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*JACC* STATE-OF-THE-ART REVIEW

# Clinical Benefit of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors

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**CME/MOC/ECME Objective for This Article:** Upon completion of this activity, the learner should be able to: 1) discuss the unexpected results of the Empagliflozin in Cardiovascular Outcomes Trial; 2) discuss the evidence that sodium-glucose cotransporter 2 inhibitors (SGLT2i) may be effective in the treatment of patients with heart failure without diabetes; and 3) discuss the mechanism responsible for the genital infections observed in patients with diabetes treated with an SGLT2i.

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**ABSTRACT**

Changes in the regulatory guidelines by the U.S. Food and Drug Administration and the European Medical Agency requiring large-scale trials that study the cardiovascular safety of new glucose-lowering drugs have improved our understanding of type 2 diabetes mellitus. Unexpectedly, these trials demonstrated that sodium-glucose cotransporter 2 inhibitors reduce adverse cardiovascular outcomes. This second part of this 2-part review summarizes the findings of recent clinical trials and their clinical implications and describes ongoing trials and future areas of research. (J Am Coll Cardiol 2020;75:435–47)


The first nonselective sodium-glucose cotransporter inhibitor phlorizin, isolated from the root bark of apple trees, was identified in 1835 (1) and its glucosuric effect was detected nearly 50 years later by Joseph von Mering, a German physician (2). However, due to its chemical instability, another century passed before this drug class was investigated as possible glucose-lowering agents in patients with type 2 diabetes mellitus (T2DM). Phlorizin, a glycoside bound to phloretin, served as a model for the development of novel sodium-glucose cotransporter 2 inhibitors (SGLT2i) with improved pharmacological properties. In particular, the modification of the glycoside binding site by replacing the O-glycosidic bond with a C-glycosidic bond has improved the pharmacokinetic properties, but further research and development of new SGLT2i is still ongoing (3). Recent large-scale clinical trials have provided evidence that SGLT2i reduce major adverse cardiovascular events (MACE), prevent hospitalizations from heart failure (HF), and are nephroprotective (4,5). Many of these findings were unanticipated and have stimulated substantial mechanistic research to improve the understanding of this drug class, which is Part 1 of this review (6). The second part of this review summarizes recent findings of clinical trials and their clinical implications and describes ongoing trials and suggests future areas of research.

## CARDIORENAL AND METABOLIC EFFECTS OF SGLT2i IN PATIENTS WITH T2DM

SGLT2i have modest glucose-lowering effects (approximately 0.5% to 1% reduction in glycosylated hemoglobin [$HbA_{1c}$]) by urinary glucosuria, reduce body weight (2 to 3 kg), and lower systolic arterial blood pressure (3 to 5 mm Hg). To date, 3 large cardiovascular outcomes trials (7–9) and 1 kidney outcome trial (5) that studied patients with T2DM and 1 trial on patients with HF and reduced ejection fraction (10) have been published; several others are ongoing (see Ongoing Trials).

The first SGLT2i cardiovascular outcomes trial (7) was the EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial, a randomized, double-blind, placebo-controlled trial that studied empagliflozin in 7,020 patients with T2DM and established atherosclerotic cardiovascular disease (**Table 1, Figure 1**). It was the first trial in T2DM that showed a significant 14% reduction (hazard ratio [HR]: 0.86; p = 0.04) of MACE, which is a composite of myocardial infarction, stroke, and cardiovascular death (**Figure 1**) (7). It reported a significant 38% reduction of cardiovascular death, a 32% reduction in all-cause death, and a 32% reduction of hospitalization for HF. Because of a trend to a reduction in hospitalization for HF by 6 months in the EMPA-REG OUTCOME trial, early hemodynamic changes were believed to mediate the improved cardiovascular survival (7).

After their exciting initial paper, the EMPA-REG OUTCOME trial investigators showed that patients randomized to empagliflozin had lower incidence of cardiovascular events across a spectrum of HF risk (11) and were consistent irrespective of a history of HF (12), a history of myocardial infarction or stroke (13), as well as the presence of electrocardiography-defined left ventricular hypertrophy (14). Another post hoc analysis indicated that treatment with

## HIGHLIGHTS

- Patients with T2DM are at high risk of major vascular complications, HF, and chronic kidney disease.
- SGLT2i reduce MACE and progression of chronic kidney disease in patients with T2DM.
- SGLT2i also reduce HF and cardiovascular death in patients with established HF and reduced ejection fraction.
- Ongoing trials are addressing the role of SGLT2i in patients with HF and preserved ejection fraction and chronic kidney disease, with and without T2DM.

empagliflozin was associated with a lower risk of HF rehospitalization and mortality in patients who had an HF event during the trial, supporting further research of SGLT2i in patients hospitalized with decompensated HF (15).

These results were followed by the CANVAS (Canagliflozin Cardiovascular Assessment Study) program, which also reported a significant 14% reduction of MACE in patients randomized to canagliflozin when compared with those on placebo (**Figure 1**) (8). Similar to EMPA-REG OUTCOME, a significant 33% reduction of hospitalization for HF was observed in canagliflozin-treated patients. The largest of the 3 SGLT2i cardiovascular outcomes trials to date, including 17,160 patients, was the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis In Myocardial Infarction 58) trial (9). Dapagliflozin significantly reduced the risk of the composite of cardiovascular death and hospitalization for HF (HR: 0.83; $p = 0.005$) driven mainly by a reduction in hospitalization for HF and was noninferior in the composite of myocardial infarction, ischemic stroke, and cardiovascular death (HR: 0.93; $p = 0.17$). A subgroup analysis of patients with prior myocardial infarction in DECLARE-TIMI 58 showed a significant 16% reduction in the relative risk ratio of MACE, including a significant 22% reduction of recurrent myocardial infarction (16). In addition to a lower rate of type 1 myocardial infarctions (i.e., due to plaque disruption), a significant reduction of type 2 myocardial infarctions (i.e., an imbalance between myocardial supply and/or oxygen demand leading to myocardial ischemia) (17) was noted.

Whereas EMPA-REG OUTCOME was limited to patients with established atherosclerotic cardiovascular disease, both the CANVAS program and DECLARE-TIMI 58 trial had substantial fractions of patients without overt atherosclerotic cardiovascular disease (34% and 59%, respectively) (**Table 1, Figure 1**). Furthermore, the proportion of patients with an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 $m^2$ differed among the trials and ranged between 7.4% in DECLARE-TIMI 58 and 25.9% in EMPA-REG OUTCOME.

The first large SGLT2i kidney outcomes trial, the CREDENCE (Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy) trial included 4,401 T2DM patients with an eGFR between 30 and 90 ml/min/1.73 $m^2$ (mean eGFR 56 ml/min/1.73 $m^2$) and substantial albuminuria (urinary albumin-to-creatinine ratio [UACR] >300 mg/g to ≤5,000 mg/g (5); median UACR 927 mg/g). CREDENCE was terminated early because it met its primary endpoint by reducing the risk of the composite endpoint of end-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death by 30%. In addition, the CREDENCE trial showed a 20% reduction in MACE (HR: 0.80; $p = 0.01$) including a 22% reduction in cardiovascular death (HR: 0.78; $p = 0.0502$) as well as a 31% reduction in the composite of cardiovascular death and hospitalization for HF (HR: 0.69; $p < 0.001$) (**Figure 1**).

Whereas these 4 trials, including a total of 38,723 patients with T2DM, differ in their proportions of patients with atherosclerotic cardiovascular disease, HF, and kidney function (**Figure 2, Table 1**), all of these trials have shown robust reductions in the risk of cardiovascular death or hospitalization for HF (**Figure 1**) and progression of chronic kidney disease. Three of these trials also reduced the risk of MACE (5,7,8).

## SGLT2i AND HF

An updated meta-analysis including the CREDENCE trial indicated that SGLT2i reduce the risk of hospitalization for HF by 32%, cardiovascular death by 17% and all-cause death by 15% (**Figure 2**). Importantly, a pooled analysis of the 3 cardiovascular outcomes trials showed that these reductions were independent of a known history of HF (4). Of interest, this meta-analysis also showed that patients with worse baseline kidney function tended to derive greater reductions in HF from SGLT2i (4).

A secondary analysis of the CANVAS program found similar reductions in heart failure with reduced

### ABBREVIATIONS AND ACRONYMS

**CI** = confidence interval

**eGFR** = estimated glomerular filtration rate

**$HbA_{1c}$** = glycosylated hemoglobin

**HF** = heart failure

**HFpEF** = heart failure with preserved ejection fraction

**HFrEF** = heart failure with reduced ejection fraction

**HR** = hazard ratio

**MACE** = major adverse cardiovascular events

**SGLT2i** = sodium-glucose cotransporter 2 inhibitor

**T1DM** = type 1 diabetes mellitus

**T2DM** = type 2 diabetes mellitus

**UACR** = urinary albumin-to-creatinine ratio

**TABLE 1 Overview of the SGLT2i CV and Kidney Outcomes Trials in Patients With T2DM**

| | EMPA-REG OUTCOME | CANVAS Program* | DECLARE-TIMI 58 | CREDENCE |
|---|---|---|---|---|
| Drug | Empagliflozin | Canagliflozin | Dapagliflozin | Canagliflozin |
| Key inclusion criteria | • $HbA_{1c}$ ≥7.0% to ≤10.0%<br>• BMI ≤45 kg/m$^2$<br>• eGFR ≥30 ml/min/1.73 m$^2$<br>• Presence of ASCVD | • $HbA_{1c}$ ≥7.0% to ≤10.5%<br>• eGFR ≥30 ml/min/1.73 m$^2$<br>• Presence of multiple risk factors for or established ASCVD | • $HbA_{1c}$ ≥6.5% to <12%<br>• Presence of multiple risk factors for or established ASCVD<br>• Creatinine clearance >60 ml/min/1.73 m$^2$ at screening | • $HbA_{1c}$ ≥6.5% to <12%<br>• eGFR ≥30 to <90 ml/min/1.73 m$^2$<br>• UACR >300 mg/g to ≤5,000 mg/g |
| Median follow-up time, yrs | 3.1 | 2.4 | 4.2 | 2.6 |
| Trial participants, n | 7,020 | 10,142 | 17,160 | 4,401 |
| Mean age, yrs | 63.1 | 63.3 | 63.9 | 63.0 |
| Female | 2,004 (28.5) | 3,633 (35.8) | 6,422 (37.4) | 1,494 (33.9) |
| Patients with established atherosclerotic cardiovascular disease | 7,020 (100) | 6,656 (66) | 6,974 (41) | 2,220 (50) |
| History of heart failure | 706 (10.1) | 1,461 (14.4) | 1,724 (10.0) | 652 (14.8) |
| Mean eGFR, ml/min/1.73 m$^2$ | 74.1 | 76.5 | 85.3 | 56.2 |
| eGFR <60 ml/min/1.73 m$^2$ | 1,819 (25.9) | 2,039 (20.1) | 1,265 (7.4) | 2,631 (59.8) |

Values are n (%) unless otherwise indicated. *The CANVAS program consisted of 2 trials but was analyzed as 1 trial.

ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CANVAS = Canagliflozin Cardiovascular Assessment Study; CREDENCE = Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy; CV = cardiovascular; DECLARE-TIMI 58 = Dapagliflozin Effect on Cardiovascular Events—Thrombolysis In Myocardial Infarction 58; eGFR = estimated glomerular filtration rate; EMPA-REG OUTCOME = Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; $HbA_{1c}$ = glycosylated hemoglobin; SGLT2i = sodium glucose cotransporter 2 inhibitor; T2DM = type 2 diabetes mellitus; UACR = urine albumin creatinine ratio.

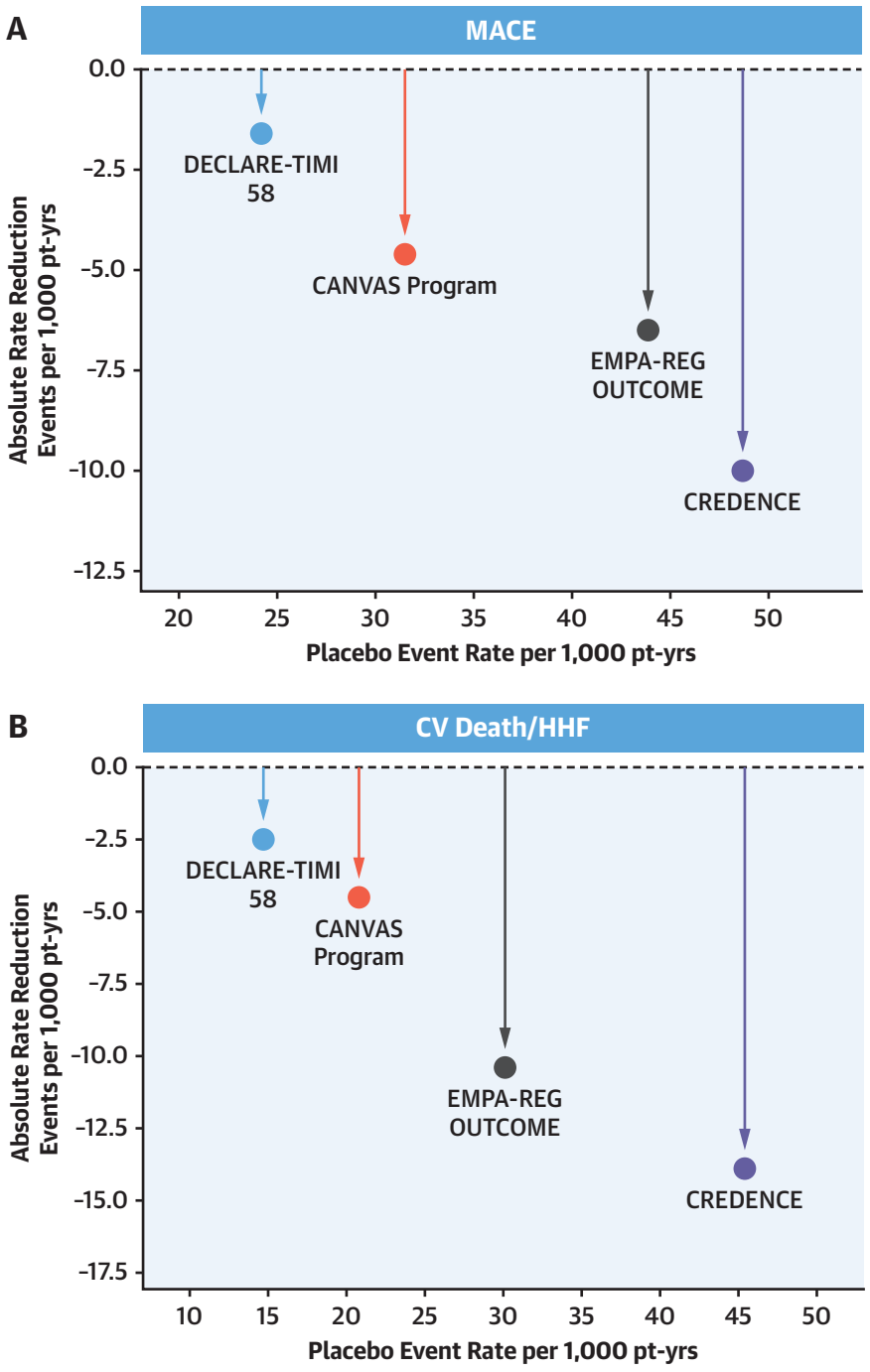
ejection fraction (HFrEF) (HR: 0.69; 95% confidence interval [CI]: 0.48 to 1.00) and heart failure with preserved ejection fraction (HFpEF) (HR: 0.83; 95% CI: 0.55 to 1.25) (18). In the DECLARE-TIMI 58 trial, similar reductions in hospitalization for HF were observed in patients with reduced as well as with preserved ejection fraction (HFrEF: HR: 0.64; 95% CI: 0.43 to 0.95, and HFpEF: HR: 0.76; 95% CI: 0.62 to 0.92). However, the reduction of cardiovascular death was limited to patients with HFrEF (HFrEF: HR: 0.55; 95% CI: 0.34 to 0.90, and HFpEF: HR: 1.08; 95% CI: 0.89 to 1.31) (19). Although the pathobiological mechanisms of these salutary effects are still under study (6), it is of interest that a mechanistic trial in 97 patients with T2DM and atherosclerotic cardiovascular disease, reported by Verma et al. (20) demonstrated that 3 months of treatment with empagliflozin, compared with placebo, significantly reduced left ventricular mass, as measured by magnetic resonance imaging. Serial measurements of biomarker concentrations reflecting different pathobiological mechanisms may add further insight into the mode of action. When compared with placebo, the SGTL2i canagliflozin has been shown to delay the rise in N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin I over 2 years (21).

The 4 previously mentioned large trials (**Table 1**) showed that both the reduction of MACE (**Figure 1A**) and of the combination of cardiovascular death and hospitalization for HF (**Figure 1B**) varied directly with the severity of the disorder. Thus, DECLARE-TIMI 58, which had the largest fraction of patients without established cardiovascular disease and the lowest placebo event rate showed the smallest reduction of event rate on treatment. In contrast, the CREDENCE trial, which included the patients with the most severe disease, exhibited the greatest beneficial responses (**Figure 1**).

When these 4 trials were begun, they were not dedicated primary HF trials and the proportion of patients with HF were limited (**Table 1**). The first dedicated HF trial, the DEFINE-HF (Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in Patients with HF with Reduced Ejection Fraction Trial) studied 263 patients with HFrEF who were randomized to either dapagliflozin or placebo. After 12 weeks of treatment, compared with placebo, a significantly higher proportion of patients treated with dapagliflozin improved in disease-specific health status assessed by the Kansas City Cardiomyopathy Questionnaire (22).

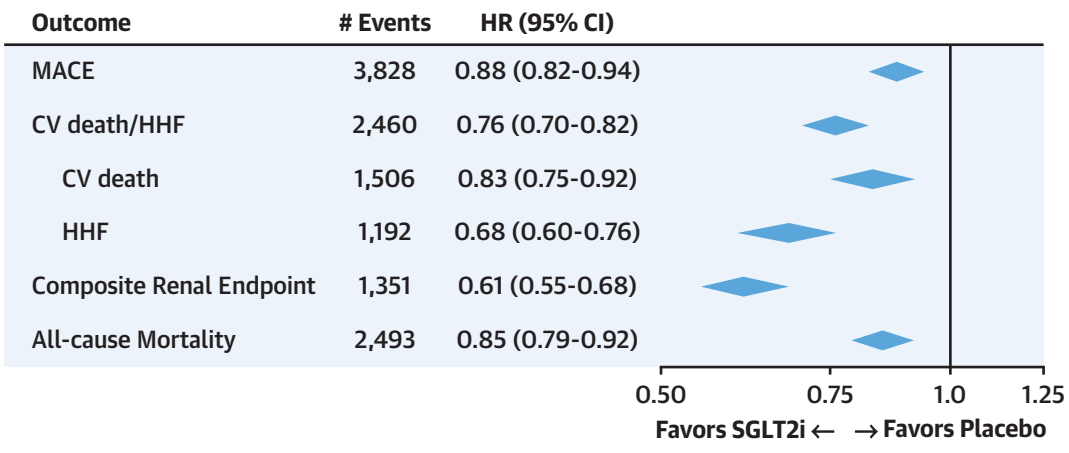
The DAPA-HF (Dapagliflozin and Prevention of Adverse-outcomes in Heart Failure) trial studied dapagliflozin in a broad population of 4,744 patients with HFrEF with and without T2DM (10,23,24). Compared with placebo, dapagliflozin significantly reduced the risk of the composite of cardiovascular death and HF by 26% ($p < 0.001$) as well as its individual components, including an 18% reduction in cardiovascular death ($p = 0.029$). Most importantly,

**FIGURE 1** Difference in Absolute Difference Risk




**(A)** Major adverse cardiovascular events (MACE) (i.e., myocardial infarction, stroke, cardiovascular death) and **(B)** the composite of cardiovascular (CV) death and hospitalization for heart failure (HHF) according to the placebo event rate. DAPA-HF (Dapagliflozin and Prevention of Adverse-outcomes in Heart Failure) (not shown in the figure) reported an absolute rate reduction of 40 events per 1,000 patient-years (pt-yrs). CANVAS = Canagliflozin Cardiovascular Assessment Study; CREDENCE = Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy; DECLARE-TIMI 58 = Dapagliflozin Effect on Cardiovascular Events–Thrombolysis In Myocardial Infarction 58; EMPA-REG OUTCOME = Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.

**FIGURE 2 Treatment Effect of SGLT2i on Cardiorenal Outcomes**




Updated meta-analysis (4) of 38,723 patients including EMPA-REG OUTCOME, CANVAS program, DECLARE-TIMI 58 trial, and the CREDENCE trial, using a fixed effects model (5). The composite renal endpoint differed slightly between the trials but consisted of a sustained 40% reduction in estimated glomerular filtration rate or doubling of serum creatinine, end-stage kidney disease, and death from renal causes. A sensitivity analysis using a random effects model employing REML and Hartung Knapp adjustment yielded similar treatment effects for all outcomes. CI = confidence interval; HR = hazard ratio; REML = restricted maximum likelihood; SGLT2i = sodium-glucose cotransporter 2 inhibitor; other abbreviations as in Figure 1.

there was a consistent treatment effect irrespective of a history of T2DM at baseline. In 2,605 patients with HF without T2DM, dapagliflozin reduced the risk of cardiovascular death/HF significantly by 27%.

These results may mark the beginning of a new treatment option for patients with HFrEF without T2DM; these benefits were achieved in a population of patients with HF who were well-treated including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (>90%), beta-blockers (>90%), mineralocorticoid-receptor antagonists (>70%), and neprilysin inhibitors (>10%) (10). The baseline characteristics of the patients enrolled in the DAPA-HF trial are similar to those in contemporary HF trials and registries (24). Several ongoing trials are investigating the role of SGLT2i in patients with HFrEF as well as with HFpEF, in patients with and without T2DM.

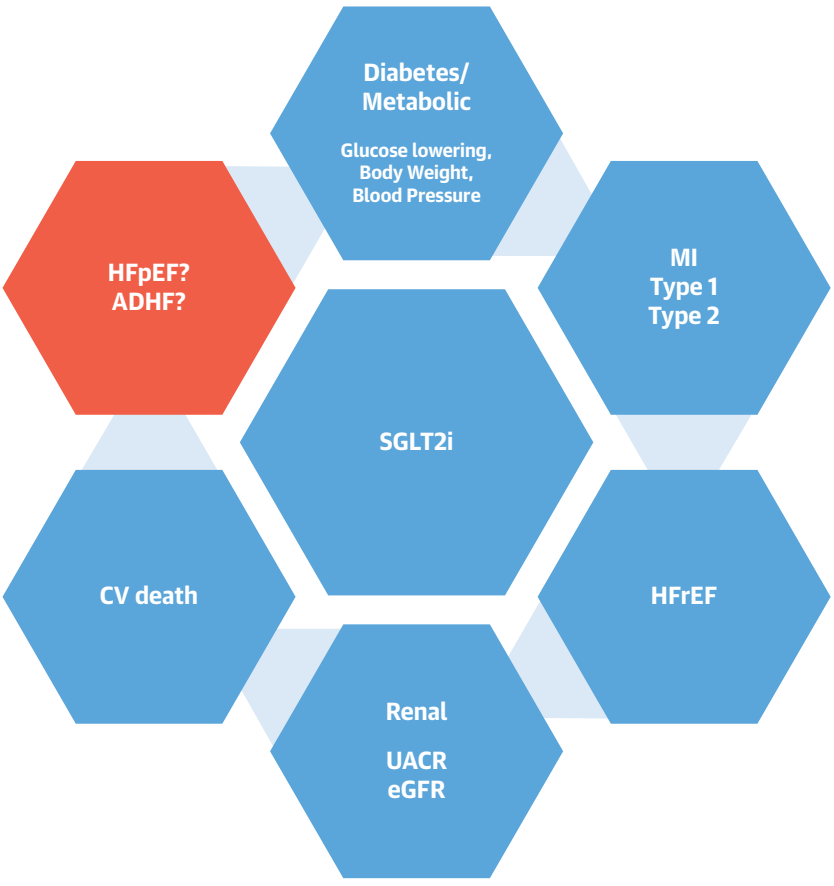
## SGLT2i AND ATHEROSCLEROTIC EVENTS

A meta-analysis of the 3 SGLT2i cardiovascular outcomes trials found modest reductions for MACE and reported that this effect was confined to patients with established atherosclerotic cardiovascular disease (HR: 0.86; $p < 0.001$) whereas no effect was observed in those who had multiple cardiovascular risk factors but no known atherosclerotic cardiovascular disease (HR: 1.00; $p = 0.98$; p for interaction = 0.05) (4). However, in CREDENCE, a consistent reduction of MACE was seen both in patients with established atherosclerotic cardiovascular disease (secondary prevention) and those with only multiple cardiovascular risk factors (primary prevention) (8). It is interesting to consider the difference in the outcomes of the CANVAS program and CREDENCE trial, because both studied the same SGLT2i, canagliflozin, but with marked differences in baseline characteristics (5,8), indicating that kidney dysfunction may modify the atherosclerotic treatment effect of SGLT2i. However, it is also possible that the primary prevention of MACE may require more time to become evident and thus more long-term follow-up data are warranted in patients without established atherosclerotic cardiovascular disease.

## SGLT2i AND CHRONIC KIDNEY DISEASE

The glucose-lowering mechanism of action of SGLT2i, which enhances urinary glucose excretion, requires kidney function that is at least moderately well preserved (i.e., an eGFR ≥45 ml/min/1.73 $m^2$). As such, both the excretion of glucose (and with it $Na^+$), as well as the reductions in $HbA_{1c}$ are lessened in patients with more seriously impaired kidney function. As a consequence, SGLT2i are currently approved by the U.S. Food and Drug Administration only in patients with an eGFR ≥45 ml/min/1.73 $m^2$. It is

**FIGURE 3** Effects of SGLT2i on Cardio-Metabolic-Renal Events




In addition to multiple metabolic effects including lowering of glycosylated hemoglobin, body weight, and arterial blood pressure, SGLT2i have been shown to reduce myocardial infarction (MI), heart failure, kidney outcomes, and CV death. SGLT2i reduce the composite of CV death and hospitalization for heart failure in patients with heart failure with reduced ejection fraction (HFrEF). Ongoing trials are currently addressing the role of SGLT2i in patients with heart failure and preserved ejection fraction (HFpEF) and acute decompensated heart failure (ADHF). eGFR = estimated glomerular filtration rate; UACR = urine albumin creatinine ratio; other abbreviations as in **Figures 1 and 2**.

important to note that this limitation concerns only the glucose-lowering effectiveness of these drugs. It is likely that the salutary effects of SGLT2i on cardiorenal events occur independently of the glucose-lowering effect, given the favorable results observed in the DAPA-HF trial in patients without T2DM (10). As such, the need for an eGFR ≥45 ml/min/1.73 $m^2$ should now be reconsidered.

SGLT2i appear to have direct renal hemodynamic effects (6). After an initial dip in eGFR, SGTL2i have been shown to preserve this function and consequently retard the progression of chronic kidney disease (6,25,26). Each of the SGLT2i outcome trials in patients with T2DM published to date have shown robust reductions by 30% to 47% in the composite of sustained worsening of eGFR, end-stage kidney disease, or death of renal cause (4,5,27,28). A pooled analysis of these 4 trials showed that SGLT2i reduced major kidney outcomes including dialysis, transplantation, or death due to kidney disease and provided protection against acute kidney injury (29). Although significant renal protections were seen irrespective of baseline levels of eGFR, a meta-analysis of the 3 SGLT2i cardiovascular outcomes trials suggested greater protective effects in patients with more preserved eGFR (i.e., eGFR >90 ml/min/1.73 $m^2$) (4). Given the presumed direct renal hemodynamic effects of this drug class, it is tempting to speculate that T2DM patients in an early stage of kidney involvement, that is, with hyperfiltration, derive greater benefit than those with later changes. A secondary analysis from the EMPA-REG OUTCOME trial

**TABLE 2 Overview of Available SGLT2i**

| SGLT2i | Selectivity of SGLT2 Over SGLT1 | Approval for T2DM |
|---|---|---|
| Empagliflozin | 2,700 | U.S., Europe, most of Asia |
| Canagliflozin | 250 | U.S., Europe, most of Asia |
| Dapagliflozin* | 1,200 | U.S., Europe, most of Asia |
| Ertugliflozin | 2,200 | U.S., Europe, most of Asia |
| Sotagliflozin* | 20 | – |
| Ipragliflozin | 360 | Japan |
| Tofogliflozin | 2,900 | Japan |
| Luseogliflozin | 1,770 | Japan |

*Approved for treatment of type 1 diabetes mellitus in Europe.
SGLT1 = sodium glucose cotransporter 1; other abbreviations as in Table 1.

revealed that a history of HF did not modify the treatment effect on kidney outcomes (30). Subgroup analyses from the 3 SGLT2i cardiovascular outcomes trials discussed, also showed consistent reductions in cardiovascular and kidney events in patients with chronic diabetic kidney disease (28–32).

Taken together these remarkable effects on cardiovascular and kidney outcomes suggest that SGLT2i are likely to be beneficial in patients with chronic kidney disease despite an attenuated glucose-lowering effect in these patients.

## SAFETY

SGLT2i increase the risk of genital infections in both sexes but do not appear to increase the risk of urinary tract infections, including pyelonephritis (33). Also, initial concerns about Fournier gangrene (34,35), a rare but life-threatening condition, have not been confirmed in more recent trials (9). SGLT2i may increase the risk of volume depletion but no increased risk of acute kidney failure has been reported.

Although infrequent, SGLT2i have been shown repeatedly to increase the risk of diabetic ketoacidosis, 74 events in 38,702 patients (0.2%) have been reported in the 3 SGLT2i T2DM cardiovascular outcomes trials and the CREDENCE trial (4,5). The recognition of diabetic ketoacidosis in patients receiving SGLT2i can be challenging as it may occur with normal glucose levels (36). Therefore, patients with suspected diabetic ketoacidosis should have blood ketones measured regardless of their glucose levels.

In addition, in the CANVAS program an increased rate of amputations, predominantly at the toe and metatarsal levels, was observed in the patients receiving canagliflozin (8,37). Although an off-target effect limited to canagliflozin cannot be excluded (38), there was no excess in amputation risk in patients with chronic kidney disease receiving canagliflozin when proper foot care was instituted in the CREDENCE trial (5). Also, the number of amputations were not increased significantly in EMPA-REG OUTCOME and DECLARE-TIMI 58. Furthermore, the increased incidence of fractures that was reported with canagliflozin in the CANVAS program was not confirmed with the same drug in the CREDENCE trial (5,8), nor in a large observational study (39).

## TYPE 1 DIABETES MELLITUS

Several SGLT2i, including canagliflozin (40), dapagliflozin (41,42), empagliflozin (43), and sotagliflozin (44) have been studied in patients with type 1 diabetes mellitus (T1DM). When added to insulin, SGLT2i reduced $HbA_{1c}$ significantly without increasing the risk of hypoglycemia. Treatment with SGLT2i in patients with T1DM receiving insulin allows a lowering of the dose of insulin and thereby reduces the side effects of insulin, including hypoglycemic episodes and weight gain (45). However, patients with T1DM receiving SGLT2i are at greater risk of developing diabetic ketoacidosis than are T2DM patients (46). The European Medical Agency has recently approved dapagliflozin (41,42,47) and sotagliflozin (44,48) as adjunctive therapy for patients with T1DM. SGLT2i therefore represent the first oral adjunct therapies for T1DM patients that have been approved (at this time, in Europe).

## CONSENSUS DOCUMENTS/GUIDELINES

An American College of Cardiology Expert Consensus Decision Pathway document (49) addressed the use of novel diabetes drugs. It recommended that SGLT2i be considered in patients with the combination of T2DM and arteriosclerotic cardiovascular disease. Guidelines by the American Diabetes Association currently recommend metformin as first-line therapy after comprehensive lifestyle modifications. The selection of additional therapy should then be based on patient-specific characteristics and preference. SGLT2i or glucagon-like peptide 1-receptor agonists should be considered, particularly in patients with established atherosclerotic cardiovascular disease, HF, or chronic kidney disease (50,51).

The updated American College of Cardiology/American Heart Association primary prevention guidelines recommend that SGLT2i use is “reasonable” in patients with T2DM who despite lifestyle modification and metformin require further glucose-lowering therapy to reduce cardiovascular risk (52). Similar recommendations have been made in

**TABLE 3 Selected Ongoing SGLT2i Trials**

| NCT Number | Trial Title | Trial Acronym | Anticipated Enrollment | Anticipated Completion | Drug |
|---|---|---|---|---|---|
| Cardiovascular outcomes trials | | | | | |
| NCT03982381 | SGLT2 Inhibitor or Metformin as Standard Treatment of Early Stage Type 2 Diabetes | SMARTEST | 4,300 | September 20, 2024 | Dapagliflozin |
| NCT01986881 | Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease | VERTIS-CV | 8,000 | December 30, 2019 | Ertugliflozin |
| NCT03315143 | Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk | SCORED | 10,500 | March 2022 | Sotagliflozin |
| Heart failure trials | | | | | |
| NCT03619213 | Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure | DELIVER | 4,700 | June 22, 2021 | Dapagliflozin |
| NCT03057951 | Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction | EMPEROR-Preserved | 5,250 | November 9, 2020 | Empagliflozin |
| NCT03057977 | Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction | EMPEROR-Reduced | 3,600 | July 20, 2020 | |
| NCT03521934 | Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure | SOLOIST-WHF | 4,000 | January 2021 | Sotagliflozin |
| Chronic kidney disease trials | | | | | |
| NCT03036150 | A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease | DAPA-CKD | 4,000 | November 27, 2020 | Dapagliflozin |
| NCT03594110 | The Study of Heart and Kidney Protection With Empagliflozin | EMPA-KIDNEY | 5,000 | June 30, 2022 | Empagliflozin |

NCT = national clinical trial; SGLT2i = sodium glucose cotransporter 2 inhibitor.

guidelines in Asian countries (53). However, the most recently updated European Society of Cardiology guidelines developed in collaboration with the European Association for the Study of Diabetes now recommend SGLT2i or glucagon like peptide 1 receptor agonist in drug-naïve patients with T2DM who have established or are at high risk for atherosclerotic cardiovascular disease (54). Although SGLT2i prevent HF in a broad population of patients with T2DM, a recently published risk score using 5 clinical variables (history of atrial fibrillation, coronary artery disease, eGFR <60 ml/min/1.73 $m^2$, and UACR >30 mg/g, and prior HF) may assist in identifying T2DM patients who are at the highest risk for hospitalization for HF and therefore derive greater absolute benefit from SGLT2i (55).

Currently, 4 SGLT2i agents (empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin) have been approved by regulatory agencies in the United States and in Europe for the treatment of patients with T2DM. Dapagliflozin has been approved for the treatment of HF. The U.S. Food and Drug Administration has also approved canagliflozin to reduce the risk of end-stage kidney disease and worsening kidney function in adults with diabetic kidney disease. In Japan, not only these 4 agents but also 3 additional SGLT2i agents—ipragliflozin, luseogliflozin, and tofogliflozin—are also approved (Online Table 1) (56). Even though the selectivity for SGLT2 over SGLT1 varies among the available SGLT2i, currently available SGLT2i all have similar mechanisms of action and in general similar pharmacokinetic and pharmacodynamic effects (57).

**TABLE 4 Lessons Learned and to Be Learned**

| |
|---|
| Lessons learned about the effect of SGLT2i in patients with T2DM |
| SGLT2i have robust effects on reducing the risk of hospitalization for HF and adverse renal outcomes. Patients with lower eGFR may derive the greatest relative benefit in HF reduction. |
| SGLT2i have moderate benefits on MACE (i.e., myocardial infarction, stroke, cardiovascular death) that appear to be limited to patients with established ASCVD. |
| Although the glucose-lowering effect of SGLT2i requires preserved kidney function, the favorable cardiorenal effects appear to occur independently of glucose lowering. |
| SGLT2i showed greater reductions for progression of kidney disease in patients with higher baseline eGFR. |
| Dapagliflozin reduced the risk of cardiovascular death and HF in patients with HFrEF without T2DM |
| Lessons to be learned |
| Should metformin remain the first-line drug of choice in patients with T2DM? |
| Will SGLT2i reduce cardiovascular death and hospitalization for HF in patients with HFpEF? If so, are there differences in patients with and without T2DM? |
| Do SGLT2i reduce progression of chronic kidney disease in patients without T2DM? If so, which kidney disease and the range of severity? |
| May SGLT2i have salutary cardiorenal effects in patients with even more severe chronic kidney disease (stages 4 and 5)? |

HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MACE = major adverse cardiovascular events; other abbreviations as in Table 1.

**CENTRAL ILLUSTRATION Overview of Favorable and Unfavorable Cardio-Metabolic-Renal Effects of Sodium-Glucose Cotransporter 2 Inhibitors**


**Zelniker, T.A. et al. J Am Coll Cardiol. 2020;75(4):435–47.**

Adapted from Zelniker and Braunwald (6).

## ONGOING TRIALS

The salutary results of SGLT2i trials summarized herein have led to a proliferation of further research with this drug class (**Figure 3, Tables 2 and 3**, Online Tables 1 to 9). Two cardiovascular outcomes trials are currently studying the efficacy and safety of ertugliflozin and sotagliflozin, respectively, in patients with T2DM (**Table 3**). Two doses of ertugliflozin are currently being studied in 8,246 patients with established atherosclerotic cardiovascular disease in the VERTIS-CV (Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Patients with Vascular Disease; NCT01986881) (58). The SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; NCT03315143) trial is comparing sotagliflozin with placebo in 10,500 patients without established atherosclerotic cardiovascular disease.

Several trials are ongoing to investigate the role of SGLT2i in patients with HFrEF and HFpEF, in patients with and without T2DM (**Figure 3**, Online Table 1). The DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; NCT03619213) trial is determining the effect of dapagliflozin in patients with HFpEF. Empagliflozin is currently being studied in patients with T2DM and HFrEF and HFpEF in the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; NCT03057977) and in the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; NCT03057951) trials, respectively. These dedicated HF trials will determine whether SGLT2i may be the first class of pharmacological agents that improves outcomes in both patients with HFrEF and patients with HFpEF (**Table 3**). Currently, the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) trial (NCT03521934) is examining the effect of sotagliflozin in the setting of acute decompensated HF (**Table 3**).

In addition, several trials are ongoing to gain further insight into the mechanisms of these important actions (Online Table 1).

Ongoing trials are also addressing the role of SGLT2i in patients with chronic kidney disease with and without T2DM and will provide data for efficacy and safety in patients with an eGFR as low as 20 ml/min/1.73 $m^2$ (**Table 3**, Online Table 2). Furthermore, the ongoing PREHYPED (Double Blind Placebo Study of Jardiance [Empagliflozin] in

Prehypertensives Type II Diabetics; NCT01001962) trial is also studying whether empagliflozin may prevent the development of hypertension in patients with T2DM.

Further research is warranted to determine whether metformin should remain a first-line therapy in patients with T2DM, as recommended by American Diabetes Association guidelines (51). Currently, a registry-based, open-label, randomized trial, SMARTEST (SGLT2 Inhibitor or Metformin as Standard Treatment of Early Stage Type 2 Diabetes; NCT03982381), is comparing dapagliflozin with metformin in the assessment of a broad composite endpoint including death, myocardial infarction, stroke, HF, diabetic nephropathy, retinopathy, or foot ulcer in T2DM patients (**Table 3**). Areas for further investigation include the efficacy and tolerability of the combination of SGLT2i and glucagon like peptide 1 receptor agonist.

## CONCLUSIONS

Since the publication of the EMPA-REG OUTCOME trial in 2015 (7), the results of trials with SGLT2i have been exhilarating in terms of progress made in the understanding and management of T2DM and its major consequences, cardiovascular and renal diseases (**Table 4**). SGLT2i have been shown to possess favorable effects beyond simply lowering glucose, to reduce atherosclerotic events, and to prevent hospitalization for HF; are renoprotective; and reduce cardiovascular and all-cause mortality. Their benefits clearly outweigh safety concerns of an increased risk of genital infections, diabetic ketoacidosis, and possibly limited amputations, all of which are preventable (**Central Illustration**). In addition, this drug class may prove to be of benefit in patients with HF and/or chronic kidney disease without T2DM.

The treatment of adult patients with T2DM is an interdisciplinary undertaking and often includes primary care physicians, diabetologists, cardiologists, nephrologists, and their nursing and pharmacist colleagues. It is important that cardiologists become more knowledgeable about T2DM and its management while diabetologists do the same with cardiac disease, especially HF. Both specialties must learn how to evaluate and treat patients with diabetic kidney disease. The pandemic proportions of both T2DM as well as of atherosclerotic cardiovascular disease, call for cross training in these specialties and, perhaps, the development of a new hybrid subspecialty—diabetocardiology (59).

For several important papers on this subject that were published after submission of this paper on October 3, 2019, please see the Online Appendix.

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**KEY WORDS** cardiorenal interaction, diabetes, heart failure, renal function, sodium-glucose cotransporter 2 inhibitor

**APPENDIX** For an addendum as well as supplemental tables, please see the online version of this paper.


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