252–62.
3. Grundy SM, Benjamin IJ, Burke GL, et al. A Statement for healthcare professionals from the American Heart Association. Circulation. 1999; pp. 1134-1146.
4. Furtado RHM, Bonaca MP, Raz I, et al. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes mellitus and previous myocardial infarction. Circulation. 2019;139(22):2516–27.
5. Schetharner G, Drexel H, Moshkovich E, et al. BMC endocrine disorders. 2019;19(1).
6. Schetharner G, Drexel H, Moshkovich E, et al. SGLT2 inhibitors in T2D and associated comorbidities—differentiating within the class. BMC Endocr Disord. 2019;19:64.
7. Brown AJ, Lang C, McCrimmon R, Struthers A. Does dapagliflozin regress left ventricular hypertrophy in patients with type 2 diabetes? A prospective, double-blind, randomised, placebo-controlled study. BMC Cardiovasc Disord. 2017;17(1):229.
8. Pereira MJ, Eriksson JW. Emerging Role of SGLT-2 inhibitors for the treatment of obesity. Drugs. 2019;79(3):219–30.
9. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28.
10. Zinman B, Inzucchi SE, Lachin JM, et al. Empagliflozin and cerebrovascular events in patients with type 2 diabetes mellitus at high cardiovascular ris. Stroke. 2017;48(5):1218–25.
11. Standards of Medical Care in Diabetes-2018. American Diabetes Association. 2018. https://diabetesed.net/wp-content/uploads/2017/12/2018-ADA-Standards-of-Care.pdf. Accessed 20 Dec 2019.
12. Verma S, Mazer CD, Fitchett D, et al. Empagliflozin reduces cardiovascular events, mortality and renal events in participants with type 2 diabetes after coronary artery bypass graft surgery: subanalysis of the EMPA-REG OUTCOME® randomised trial. Diabetologia. 2018;61(8):1712–23.
13. Wanner C, Lachin JM, Inzucchi SE, et al. Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. Circulation. 2018;137(2):119–29.
14. EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin). ClinicalTrials.gov. 2018. https://clinicaltrials.gov/ct2/show/NCT03594110. Accessed 26 Oct 2019.
15. Study Tests Empagliflozin in Patients With Chronic Heart Failure With Reduced Ejection Fraction (HFrEF). The study looks at how far patients can walk in 6 minutes and at their heart failure

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symptoms. ClinicalTrials.gov. 2018. https://clinicaltrials.gov/ct2/show/NCT03448419. Accessed 26 Oct 2019.
16. This Study Tests Empagliflozin in Patients With Chronic Heart Failure With Preserved Ejection Fraction (HFpEF). The study looks at how far patients can walk in 6 minutes and at their heart failure symptoms. ClinicalTrials.gov. 2018. https://clinicaltrials.gov/ct2/show/NCT03057951. Accessed 26 Feb 2019.
17. EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved). ClinicalTrails.gov. 2017. https://clinicaltrials.gov/ct2/show/NCT03057951. Accessed 26 Oct 2019.
18. EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced). https://clinicaltrials.gov/ct2/show/NCT03057977. 2017. https://clinicaltrials.gov/ct2/show/NCT03057977. Accessed 26 Oct 2019.
19. INVOKANA® (canagliflozin) tablets. September 2019. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVOKANA-pi.pdf. Accessed 20 Dec 2019.
20. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–57.
21. Zhou Z, Lindley RI, Radholm K, et al. Canagliflozin and stroke in type 2 diabetes mellitus. Stroke. 2019;50(2):396–404.
22. Radholm K, Figtree G, Perkovic V, et al. Canagliflozin and heart failure in type 2 diabetes mellitus. Circulation. 2018;138(5):458–68.
23. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease. Circulation. 2003;108(17):2154–69.
24. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295–306.
25. Farxiga® (dapagliflozin tablets): US prescribing information. Princeton, NJ: Bristol-Myers Squibb, 2014.
26. Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF). ClinicalTrials.gov. 2017. https://clinicaltrials.gov/ct2/show/NCT03036124. Accessed 20 Dec 2019.
27. FARXIGA met primary endpoint in landmark Phase III DAPA-HF trial for the treatment of patients with heart failure. *AstraZeneca*. 2019. https://www.astrazeneca-us.com/content/az-us/media/press-releases/2019/farxiga-met-primary-endpoint-in-landmark-phase-iii-dapa-hf-trial-for-the-treatment-of-patients-with-heart-failure-08202019.html. Accessed 20 Dec 2019.
28. McMurray JJ, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019; p. 3396–3404.
29. Does Dapagliflozin Regress Left Ventricular Hypertrophy In Patients With Type 2 Diabetes? (DAPA-LVH). ClinicalTrails.gov. https://clinicaltrials.gov/ct2/show/NCT02956811. Accessed 20 Dec 2019.
30. Akerblom A, Oldgren J, Latva-Rasku A, et al. Effects of DAPAgliflozin on CARDiac substrate uptake, myocardial efficiency, and myocardial contractile work in type 2 diabetes patients-a description of the DAPACARD study. Upsala J Med Sci. 2019;124(1):59–64.
31. Dapagliflozin Effect on Symptoms and Biomarkers in Patients With Heart Failure (DEFINE-HF). *ClincalTrials.gov*. 2016. https://clinicaltrials.gov/ct2/show/NCT02653482. Accessed 20 Dec 2019.
32. A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (Dapa-CKD). ClinicalTrials.gov. 2017. https://clinicaltrials.gov/ct2/show/NCT03036150. Accessed 20 Dec 2019.
33. Left Ventricular Functional Changes of Uncontrolled Diabetes by Dapagliflozin Treatment Trial (ELUCIDATE). *ClinicalTrials.gov*. 2019. https://clinicaltrials.gov/ct2/show/NCT03871621. Accessed 20 Dec 2019.
34. Dapagliflozin in PRESERVED Ejection Fraction Heart Failure (PRESERVED-HF). *ClinicalTrials.gov*. 2017. https://clinicaltrials.gov/ct2/show/NCT03030235. Accessed 20 Dec 2019.
35. Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure. (DELIVER). ClinicalTrials.gob. 2018. https://clinicaltrials.gov/ct2/show/NCT03619213. Accessed 20 Dec 2019.
36. DETERMINE-preserved - Dapagliflozin Effect on Exercise Capacity Using a 6-minute Walk Test in Patients With Heart Failure With Preserved Ejection Fraction. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT03877224. Accessed 20 Dec 2019.
37. Highlights Of Prescribing Information-Steglatro. *accessdata*. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209803s000lbl.pdf. Accessed 20 Dec 2019.
38. Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease, The VERTIS CV Study (MK-8835-004). ClinicalTrials.gov. 2013. https://clinicaltrials.gov/ct2/show/NCT01986881. Accessed 20 Dec 2019.
39. Cannon P, McGuire DK, Pratley R, et al. Design and baseline characteristics of the eValuation of ERTugliflozin efficacy and Safety CardioVascular outcomes trial (VERTIS-CV). Am Heart J. 2018;206:11–23.
40. Study of Safety and Efficacy Of Ertugliflozin (PF-04971729, MK-8835) In Participants With Type 2 Diabetes And Hypertension (MK-8835-042). ClinicalTrials.gov. 2010. http://clinicaltrials.gov/ct2/show/NCT01096667. Accessed 20 Dec 2019.
41. Amin NB, Wang X, Mitchell JR, Lee DS, Nucci G, Rusnak JM. Blood pressure-lowering effect of the sodium glucose co-transporter-2 inhibitor ertugliflozin, assessed via ambulatory blood pressure monitoring in patients with type 2 diabetes and hypertension. Diabetes Obe Metab J Pharmacol Therap. 2015;17(8):805–8.
42. ERtugliflozin triAl in DIabetes With Preserved or Reduced ejeCtion FrAcTion mEchanistic Evaluation in Heart Failure (ERADICATE-HF). ClinicalTrials.gov. 2018. http://clinicaltrials.gov/ct2/show/NCT03416270. Accessed 20 Dec 2019.
43. Effect of Ertugliflozin on Cardiac Function in Diabetes (ERTUGLS). ClinicalTrials.gov. October 24, 2018. http://clinicaltrials.gov/ct2/show/NCT03717194. Accessed 20 Dec 2019.
44. Evaluating Metabolic Mechanisms of Ertugliflozin in Diabetes & Heart Failure (EMMED-HF). ClinicalTrials.gov. 2019. http://clinicaltrials.gov/ct2/show/NCT04071626. Accessed 20 Dec 2019.
45. Comparison of Pharmacodynamic Effects of Sotagliflozin and Empagliflozin in T2DM Patients With Mild to Moderate Hypertension. ClinicalTrials.gov. March 12, 2018. http://clinicaltrials.gov/ct2/show/NCT03462069. Accessed 20 Dec 2019.
46. Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF Trial). ClinicalTrials.gov. 2018. http://clinicaltrials.gov/ct2/show/NCT03521934. Accessed 20 Dec 2019.
47. Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED). ClinicalTrials.gov. 2017. http://clinicaltrials.gov/ct2/show/NCT03315143. Accessed 20 Dec 2019.
48. Safety, Tolerability and Pharmacodynamic Activity of Sotagliflozin in Hemodynamically Stable Patients With Worsening Heart Failure. ClinicalTrials.gov. 2017. http://clinicaltrials.gov/ct2/show/NCT03292653. Accessed 20 Dec 2019.
49. American College of Cardiology. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. 2019. http://

Author's personal copy

www.onlinejacc.org/content/accj/74/10/e177.full.pdf. Accessed 20 Dec 2019.
50. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. The Lancet. 2019;7(10):776–85.
51. Yuliya L, Petter B, Udell JA, Lovshin JA, Cherney DZ. Sodium glucose cotransporter-2 inhibition in heart failure. Circulation. 2017;136(17):1643–58.
52. Trujillo JM, Nuffer WA. Impact of sodium-glucose cotransporter 2 inhibitors on. Pharmacotherapy. 2017;37(4):481–91.
53. Rajeev SP, Wilding JP. SGLT2 inhibition and ketoacidosis—should we be concerned? Br J Diabetes. 2015;15(4):155–8.
54. Burke KR, Schumacher CA, Harpe SE. SGLT2 Inhibitors: a Systematic Review of Diabetic Ketoacidosis and Related Risk Factors in the Primary Literature. Pharmacotherapy. 2017;37(2):187–94.