# The dawn of the four-drug era? SGLT2 inhibition in heart failure with reduced ejection fraction

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**Abstract:** Sodium-glucose cotransporter type 2 (SGLT2) inhibitors are a relatively new class of antihyperglycemic drug with salutary effects on glucose control, body weight, and blood pressure. Emerging evidence now indicates that these drugs may have a beneficial effect on outcomes in heart failure with reduced ejection fraction (HFrEF). Post-approval cardiovascular outcomes data for three of these agents (canagliflozin, empagliflozin, and dapagliflozin) showed an unexpected improvement in cardiovascular endpoints, including heart failure hospitalization and mortality, among patients with type 2 diabetes mellitus (T2DM) and established cardiovascular disease or risk factors. These studies were followed by a placebo controlled trial of dapagliflozin in patients with HFrEF both with and without T2DM, showing a reduction in all-cause mortality comparable to current guideline-directed HFrEF medical therapies such as angiotensin-converting enzyme inhibitors and beta-blockers. In this review, we discuss the current landscape of evidence, safety and adverse effects, and proposed mechanisms of action for use of these agents for patients with HFrEF. The United States (US) and European guidelines are reviewed, as are the current US federally approved indications for each SGLT2 inhibitor. Use of these agents in clinical practice may be limited by an uncertain insurance environment, especially in patients without T2DM. Finally, we discuss practical considerations for the cardiovascular clinician, including within-class differences of the SGLT2 inhibitors currently available on the US market (217/300).

*Keywords:* cardiomyopathy, diabetes, HFrEF, heart failure, SGLT2 inhibitors

## Introduction

Heart failure with reduced ejection fraction (HFrEF) is a common and frequently morbid condition with high short-term mortality.[1,2] While heart failure refers to the clinical syndrome resulting in dyspnea, exercise intolerance, or fluid retention, a reduced left ventricular ejection fraction is the *sine qua non* of HFrEF.[3] Because HFrEF may be the ultimate result of dozens of heterogenous diseases, it is remarkable that over the past three decades, a consistent body of evidence has shown the effectiveness of several pharmacological therapies in improving quality of life and preventing death.

The pharmacological mainstay of established HFrEF therapy has, until recently, been a three-drug approach with renin–angiotensin system (RAS) inhibitors, beta-blockers, and mineralocorticoid antagonists.[4] This regimen has been relatively unchanged over the past decade. The most recent notable addition has been the addition of the combined angiotensin receptor-neprilysin inhibitor sacubitril-valsartan, as now recommended in the 2017 HFrEF United States (US) focused guideline update.[5,6] While other drug classes, such as the combination of hydralazine-nitrate or ivabradine, have conditional uses, only RAS inhibitors, beta-blockers, and mineralocorticoid antagonists carry class I recommendations for most patients with HFrEF. Into this landscape, the antihyperglycemic sodium-glucose cotransporter type 2 (SGLT2) inhibitors have emerged as a possible fourth drug in front-line therapy.

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Diabetes is highly prevalent among patients with HFrEF, with estimates generally over 40%, depending on the population studied.[7] Patients with HFrEF and comorbid diabetes are at higher risk of hospitalization, morbidity, and mortality, probably due to a combination of non-cardiac end-organ impairment, myocardial ischemia, and risk of infection, among other possible mechanisms.[7–11] This review will focus on the evidence for use of SGLT2 inhibitors in patients with HFrEF with and without type 2 diabetes mellitus (T2DM), discuss the molecular biology and proposed mechanisms of action, and explore the regulatory and prescribing environment for these agents in clinical practice in the US.

### The sodium-glucose cotransporter 2

The existence of a transporter protein capable of using Na+ anions to transport glucose molecules against an uphill concentration gradient was first proposed in 1960 as a key factor in gut absorption of nutritional glucose.[12] Subsequent molecular studies soon revealed that sodium-glucose cotransporter type 1 (SGLT1) was this hypothesized protein. Lining the intestinal brush border, SGLT1 is a high-affinity transmembrane protein that binds Na+ anions and hexose sugar molecules and then undergoes a conformational change to deliver its ligands into cell cytoplasm. The sugar then leaves the cell *via* a facilitated glucose transporter (GLUT) across the basolateral membrane.

After the identification of SGLT1 as the mechanism of intestinal glucose absorption, a similar mechanism was believed to be responsible for glucose reabsorption in the kidney.[13] The glomerulus freely filters plasma glucose; without a resorptive mechanism, about 180 g of glucose per day would be lost in the urine. However, under normal conditions, no glucose is detectable in the urine until plasma glucose levels become super-physiological, such as in suboptimally managed T2DM. SGLT1 would be a reasonable candidate for this renal glucose transporter, and indeed, early studies showed that it is expressed in glomerular cells.[14] However, it was observed that patients with glucose-galactose malabsorption, a very rare autosomal recessive disorder causing congenital absence of SGLT1, only had a mild degree of glucosuria, suggesting the presence of an additional, more important, regulator of glucose reabsorption.[12,15] This transporter, eventually named SGLT2,

functions similarly to SGLT1 in using the action of Na+ transport down its electrochemical gradient to cotransport a glucose molecule.[16] Unlike SGLT1, SGLT2 only transports glucose and does not bind other hexose sugars.[17] SGLT1 binds Na+ and a sugar in a 2:1 ratio and is considered a high-affinity, low volume transporter, while SGLT2 binds 1:1 and is lower affinity but higher capacity.[18] Approximately 90% of glomerular glucose resorption occurs in the first segment of the proximal convoluted tubule by SGLT2; the remainder in the distal segment of the proximal convoluted tubule by SGLT1.[16]

Due to its importance in glucose reabsorption, SGLT2 was identified as a promising pharmacological target in T2DM.[19] Phlorizin, a naturally occurring non-selective competitive SGLT2 inhibitor found in the bark of the apple tree, was used as a starting point for the development of several new synthetic analogues.[20] These new drugs were found to be highly selective for SGLT2, causing a sustained increase in urinary glucose excretion of about 60–80 g/day.[16,21] Importantly, currently available SGLT2 inhibitors, unlike phlorizin, all have relatively long (>12 h) half-lives and are bioavailable when taken orally.[22] The increased glucose excretion caused by SGLT2 inhibition provides a sustained blood glucose-lowering effect which is independent of insulin, a contrast to many other antihyperglycemic therapies.[16]

### HFrEF outcomes with SGLT2 inhibition: trial evidence

All four currently available SGLT2 inhibitors on the US market (Table 1) have completed or have in-process cardiovascular outcomes trial (CVOT) data available, although not often in populations with HFrEF specifically (Table 2).

Empagliflozin was shown to have beneficial effects on hemoglobin A1c, blood pressure, and body weight, and was approved[25] as an antihyperglycemic in 2014.[35,36] As per regulatory mandate for all new diabetes drugs,[37] a CVOT was undertaken. This trial, EMPA-REG OUTCOME, showed a significantly reduced combined cardiovascular endpoint in high cardiovascular risk patients with T2DM taking empagliflozin, including a remarkable 38% relative risk reduction in all-cause cardiovascular mortality and 35% relative risk reduction in heart failure hospitalization.[26]

**Table 1.** Comparison of approved SGLT2 inhibitors in the US.

| Drug (US trade name), approval year | Dose range | High level cardiovascular outcome trial evidence | Current indications | Use considerations |
|---|---|---|---|---|
| Canagliflozin (Invokana), 2013[23] | 100 mg with breakfast, may increase to 300 mg with breakfast if eGFR >60 mL/min/1.73 m² | CANVAS[24] | • To reduce risk of major cardiovascular events in patients with T2DM and cardiovascular disease<br>• To reduce risk of worsening kidney function, cardiovascular death, and hospitalization for heart failure in patients with T2DM and albuminuria >300 mg/day | 65% oral bioavailability<br><br>Not recommended in severe hepatic impairment<br><br>Not recommended if eGFR <30 mL/min/1.73 m²<br><br>Black box warning for increased risk of amputation |
| Empagliflozin (Jardiance), 2014[25] | 10 mg daily, may increase to 25 mg if being used for glycemic control | EMPA-REG OUTCOME[26]<br><br><br>EMPEROR-Reduced*[27] | • To reduce risk of cardiovascular death in patients with T2DM and established cardiovascular disease | Should be discontinued if eGFR is persistently less than 45 mL/min/1.73 m² according to labeling; however only eGFR <20 mL/min/1.73 m² were excluded from EMPEROR-Reduced<br><br>May be used in hepatic impairment 78% bioavailable |
| Dapagliflozen (Farxiga), 2014[28] | 5 mg daily, may increase to 10 mg daily<br><br><br>Start at 10 mg daily for cardiovascular indications | DECLARE-TIMI 58†[29]<br><br><br><br>DAPA-HF*[30] | • To reduce risk of hospitalization for heart failure in adults with T2DM and established cardiovascular disease or risk factors<br>• To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA II–IV) | No dose adjustment in liver dysfunction, but understudied in severe hepatic impairment<br><br><br><br>Not recommended if eGFR <45 mL/min/1.73 m²; contraindicated if eGFR <35 mL/min/1.73 m² |
| Ertugliflozin (Steglatro), 2017[31] | 5 mg daily, may increase to 15 mg daily | VERTIS-CV (ongoing)[32] | None | 100% bioavailable. Not studied in severe hepatic impairment. Not recommended when eGFR is 30–60 mL/min/1.73 m²; contraindicated <30 mL/min/1.73 m² |

*CVOT primarily or completely enrolling HFrEF patients.
†CVOT with significant numbers of HFrEF patients, assessed at baseline.
CVOT, cardiovascular outcomes trial; GFR, glomerular filtration rate; NYHA, New York Heart Association functional class; T2DM, type 2 diabetes mellitus.

A secondary analysis of the EMPA-REG data showed that a high heart failure risk subgroup may have in fact fared even better than average, compared to all trial participants.[38] In EMPA-REG, 10.5% of participants had heart failure at baseline, but they were not phenotyped as preserved *versus* reduced ejection fraction.

EMPA-REG was considered a surprising result at the time, and there was considerable excitement to discover if these beneficial cardiovascular effects might be class wide. The first approved selective SGLT2 inhibitor in the US, canagliflozin,[23] had published results from its key CVOT (CANVAS) shortly thereafter, in 2017.

**Table 2.** Summary of notable forthcoming and existing randomized trial evidence of SGLT2 inhibitors in patients with HFrEF.

| Study | Drug | *N*, Population | Primary outcome | Comment |
|---|---|---|---|---|
| CHIEF-HF (NCT04252287) | Canagliflozin *versus* placebo | 1900, HFrEF or HFpEF, with or without T2DM | Change in Kansas City cardiomyopathy questionnaire at week 12 | Recruiting |
| EMPEROR-Reduced[33] | Empagliflozin *versus* placebo | 3730, HFrEF with or without T2DM | Improved risk of cardiovascular death or heart failure hospitalization [HR 0.75 (95% CI, 0.65–0.86)]; non-significant mortality benefit [HR 0.92 (95% CI 0.77–1.10)] | 10 mg daily dose, without titration |
| DECLARE-TIMI 58; HFrEF subgroup analysis[34] | Dapagliflozin *versus* placebo | 671, HFrEF and T2DM | Improved risk of cardiovascular death or heart failure hospitalization [HR 0.62 (95% CI 0.45–0.86)]; driven by mortality benefit [HR, 0.55 (95% CI 0.34–0.90)] | |
| DAPA-HF[30] | Dapagliflozin *versus* placebo | 4744, HFrEF with or without T2DM | Improved risk of cardiovascular death or heart failure hospitalization (HR 0.74; 95% CI 0.65–0.85) | 10 mg daily dose, without titration |

CI, confidence interval; HFpEF, heart failure with reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus.

In CANVAS, canagliflozin caused a 14% reduction in the combined cardiovascular events endpoint of cardiovascular death, myocardial infarction, or stroke over 3.6 years of follow-up.[24] Patients enrolled in CANVAS had T2DM and a history of cardiovascular disease or risk factors but were not selected for heart failure. Accordingly, only 14% of participants had a reported history of heart failure at enrollment, and ejection fraction was not assessed at baseline. In all participants, however, incident heart failure of both preserved and reduced ejection fraction types seemed to be attenuated by canagliflozin.[39,40] In a separate cohort focused on older adults, a beneficial effect of canagliflozin was also seen on plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP).[41]

Dapagliflozin is a similarly well-tolerated selective SGLT2 with beneficial effects on body weight,[42] glycemic control,[43] and blood pressure[1] in patients with T2DM. In DECLARE-TIMI 58 (published in 2019), patients with established cardiovascular disease or cardiovascular risk factors (including 10% with prevalent heart failure of any type) treated with dapagliflozin had no difference in rates of cardiovascular death, myocardial infarction, or ischemic stroke.[29] Yet, dapagliflozin-treated patients did have a 17% reduction in cardiovascular death or heart failure hospitalization, a finding driven by a 27% relative reduction in the risk of hospitalization for

heart failure. Unlike in previous SGLT2 CVOTs, patients' heart failure at baseline was assessed and categorized. Of 17,160 randomly assigned patients, 671 (3.9%) had prevalent HFrEF at baseline. Among these patients, the reduction in cardiovascular death or heart failure hospitalization was substantial: 38% relative risk reduction, driven by a 45% relative reduction in cardiovascular death.[34] Just as in EMPA-REG, in which a high heart failure risk subgroup showed evidence of differential benefit above and beyond the rest of the cohort, in DECLARE-TIMI 58, patients with HFrEF benefited more from SGLT2 inhibition than other patients in the study.

Based on the suspicion of benefit to patients with HFrEF irrespective of T2DM status, the DAPA-HF study was designed, and first results became available in 2019.[30] Enrolling 4744 patients with American College of Cardiology/American Heart Association stage C and D HFrEF, DAPA-HF found marked reductions in cardiovascular mortality and heart failure hospitalization, with a 26% absolute risk reduction for the combined endpoint and a 17% reduction in all-cause mortality. Although the trial did not require participants to have T2DM, 42% of participants had T2DM at baseline. Dapagliflozin was equally efficacious in patients with and without T2DM with respect to the prevention of cardiovascular death and heart failure

hospitalization.[44] Patients randomly assigned to dapagliflozin also had significant improvements in hematocrit, NT-proBNP, weight, and systolic blood pressure.

Most recently, the EMPEROR-Reduced trial enrolled 3730 symptomatic HFrEF patients randomly assigned to empagliflozin or placebo.[27] After a median of 16 months, empagliflozin showed a 25% reduction in combined cardiovascular death or heart failure hospitalization and an 8% reduction in all-cause mortality, although the latter was not statistically significant [hazard ratio (HR) 0.92, 95% confidence interval (CI) 0.77–1.10]. Like dapagliflozin in DAPA-HF, the beneficial effect of empagliflozin with respect to the primary outcome was independent of diabetes status.

For canagliflozin, while no CVOT analogous to DAPA-HF or EMPEROR-Reduced is yet underway, a placebo controlled trial assessing heart failure-related quality of life outcomes is currently being planned (CHIEF-HF, NCT04252287).

It is worth contemplating the size of the observed effect. The relative risk reduction in all-cause mortality of 17% for dapagliflozin compares to a 23% reduction for angiotensin-converting enzyme inhibitors *versus* placebo,[45] 34–65% reduction for beta-blockers *versus* placebo,[33,46] and 30% reduction for spironolactone *versus* placebo.[47] While the SGLT2 inhibitor effect size is slightly smaller, one might expect diminishing returns from each cumulative therapy.[48] Sacubitril-valsartan, for example, showed a similar 16% absolute mortality reduction over enalapril, and this finding has quickly changed guidelines and practice; should DAPA-HF and EMPEROR-Reduced be expected to do the same?[5,49]

### Comparison of individual agents in HFrEF

While all SGLT2 inhibitors appear to be safe and effective for treating T2DM in patients with HFrEF, the most important difference among the individual agents is the uneven evidence base for use of these drugs as heart failure-specific therapy. While intensive study in HFrEF is still underway, there is not yet evidence that benefit will be confined to only one member of this drug class (Table 2). It should be noted that canagliflozin, empagliflozin, and dapagliflozin have all been associated with marked reductions in heart failure hospitalization in their key CVOTs [HR 0.67

(95% CI 0.52–0.87), HR 0.65 (95% CI 0.50–0.85), and HR 0.73 (95% CI 0.61–0.88), respectively].[50] Secondary analysis of EMPA-REG OUTCOME has also suggested efficacy at primary prevention of heart failure,[38] leading to a new weak (IIb) recommendation for the use of SGLT2 inhibitors to prevent incident heart failure in at-risk patients with T2DM.[51] Interestingly, this recommendation was given to the class, rather than to a particular agent.

Ertugliflozin is the latest entrant in the class to be approved in the US.[31] As such, although it has demonstrated antihyperglycemic efficacy, there is the least amount of available evidence to assess its effects in a HFrEF population. The key CVOT (not HFrEF-specific) is the VERTIS-CV trial,[52] which does not yet have full results available to the scientific community. However, early reports from the sponsor have indicated that unlike the other agents in the class, there was no evidence of benefit on a combined cardiovascular outcome.[53]

### Proposed mechanisms of efficacy

Several novel mechanisms have been proposed for the apparent beneficial effect of SGLT2 inhibition on heart failure.[54] It is likely that SGLT2 inhibition has pleotropic effects on myriad physiological systems in HFrEF. A full accounting of the processes involved has yet to be fully understood.[55]

The most convincing proof that SGLT2 inhibition has a beneficial effect on HFrEF outcomes independent of the anti-hyperglycemic effect comes from a secondary analysis of DAPA-HF. In this analysis, patients with and without T2DM had remarkably consistent reductions in the combined efficacy endpoint of cardiovascular death or heart failure hospitalization: HR 0.74 (95% CI 0.59–0.94) *versus* 0.67 (95% CI 0.47–0.96), respectively (interaction *p*-value 0.72).[44] Subjects with and without T2DM taking dapagliflozin had similar reductions in weight, blood pressure, and NT-proBNP. However, patients without T2DM had no reduction in hemoglobin A1c on dapagliflozin *versus* placebo. Even in patients with T2DM, the reduction in hemoglobin A1c on study drug was only modest (−0.2%). Furthermore, study of the outcomes curves in DAPA-HF shows an early separation of the curves. This suggests a time course of action too short to be mediated by anti-hyperglycemic effect.

One hypothesized mechanism of efficacy is prevention of heart failure decompensation by osmotic diuresis. In particular, unlike loop diuretics which tend to worsen the glomerular filtration rate (GFR) over the long term, SGLT2 inhibition is associated with a renal protective effect, especially in those with diabetic nephropathy and albuminuria.[56,57] On the other hand, SGLT2-effected diuresis is typically mild, in the order of 300 mL per 24 h.[16] Perhaps this osmotically mediated diuresis is more physiologically favorable than fluid loss from loop diuretics, but this is conjecture.[58]

SGLT2 inhibition has been shown to improve body weight, blood pressure, and arterial stiffness.[16,32,59] This may decrease afterload and thus cardiac workload and myocardial oxygen ($O_2$) consumption. Changes in arterial stiffness associated with SGLT2 inhibitors may not be just a decreased blood volume effect; an analysis of patients taking empagliflozin suggested that patients with the most marked change in markers of vascular stiffness also had the greatest reductions in high-sensitivity C-reactive protein, suggesting an anti-inflammatory mechanism.[60] Other anti-inflammatory effects have been observed as well.[61]

A sodium hypothesis has also emerged. This suggests that SGLT2 inhibitor-derived natriuresis, combined with inhibition of the sarcolemmal $Na+/H+$ exchanger, decreases pathologically elevated intracellular sodium content in HFrEF. This improves mitochondrial calcium handling and perhaps myocyte function.[62–64] A related, intriguing observation is the reversal by empagliflozin of myocyte damage and dysfunction induced by direct hyperglycemic effects in cell culture.[65] However, this would not explain the benefit of SGLT2 inhibitors in HFrEF patients without T2DM. Still, patients without T2DM have altered and dysfunctional myocyte metabolism in HFrEF, which may affect energetics and subsequently myocyte performance. A metabolic shift away from free fatty acids and towards more energy efficient β-hydroxybutyrate has been described in patients taking SGLT2 inhibitors.[66]

### Adverse events

The four currently available SGLT2 inhibitors on the US market (canagliflozin, empagliflozin, dapagliflozin, and ertugliflozin) are similar with respect to half-life and are all orally bioavailable.

Adverse events are mostly common to all agents within the class. Most adverse events are secondary to the increased glucosuria, which may lead to hypovolumia due to osmotic diuresis as well as genitourinary infections, including mycotic infections. Quantitative data from the three pivotal CVOTs plus DAPA-HF suggest that canagliflozin, empagliflozin, and dapagliflozin are well tolerated overall. Despite the theoretical risk of urinary tract infection, rates were actually similar between active drug and placebo in many of the trials.[24,26,30,34] Hypovolemia was more frequent among patients taking canagliflozin in CANVAS, occurring at a rate of 26 per 1000 patient-years, compared to 19 per 1000 patient-years with placebo. Mycotic genital infection, especially in women, occurred in patients taking SGLT2 inhibitors at a rate four to eight times that of patients taking placebo across CANVAS, EMPA-REG, DECLARE, and DAPA-HF. However, the infections were rarely serious, and <1% required discontinuation of study drug.

As of 2018, there is a US Food and Drug Administration (FDA) warning about the possible risk of Fournier's gangrene due to post-marketing reports of this serious complication in patients on SGLT2 inhibitor therapy.[67] However, across DECLARE-TIMI 58 and DAPA-HF, the incidence of Fournier's was one in 10,955 total patients in the dapagliflozin inhibitor group and six in 10,949 in the placebo group. EMPEROR-Reduced reported only the rate of serious genital infection, not Fournier's specifically, which occurred in 6/1863 in the empagliflozin group and 5/1863 in the placebo group. No cases of Fournier's were reported in EMPA-REG or CANVAS, but Fournier's was not a prespecified adverse event in either trial.

In CANVAS, patients taking canagliflozin had an almost two-fold increase in risk of amputation, 6.3 *versus* 3.4 per 1000 patient-years. Of these, about two-thirds were minor amputations at the level of the toe or transmetatarsal; however, major amputations at the level of the ankle or above were also increased two-fold in the canagliflozin group. Re-analysis of other SGLT2 inhibitor randomized trials, as well as study of non-randomized data, has shown inconsistent evidence for this heightened risk of amputation in canagliflozin and little sustained evidence in the other SGLT2 inhibitors.[68] The canagliflozin label carries a 'black box' warning alerting the prescriber to consider

avoidance of canagliflozin in patients with a history of prior amputation, peripheral vascular disease, neuropathy, or diabetic foot ulcers.[23]

Although uncommon, clinicians need to be aware of the risk of ketoacidosis, particularly euglycemic ketoacidosis, which may occur with use of SGLT2 inhibitors. The mechanism is not fully understood, but probably occurs in the setting of significant mismatch between insulin supply and demand.[69,70] Reported triggers include inappropriate discontinuation of insulin, surgery, severe dehydration, or metabolic stress. The presentation may be more subtle than classic diabetic ketoacidosis, as acidosis can develop in the absence of hyperglycemia. It is not yet clear if ketoacidosis may develop in non-diabetic HFrEF patients on SGLT2 inhibitors. In DAPA-HF and EMPEROR-Reduced, 3/4236 patients taking SGLT2 inhibitors developed ketoacidosis, while 0/4234 taking placebo did. Data are not available on whether those three patients who developed ketoacidosis in the active arm had a history of diabetes or were taking other antihyperglycemic therapy. No formal guidelines exist, but SGLT2 inhibitors should probably be held 2–3 days prior to major surgery to avoid the risk of ketoacidosis.

## The prescribing and regulatory landscape

While an absolute mortality benefit for the use of SGLT2 inhibitors in HFrEF was only seen in one randomized trial (DAPA-HF), the enthusiasm for these agents is understandable given the supporting evidence of benefit in EMPEROR-Reduced and the HFrEF plus T2DM subgroup analysis in DECLARE-TIMI 58. A benefit is also supported by the lower rate of heart failure hospitalization among T2DM patients taking canagliflozin, empagliflozin, and dapagliflozin in the key CVOTs, as well as the basic science and mechanistic studies summarized above. As of this writing, the US FDA has granted heart failure-specific indications to dapagliflozin to reduce the risk of cardiovascular death and hospitalization for heart failure in HFrEF and to reduce heart failure hospitalization in patients with T2DM and established cardiovascular disease or risk factors.[28] The FDA has also approved canagliflozin for reduced heart failure hospitalization in patients with T2DM and albuminuria.[23] Current use of SGLT2 inhibitors other than dapagliflozin to treat unselected non-diabetic HFrEF patients to prevent hospitalization or death is off-label in the US.

These drugs are also new and remain on patent. The patient-facing website GoodRx.com reports that copays for SGLT2 inhibitors range from less than US$10 to almost US$600 monthly.[71] Canagliflozin, empagliflozin, and dapagliflozin are mostly covered by the large national pharmacy benefit managers—entities that contract with commercial insurance providers and effectively determine the plan's formulary—however, various levels of 'step therapy' may be required.[72] The availability of these drugs to patients with public insurance is improving as well.[73]

## Current state of SGLT2 inhibitors in guidelines

In 2016, the European Society of Cardiology heart failure guideline recommended consideration of empagliflozin in patients with T2DM to prevent or delay the onset of heart failure or prolong life.[74] In the 2019 guideline update, the society added a suggestion for consideration of canagliflozin or dapagliflozin in patients with T2DM and either established cardiovascular disease or risk factors to prevent or delay the onset of heart failure hospitalizations. No specific recommendation was made for patients with established heart failure, including HFrEF.[75] The most recent American College of Cardiology/American Heart Association HFrEF guideline update, in 2017, does not include SGLT2 inhibitor recommendations.[6]

The next full European and US guidelines are expected in 2021 and 2022, respectively, at which point a recommendation may be issued about the use of SGLT2 inhibitors in a general HFrEF population. As of 2020, the American Diabetes Association now recommends an SGLT2 inhibitor for patients with T2DM and any cardiovascular disease (including heart failure) after initial therapy of diet and lifestyle changes plus metformin.[76] Co-equal status is given to glucagon-like peptide 1 receptor agonists with demonstrated cardiovascular disease benefit as an alternative to SGLT2 inhibitors. This may be expected to change if HFrEF-specific recommendations are made in the future.

## SGLT2 inhibitors in clinical practice

Consideration of the specific patient population included in the trial literature is always an important concern when translating study outcomes into real-world practice. 'Will my patient benefit from this therapy?' and 'Is my patient reflective

of the types of patients included in the literature?' are two related but distinct questions. Clinicians familiar with PARADIGM-HF, the trial that led to the approval of sacubitril-valsartan, will notice much similarity in the inclusion criteria for DAPA-HF. In both cases, patients were required to have an ejection fraction <40%, New York Heart Association class II–IV symptoms, a plasma NT-proBNP level of ≥600 pg/mL (or ≥400 pg/mL if hospitalized within the preceding 12 months), and an estimated GFR ≥30 ml/min$^{-1}$/1.73 m$^{-2}$. Due to the distribution of international study sites, the DAPA-HF study cohort was underrepresentative of blacks (4.6%) and overrepresentative of Asians (23.5%) compared to the American population. Patients were generally on good guideline-directed medical therapy, with uptake of RAS inhibitors, beta-blockers, and mineralocorticoid receptor antagonists of 94%, 96%, and 71%, respectively. Thus, patients in DAPA-HF are reasonably similar to patients with HFrEF probably encountered in routine practice. Answering the first question, of universal benefit, is more difficult, but so far there is no suggestion that there is a differential response to therapy among patients of different HFrEF etiologies or T2DM risk status.

Patient selection is important in deciding in whom to start therapy. Appropriate candidates include those with or without T2DM and GFR ≥30 ml/min$^{-1}$/1.73 m$^{-2}$; however, the GFR cut-off for inclusion into EMPEROR-Reduced was ≥20 ml/min$^{-1}$/1.73 m$^{-2}$. Significant peripheral arterial disease or risk factors for limb amputation should be considered relative contraindications for canagliflozin and perhaps the class as a whole. Patients without T2DM may be preferentially considered for treatment with either dapagliflozin or empagliflozin; patients with T2DM can be considered for treatment with canagliflozin, empagliflozin, or dapagliflozin.

Patients should be cautioned about the common side effects, especially the most frequent two: volume depletion and urogenital mycotic infection. For patients already taking a loop diuretic, it is reasonable to consider reduction in the dose of the diuretic when starting the SGLT2 inhibitor. However, in most cases, we do not typically adjust the diuretic dose prospectively, but instead warn the patient to be aware of signs of volume depletion such as orthostasis. For most urogenital infections, appropriate anti-microbial therapy is effective and the SGLT2 inhibitor does not have

to be discontinued. Recurrent infections should prompt re-evaluation and/or specialist care. In patients taking insulin at baseline, multidisciplinary coordination with the patient's endocrinologist or primary care physician prior to starting an SGLT2 inhibitor is prudent.

It is notable that in DAPA-HF, all patients randomly assigned to dapagliflozin were started at 'full dose'—10 mg daily. EMPEROR-Reduced used a dose of 10 mg daily of empagliflozin, without escalation up to the maximum dose of 25 mg used in glycemic control. Thus, for either dapagliflozin or empagliflozin, a dose of 10 mg daily without titration is likely to be appropriate as long as it is tolerated.

At the present time, there is no evidence-based approach to guide stepwise introduction of SGLT2 inhibitor therapy into a patient's drug regimen. One reasonable and practical approach would be to imitate the conditions of DAPA-HF or EMPEROR-Reduced by adding an SGLT2 inhibitor on top of a maximally tolerated RAS inhibitor, beta-blocker, and mineralocorticoid antagonist. Some conditions that warrant earlier consideration of SGLT2 inhibitor initiation might include diabetes patients who are in need of improved glycemic control or with proteinuria, patients who desire weight loss, or patients unable to escalate traditional HFrEF therapies due to hyperkalemia or hypotension. Of note, in DAPA-HF, treatment with dapagliflozin led to a decrease in systolic blood pressure of only 1.3 mmHg compared with placebo.

## Conclusions

SGLT2 inhibitors represent a relatively new class of antihyperglycemic agent that has shown considerable evidence for benefit in HFrEF patients with and without T2DM. High-level outcomes data are available only for dapagliflozin, showing treatment effects comparable to current guideline-directed medical therapy agents for HFrEF. Emerging clinical and basic science data add support to the hypothesis that SGLT2 inhibitors may become important disease-modifying therapy in HFrEF. Currently, heart failure specialists and others hoping to use SGLT2 inhibitors to treat HFrEF patients should be aware that these drugs lack federal approval to treat HFrEF, are not yet covered by current professional society guidelines, and face an uncertain payor landscape. However, it seems likely that familiarity and comfort with

SGLT2 inhibitors will become an important tool in the repertoire of clinicians caring for this vulnerable patient population.

## Conflict of interest statement

## ORCID iDs
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