ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 2239–2248
Published online 1 June 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14005

REVIEW

Promise of sodium–glucose co-transporter-2 inhibitors in heart failure with mildly reduced ejection fraction

Xizi Shen[1] and Xingping Shen[2]*

[1]*Faculty of Medicine, The University of Queensland, Brisbane, Australia; and* [2]*Department of Endocrinology, Zhongshan Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China*

Abstract

Heart failure with mildly reduced ejection fraction (HFmrEF) is associated with comparable poor outcomes as other subtypes of heart failure and remains a medical unmet need due to the paucity of effective therapies. According to large cardiovascular (CV) outcome trials in patients with heart failure, sodium–glucose co-transporter-2 inhibitors (SGLT2is) reduce CV mortality and hospitalizations for heart failure in patients with heart failure across the spectrum of left ventricular ejection fraction (LVEF). There has been a lack of dedicated trials in HFmrEF. However, several large outcome trials in heart failure that enrolled patients with HFmrEF could provide a hint on the role of SGLT2is in this subgroup. This review focuses on CV effects of three major SGLT2is—dapagliflozin, empagliflozin, and sotagliflozin—in patients with HFmrEF. A narrative review of trials investigating the efficacy of each medication in treating heart failure with LVEF $>$ 40% is provided with a focus on their LVEF subgroup analyses. The purpose of this review is to discuss the current state of evidence regarding the potential of SGLT2is in HFmrEF management. Current limited evidence suggests that SGLT2is might be a favourable treatment modality for patients with HFmrEF to reduce hospitalization for heart failure and CV mortality. This conclusion needs to be further supported by clear HFmrEF subgroup analysis of the existing trials. Further outcome trials involving sufficient patients with different subtypes of HFmrEF are needed to confirm and assess CV benefits of SGLT2is in HFmrEF. Possible mechanisms by which SGLT2is exert their cardioprotective effect are also described briefly.

Keywords Sodium-glucose co-transporter-2 inhibitors (SGLT2is); Heart failure with mildly reduced ejection fraction (HFmrEF); Empagliflozin; Sotagliflozin; Dapagliflozin

Received: 8 February 2022; Revised: 14 May 2022; Accepted: 19 May 2022
**Correspondence to: Xingping Shen, Department of Endocrinology, Zhongshan Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China.*
Email: sxpsxzlg@qq.com

Background

Heart failure (HF) is a progressive clinical syndrome that directly results from abnormal cardiac function and/or structure, leading to inadequate cardiac output at rest and/or during exercise.[1] It has become a global pandemic with considerable morbidity and mortality,[1] requiring enormous healthcare expenditure.[2] It is estimated that 26 million adults worldwide live with HF[3] and 1–2% of adults in developed countries are affected.[4] The prevalence of HF is increasing rapidly[5] owing to the ageing population and increased survival after myocardial infarction.[6–9] Despite the improvements in HF therapies, the prognosis for patients diagnosed with the disease remains poor.[2] HF has become the leading cause of hospitalization among adults of multiple nations, with the 1-year mortality of 10–35%.[10,11] In the USA, the total costs for HF were estimated to be US $30.7 billion in 2012 and are projected to increase by 27% by 2030.[5]

HF can be broadly classified on the basis of whether the left ventricular ejection fraction (LVEF) is reduced (≤40%), preserved (≥50%), or mildly reduced (41–49%).[1] Heart failure with mid-range ejection fraction (HFmrEF) is a new category introduced by the European Society of Cardiology (ESC) Heart Failure guideline in 2016 to foster research of this entity.[12] This is because HFmrEF accounts for 20% of all cases of HF.[13] These patients experience comparable poor outcomes with those with HF with reduced (HFrEF) or preserved LVEF (HFpEF), but there is a paucity of effective therapies for such

© 2022 The Authors. ESC Heart Failure published by John Wiley & Sons Ltd on behalf of European Society of Cardiology.
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

cases.[3] It is thus essential to identify effective and safe therapies for this patient group.

There have been great improvements in pharmacological therapies for HFrEF. Four classes of disease-modifying therapies are now recommended in clinical guidelines as the new backbone of HFrEF therapies, and they include angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs) or angiotensin receptor neprilysin inhibitors (ARNis), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium–glucose transport protein 2 inhibitors (SGLT2is).[1] In contrast, there has been far less progress in the pharmacological treatment for patients with HFmrEF, making HFmrEF an unmet medical need. Although the use of sacubitril/valsartan has recently been extended to treat HFmrEF in the USA,[14] the drug therapies in the European Union are still limited to diuretics for symptom control owing to a lack of published evidence that demonstrates a clear mortality benefit in HFmrEF.[1]

The HFmrEF phenotype has been described as an intermediate between HFrEF and HFpEF, given the presence of both cardiac stretch and inflammation[15] as well as the mixed left ventricular dysfunction.[16] However, the similarities in clinical characteristics and treatment response between HFrEF and HFmrEF engender the potential for shared treatments. Similar to HFrEF, HFmrEF is more common in older adults, a population with co-morbidities and frailty.[17] Co-morbidities, particularly diabetes mellites, ischaemic heart disease, and chronic kidney disease, are common in both of the HF subgroups.[17] Furthermore, subgroup analyses of several randomized controlled trials (RCTs) in HF have shown that patients with HFmrEF respond to the same treatments as those with HFrEF; these treatments include beta blockers,[18] candesartan,[19] spironolactone,[20] sacubitril/valsartan,[21] and empagliflozin.[22]

In fact, in clinical practice, HFrEF medications have frequently been used in the setting of HFmrEF perhaps because of their effects on managing those common comorbidities.[17,23] Because LVEF is a dynamic parameter that either improves from HFrEF or deteriorates from HFpEF, the clinical benefit of HFrEF therapies in patients with HFmrEF can be due to the fact that some patients with HFrEF continue their treatment even while their LVEF has improved to above 40%.[17,24–28]

Among the HFrEF medications, SGLT2is have recently gained an increasing attention in treating HF due to their cardiorenal protection across HFrEF, HFmrEF, and HFpEF alongside their anti-hyperglycaemic action. SGLT2is were initially used exclusively in patients with diabetes due to their insulin-independent reduction effect on blood glucose concentration.[29] All SGLT2is have a dual-receptor binding affinity for primarily renal-expressed SGLT1 and primarily intestinally expressed SGLT2 with varying SGLT2 over SGLT1 selectivity; for instance, 2680-fold for empagliflozin, 1242-fold for dapagliflozin, and 20-fold for sotagliflozin.[30,31] SGLT2 inhibition enhances renal glucose excretion, whereas SGLT1 inhibition delays post-prandial intestinal absorption of glucose by stimulating a sustained increase in glucagon-like peptide 1 (GLP-1) and GIP[32,33]; this consequently makes SGLT2is successful anti-diabetic agents.[34]

However, the benefits of SGLT2is have extended beyond glycaemic control to decreasing body weight and blood pressure, preventing HF and other cardiovascular (CV) events, and reducing mortality.[35] The striking CV mortality benefits of SGLT2is were found in patients with diabetes enrolled in several pioneering RCTs, such as EMPA-REG OUTCOME trial, CANVAS trial, and DECLARE-TIMI58 trial.[36,37] In contrast, VERTIS-CV trial reported no CV benefits of ertugliflozin in patients with diabetes.[38] The promising effects of the majority of SGLT2is have sparked a series of studies to evaluate the efficacy and safety of SGLT2is in patients with HF. Specifically, DAPA-HF,[39] SOLOIST WHF,[40] and EMPEROR-reduced trials[41] have shown the efficacy of dapagliflozin, sotagliflozin, and empagliflozin, respectively, in reducing hospitalizations for heart failure (HHF) and death from a CV cause in patients with HFrEF in the ambulatory setting. The efficacy of SGLT2is in HFrEF also elicits great expectations for their potential role in HF with higher LVEF. In parallel, SGLT2is also have a renal-protective effect, which makes their use in patients with HFmrEF more appealing given the high prevalence of cardio-renal syndrome and chronic kidney disease in this population.[42] Many CV outcome trials reported a delayed decrease in glomerular filtration rate, less progression to macroalbuminuria, and a 30% reduction in the risk of developing severe renal events in patients with diabetes.[43]

Furthermore, the unique mechanism of action might give SGLT2is an advantage over other HF agents with respect to efficacy and safety. Some of the mechanisms by which SGLT2is exert their effects in HFrEF appear to be beneficial in HFmrEF. They reduce cardiac volume,[44] reverse ventricular remodelling,[45] and reduce epicardial accumulation of adipose tissue,[46] all of which are mechanistic factors associated with HF with higher LVEF. Moreover, among the aforementioned four classes of HFrEF therapies, SGLT2is are the only non-neurohormonal modulators, which may be safer and more effective in patients with HFmrEF. For instance, the vasodilating effect caused by the neurohormonal HF agents is beneficial in HFrEF but may lead to greater reduction in blood pressure in patients with higher LVEF.[47] In addition, several studies observed a reduction in efficacy of neurohormonal modulators with increasing LVEF,[19–21,48] whereas RCTs with SGLT2is reported consistent CV benefits across the LVEF spectrum.[40,49,50]

Despite the lack of published evidence from dedicated RCTs for HFmrEF, many large-scale trials in HFpEF enrolled patients with HFmrEF and reported a consistent treatment effect of SGLT2is in this subgroup. Additionally, although the HFmrEF subgroup has not been analysed separately in those trials, the subgroup analysis of HF patients with

LVEF > 40% could still provide a hint on the potential of SGLT2is for the treatment of HFmrEF. This review focuses on the primary CV outcomes of three major SGLT2is in patients with HFmrEF. A narrative review of trials investigating the efficacy of each medication in treating HF with LVEF > 40% is provided, with a focus on their subgroup analyses that include HFmrEF patients. The purpose of this review is to discuss the current state of evidence with respect to the role of four SGLT2is in HFmrEF management.

Current clinical guidelines

To optimize HF management, dapagliflozin and empagliflozin have been added to the evidence-based guideline-directed medical therapy for HFrEF.[51] SGLT2is have been recommended as a core therapy for all patients with HF in the latest consensus document of the Heart Failure Association of the European Society of Cardiology (ESC).[52] However, the 2021 ESC clinical guideline has not yet included SGLT2is as the Class I and II recommendation for treatment of HFmrEF.[1] In early 2022, the US Food and Drug Administration[53] and the European Medicines Agency[54] approved the use of empagliflozin for all patients with HF regardless the value of LVEF. These breakthrough approvals have made empagliflozin a treatment option for patients with HFmrEF.

Therapeutic efficacy of dapagliflozin in HFmrEF

The CV benefits were first reported in a DECLARE-TIMI 58 trial. Specifically, 10 mg dapagliflozin daily reduced HHF in patients with Type 2 diabetes mellitus (T2DM) who were at risk of atherosclerotic CV disease (hazard ratio [HR], 0.73; 95% CI, 0.61–0.88).[55] Subsequently, the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial specifically investigated dapagliflozin in the context of HFrEF. The study found that 10 mg/day dapagliflozin led to a significant reduction in CV death (HR, 0.82; 95% CI, 0.69–0.98), HHF (HR, 0.70; 95% CI, 0.59–0.83), and renal composite outcome (HR, 0.71; 95% CI, 0.44–1.16) in patients with HFrEF regardless of comorbid diabetes or baseline HF therapies. Although these results support the recent approval of dapagliflozin in the USA[56] and the European Union[57] for treating HFrEF, the use of dapagliflozin in HFmrEF has not yet been approved due to inadequate evidence. However, subgroup analyses for LVEF > 40% in several RCTs provide a hint on the potential therapeutic efficacy of dapagliflozin in patients with HFmrEF.

PRESERVED-HF trial[58]

The Dapagliflozin in Preserved Ejection Fraction Heart Failure (PRESERVED-HF) trial, a multicentre RCT, was conducted at multiple sites in the USA, and revealed a promising effect of 10 mg dapagliflozin in HFmrEF. The study reported that a short course of dapagliflozin was well tolerated in HF with LVEF > 45% and significantly improved patient-reported symptoms associated with HF, walking limits, and exercise function. The primary endpoint was the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CS), which measured a self-reported HF-related health status. A total of 324 patients with LVEF > 45% (median LVED, 60% [55%, 65%]) were randomized to receive 12 weeks of 10 mg/day dapagliflozin or placebo. Dapagliflozin significantly increased KCCQ-CS at 12 weeks by 5.8 points (95% CI, 2.3–9.2; P = 0.001) (49.4% vs. 38.2%; adjusted OR, 1.64 (95% CI, 0.98–2.75); P = 0.06), as a result of the improvements in KCCQ total symptom score (KCCQ-TS) by 5.8 points (95% CI, 2.0–9.6; P = 0.003) and physical limit scores by 5.3 points (95% CI, 0.7–10.0; P = 0.026). Also, dapagliflozin improved the results of 6-min walk test with a mean effect size of 20.1 m (95% CI, 5.6–34.7; P = 0.007) and promoted weight loss (mean effect size, 0.72 kg) (95% CI, 0.01–1.42; P = 0.046). The magnitude of treatment effect was also clinically meaningful and consistent in patients with 45% < LVEF < 60% and with or without diabetes. In terms of safety, there was no significant difference in adverse events between the dapagliflozin group (27.2%) and the placebo group (23.5%). Although this trial enrolled only a part of patients with HFmrEF (45% < LVEF < 49%), it was the first trial to show that a short course of dapagliflozin treatment may improve self-reported health status (consisting of symptoms, functional status, and quality of life) and objectively measured physical function in this population. Additionally, this benefit of dapagliflozin was not seen in empagliflozin, given that the EMPERIAL-PRESERVED trial, which tested empagliflozin in patients with HFpEF,[59] reported nonsignificant improvements in KCCQ-CS and 6-min walk test distance with empagliflozin treatment. Thus, further evidence is needed to determine whether the observed discrepancy was due to the differences in baseline characteristics of patients in these trials or due to the pharmacodynamic differences between empagliflozin and dapagliflozin.

DELIVER trial[50]

The ongoing Phase III, randomized Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction HF (DELIVER) trial will soon close a number of gaps in knowledge. The recruitment was completed in January 2021 with 6263 patients with NYHA Class II–IV HF and

DOI: 10.1002/ehf2.14005

LVEF > 40%, including a fair number of patients with HFmrEF and patients with HFrEF previously, at 353 sites in 20 countries. This allows for two important subgroups of HFmrEF to be studied in this trial—patients with HFmrEF at the time of diagnosis and patients who had improved from HFrEF. The primary outcome will be a composite of CV death, HHF, and urgent HF-related care visits (requiring intravenous diuretic therapy), which will help to determine whether the CV benefits of dapagliflozin in HFrEF can be extended to HFmrEF. Furthermore, the findings can complement the DAPA-HF trial; pooled analysis can be conducted to test whether the CV benefits of dapagliflozin are dependent on LVEF range. Also, changes in the number of urgent care visits for HF will indicate the role of SGLT2is in promoting outpatient management of worsening HF in patients with HFmrEF, which is clinically meaningful given the current trend in care delivery and patient preferences.

Therapeutic efficacy of empagliflozin in HFmrEF

A recently published subgroup analysis of the landmark EMPA-REG OUTCOME trial has supported the great promise of empagliflozin for treating patients with HFmrEF.[22] In the EMPA-REG OUTCOME trial, which reported the efficacy of empagliflozin in diabetes patients with and without a history of HF,[60] no LVEF data were collected. Thus, a validated ejection fraction predictive model was applied to the subpopulation with HF to determine the association between the treatment effect and LVEF.[22] The model was based on the participants' characteristics and the received treatment to estimate their types of LVEF. Cox regression was used subsequently to compare the effect of empagliflozin on HHF, CV mortality, and all-cause death in patients with no HF, with predicted HFrEF/HFmrEF (LVEF <50%), and with predicted HFpEF.[60] Approximately 10% (*n* = 687) of patients with diabetes who were enrolled in the EMPA-REG OUTCOME trial (*n* = 7001) had a history of HF; 69.7% of them (*n* = 479) were predicted to have HFmrEF/HFrEF and 30.3% (*n* = 208) to have HFpEF.[60] Over a median follow-up of 3.1 years, empagliflozin was shown to be effective in reducing the risk of the primary composite outcome of CV death or HHF, the risk of CV death and HHF individually, and the risk of all-cause death in patients with T2DM and HF regardless of the predicted LVEF.[60] Such benefits were consistent in non-HF (HR, 0.63; 95% CI, 0.50–0.78), predicted HFpEF (HR, 0.60; 95% CI, 0.31–1.17), and HFmrEF/HFrEF (HR, 0.79; 95% CI, 0.51–1.23) (*P* interaction = 0.62). These findings are consistent with the more recent EMPEROR-Preserved trial, which investigated the role of empagliflozin in treating HFmrEF and HFpEF.

EMPEROR-Preserved trial[49]

The double-blind EMPEROR-Preserved trial was the first trial to evaluate the efficacy and safety of empagliflozin in patients with HFmrEF and HFpEF who may or may not have had DM. A total of 5988 patients (mean age, 71 years) with NYHA II–IV HF and LVEF greater than 40% at 622 sites across 23 countries were enrolled; one-third of patients had HFmrEF. Patients were randomized to receive 10 mg empagliflozin once daily (*n* = 2997) or placebo (*n* = 2991). Over a median follow-up of 26.2 months, the incidence of overall primary composite outcome (HHF or CV death) was 13.8% in the empagliflozin group, which was significantly lower than that in the placebo group (17.1%) (HR, 0.79; 95% CI, 0.69–0.90; $P < 0.001$). This favourable effect was driven by a 29% lower risk of HHF with empagliflozin, which was similar to the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-Reduced) trial.[41] Furthermore, the subgroup analysis demonstrated that the HHF benefit was consistent regardless of LVEF and co-morbid diabetes. However, there was heterogeneity in the treatment effects for HHF in patients with a baseline LVEF ≥ 60% (HR 1.06), 40% < LVEF<50% (HR 0.57), and 50% < LVEF <60% (HR 0.66) (*P* trend = 0.008), suggesting a possible decrement of HHF benefit in patients with a higher LVEF.[41] Similar attenuated response has also been reported in a separate analysis published more recently by the EMPEROR-PRESERVED researchers. The analyses showed a significant reduction in the incidence of inpatient and outpatient worsening HF events (defined as CV death, HHF, or urgent care visit for HF) in the empagliflozin group in comparison with the placebo group (432 vs. 546; HR 0.77; 95% CI, 0.67–0.87); this benefit was consistent across the spectrum of LVEF.[61] However, there appeared to be an interaction between LVEF and the magnitude of treatment effect on total (first and recurrent) HHF (*P* trend = 0.008) and on all CV hospitalizations (*P* trend = 0.02). Specifically, the favourable effect on total HHF was similar in patients with HFmrEF and those with HF with LVEF between 50 and 60%, but was attenuated in patients with LVEF ≥ 60%.[61] This appears to be an important point as the largest benefits on the primary composite outcome were observed for LVEF 40–50%, implying that empagliflozin might be more beneficial for patients with HFmrEF than for those with HFpEF, particularly with LVEF ≥ 60%. However, further analyses and studies specifying patients' LVEF range are warranted for clarification.

In contrast, not much improvement in CV mortality was seen with empagliflozin therapy in the setting of HFmrEF and HFpEF. A numerical, but not statistically significant, reduction (9%) in CV mortality (HR, 0.91; 95% CI, 0.67–1.09) was observed in this trial, and the effect on death of any cause was neutral (HR, 1.00; 95% CI, 0.87–1.15). Similarly, in the EMPEROR-Reduced trial, empagliflozin did not significantly reduce CV mortality in patients with HFrEF.[41] However,

a meta-analysis combining data from the EMPEROR-Reduced trial and the DAPA-HF trial reported that dapagliflozin significantly reduced CV death in HFrEF,[39] and reported no heterogeneity in the treatment effect of these two SGLT2is on CV death in the context of HFrEF.[62] Similar analysis could be conducted combining the findings of the DELIVER and EMPEROR-Preserved trials to test whether such a pattern of treatment effect also exists in the setting HFmrEF.

With respect to safety, uncomplicated genitourinary tract infections and hypotension were more common with empagliflozin therapy, but no significant difference in serious adverse events was observed in the trial.[49] However, empagliflozin appeared to have less renoprotective effect in patients with HFpEF and HFmrEF than in those with HFrEF, according to a pooled analysis of the results from the EMPEROR-Reduced and EMPEROR-Preserved trials.[41] Although the incidence of a primary endpoint event (a composite of major adverse renal outcomes, including sustained decreases in eGFR and renal replacement therapy) was small (2.8% in the empagliflozin group; 3.5% in the placebo group), the favourable effect of empagliflozin with respect to the renal primary outcome was significantly lower in the EMPEROR-Preserved trial (HR, 0.51; 95% CI, 0.33–0.79) than in the EMPEROR-Reduced trial (HR, 0.95; 95% CI, 0.73–1.24).[41] This implies that the renoprotective effect of empagliflozin may attenuate with higher LVEF and the use of empagliflozin in patients with HFmrEF may require additional caution. Also, given the aforementioned similar HHF benefit with empagliflozin in HF with LVEF $>$ 40% and $<$40%, renal protection may not be the main mechanism by which empagliflozin prevents HHF.

Therapeutic efficacy of sotagliflozin in HFmrEF

SOLOIST-WHF trial[40]

The double-blind, Phase III, Sotagliflozin in Patients with Diabetes and Recent Worsening HF (SOLOIST-WHF) trial was the first RCT that demonstrated the potential efficacy and safety of early initiation of sotagliflozin after an episode of decompensated HF with **mildly reduced** LVEF in patients with T2DM. Although not designed to test SGLT2is in HFmrEF as the primary hypothesis, the trial included patients hospitalized for HFmrEF who received intravenous diuretics. A total of 1,222 patients (mean age of 69 years) with T2DM who were stabilized after recent hospitalization for acute decompensated HF with a median LVEF of 35% at 306 sites in 32 countries were enrolled. Among the enrolled patients, 79.1% had LVEF of less than 50%, but the exact fraction of HFmrEF was not specified. Patients were randomized to receive sotagliflozin (n = 608) or placebo (n = 614). Sotagliflozin (200 mg daily) was initiated (with a target dose of 400 mg depending on side effects) either before discharge in 48.8% of the participants, or at a median of two days after discharge in 51.2% of the patients.

After a median follow-up of 9 months, the rate (the number of events per 100 patients-years) of the overall primary composite outcome, consisting of CV deaths, HHF, and urgent care visits for HF, was 51.0 in the sotagliflozin group versus 76.3 in the placebo group (HR, 0.67; 95% CI, 0.52–0.85; $P < 0.001$). However, when individual outcomes were assessed, sotagliflozin did not reach statistical significance in lowering the rate of CV death (10.6 in the sotagliflozin group vs. 12.5 in the placebo; HR, 0.84; 95% CI, 0.58–1.22); this may be ascribed to inadequate power of the trial due to loss of funding and early termination. However, the point estimate for CV death is consistent with a meta-analysis of all available SGLT2is that reported an approximately 30% decrease in CV death in patients with HF (HR, 0.83, 95% CI, 0.67–1.03; $P = 0.0924$).[63]

These benefits of sotagliflozin were consistent regardless of LVEF and the timing of the first dose. Although subgroup analysis suggested no interaction between the LVEF range and the treatment response, it is difficult to reliably estimate the treatment effect in patients with HFmrEF as the number of these patients was not specified in the trial. Furthermore, due to the early termination of the trial and the fact that only 20% of participants had LVEF $>$ 50%, more data are needed to draw a firm conclusion regarding the association between LVEF range and treatment effect of sotagliflozin.

Furthermore, the trial suggested that sotagliflozin performed almost equally well as the aforementioned selective SGLT2is performed in reducing CV death and HHF.[64] However, it remains uncertain in this trial whether the addition of SGLT1 blockade with sotagliflozin therapy could be an additional mechanism of cardioprotection that patients with HFmrEF would benefit from. Compared with other available SGLT2is, sotagliflozin provides greater inhibitory effect on SGLT1s, which are also found in human ventricular and atrial myocardium.[65,66] There are several advantages of SGLT1 inhibition. First, individuals with a decreased SGLT1 function (those with heterozygous missense variant of SLC5A1) exhibited reduced incidence rates of HF, mortality, and diabetes.[35] Second, knockdown of cardiac SGLT1 in mice was associated with improved ventricular dysfunction and myocardial hypertrophy, which are thought to play a pivotal role in HFmrEF.[67] However, more studies are required to reveal the molecular mechanisms underlying the cardiac benefits of dual SGLT inhibition. Also, to test whether there is any incremental value of SGLT1 inhibition aside from SGLT2 blockade in patients with HFmrEF, further direct comparative trials with selective SGLT2is are needed.

Mechanisms of cardioprotective effects

SGLT2is are novel anti-diabetic agents that do not depend on insulin secretion to improve glycaemic control. However, the CV benefits in HF cannot be explained only by the action of SGLT2is to lower blood glucose concentration. Similar effects have not been seen with other traditional hypoglycaemic agents, such as metformin, sulfonylureas, and dipeptidyl peptidase inhibitors, which have similar or greater anti-hyperglycaemic effects.[68] Although the exact mechanisms of the CV benefit remain uncertain, several unique mechanisms of SGLT2is focusing on the effects beyond glycaemic control may explain why the cardioprotective effect has been reported with the use of SGLT2is but not with other anti-diabetic agents.

Diuretic effect

SGLT2is diminish sodium and glucose reabsorption, thereby leading to osmotic diuresis.[69] In comparison with loop diuretics, the natriuretic action of SGLT2is is associated with greater fluid reduction in the interstitial compartment than in the intravascular compartment; this improves congestion while not significantly affecting the effective circulating volume and organ perfusion.[70] Additionally, the modest effect on plasma volume appears to reduce both preload and afterload, which helps reverse cardiac remodelling[71] without increasing sympathetic nervous activity.[72] However, many studies have shown that the diuretic effect of SGLT2is is relatively short lived; some studies have even reported no association between volume status and SGLT2is' benefit in HFrEF.[73]

Adaptive cellular reprogramming

By promoting urinary caloric loss via glycosuria, SGLT2is can induce a "fasting-mimicry"[74] metabolic state in myocardium, where sirtuin 1 (SIRT1) and adenosine monophosphate-activated protein kinase (AMPK) signalling pathway are activated and Akt/mTOR is suppressed.[75] These changes consequently enhance anti-oxidant activity, normalize mitochondrial structure and function, increase autophagy, suppress inflammation, improve contractile activity, reduce coronary microvascular injury, and attenuate the development of cardiomyopathy; all these effects promote homoeostasis and survival.[74] Some of these consequences of the adaptive cellular changes have been supported by experimental data from animal models.[76] However, dedicated studies and evidence from human studies are needed to test this hypothesis.

Inhibition of sodium–hydrogen antiport

In rabbits and rats, SGLT2is were shown to downregulate myocardial sodium–hydrogen exchanger, thereby reducing cytosolic sodium and calcium in the myocardium[77] and increasing the amount of mitochondrial calcium. These effects subsequently improved cardiac contractile activity, improved mitochondrial function, reduced oxidative stress, and potentially reduced cardiac hypertrophy, fibrosis, and cardiac remodelling.[78] However, it remains unknown whether these changes can be translated into clinically meaningful effects in HF.

Myocardial energy supply

SGLT2is may enhance myocardial ATP production by enhancing the availability of ketone bodies, which are more energy-efficient substrates than fatty acids or glucose.[79] The enhanced ketone metabolism subsequently improves myocardial energy efficiency in an energetically challenged heart, which appears to reduce myocardial inflammation and fibrosis.[80] However, further studies are needed to test whether the myocardial ketone metabolism is necessary and sufficient to cause CV benefits in HF.[81]

In summary, based on the currently available evidence, SGLT2is (empagliflozin, dapagliflozin, and sotagliflozin specifically) may serve not only as an advantageous option for patients with diabetes to prevent CV events but also potentially a favourable treatment modality for patients with HFmrEF to reduce HHF and CV mortality. Although the findings of large CV outcome trials are promising, there is still much left to investigate. First, despite an increased number of RCTs addressing HF with LVEF $>$ 40%, the number of participants with HFmrEF enrolled in the trials is still insufficient to produce an adequate statistical power to assess this population. Dedicated RCTs with a large sample size of patients with HFmrEF are required to confirm and assess the CV benefits of SGLT2is in this patient population. Second, the currently available subgroup analyses of HF with LVEF $>$ 40% can only suggest a possibility of cardioprotective effects of SGLT2is in this subgroup because the statistical significance may be attributed to HFpEF (LVEF $>$ 50%) benefitting more from the therapy. Therefore, clear HFmrEF subgroup analysis using data from the major CV outcome trials is needed to support the CV effects of SGLT2is in this subpopulation. Third, studies comparing sotagliflozin and other selective SGLT2is for the treatment of HFmrEF are still needed, given that the additional SGLT1 inhibition with sotagliflozin may confer unique benefits in this subgroup of HF. Fourth, an important subgroup of HF, namely, HF with improved EF, was excluded in most of the interventional trials in HF with LVEF $>$ 40%. Although the effect of SGLT2is in this subpopulation will be demonstrated in the DELIEVER trial, more studies including patients with HFmrEF

who previously had HFrEF are warranted. Moreover, although several meta-analyses[82–84] of the aforementioned RCTs included ejection fraction–stratified analysis, absolute conclusion cannot be drawn regarding the association between LVEF and the magnitude of treatment effect because LVEF categories in these trials were not uniform. Finally, although several direct and systemic effects of SGLT2is have been proposed, the unifying mechanisms that explain the CV benefit of SGLT2is irrespective of the aetiology of HF or the baseline LVEF remain unclear.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray J, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, ESC Scientific Document Group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association of the ESC. *Eur Heart J* 2021; **42**: 3599–3726.
2. Thorvaldsen T, Benson L, Dahlström U, Edner M, Lund LH. Use of evidence-based therapy and survival in heart failure in Sweden 2003–2012. *Eur J Heart Fail* 2016; **18**: 503–511.
3. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, Abdelalim A, Abdollahpour I. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the global burden of disease study 2017. *Lancet* 2018; **392**: 1789–1858.
4. McMurray JJ, Adamopoulos S, Anker SD, ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. *Eur Heart J* 2012; **33**: 1787–1847.
5. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, Elkind MS. Heart disease and stroke statistics—2021 update: A report from the American Heart Association. *Circulation* 2021; **143**: e254–e743.
6. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJ, Rahimi K. Temporal trends and patterns in heart failure incidence: A population-based study of 4 million individuals. *Lancet* 2018; **391**: 572–580.
7. Jernberg T, Johanson P, Held C, Svennblad B, Lindbäck J, Wallentin L. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. *JAMA* 2011; **305**: 1677–1684.
8. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: The prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail* 2016; **18**: 242–252.
9. Taylor CJ, Ordóñez-Mena JM, Roalfe AK, Lay-Flurrie S, Jones NR, Marshall T, Hobbs FR. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: Population based cohort study. *BMJ* 2019; **13**: 364.
10. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CS, Sato N, Shah AN, Gheorghiade M. The global health and economic burden of hospitalizations for heart failure: Lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014; **63**: 1123–1133.
11. Lund LH, Carrero JJ, Farahmand B, Henriksson KM, Jonsson Å, Jernberg T, Dahlström U. Association between enrolment in a heart failure quality registry and subsequent mortality—A nationwide cohort study. *Eur J Heart Fail* 2017; **19**: 1107–1116.
12. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the heart failure association (HFA) of the ESC. *Eur J Heart Fail* 2016; **37**: 2129–2200.
13. Lam CS, Solomon SD. The middle child in heart failure: Heart failure with mid-range ejection fraction (40-50%). *Eur J Heart Fail* 2014; **16**: 1049–1055.
14. Vaduganathan M, Claggett BL, Greene SJ, Aggarwal R, Bhatt AS, McMurray JJ, Fonarow GC, Solomon SD. Potential implications of expanded US Food and Drug Administration labeling for sacubitril/valsartan in the US. *JAMA Cardiol* 2021; **6**: 1415–1423.
15. Tromp J, Khan MA, Mentz RJ, O'Connor CM, Metra M, Dittrich HC, Ponikowski P, Teerlink JR, Cotter G, Davison B, Cleland JG. Biomarker profiles of acute heart failure patients with a mid-range ejection fraction. *JACC Heart Fail* 2017; **5**: 507–517.
16. Malik A, Brito D, Vaqar S, Chhabra L, Doerr C. *Congestive Heart Failure (Nursing)*. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK574497/
17. Koh AS, Tay WT, Teng TH, Vedin O, Benson L, Dahlstrom U, Savarese G, Lam CS, Lund LH. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. *Eur J Heart Fail* 2017; **19**: 1624–1634.
18. Cleland JG, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJ, Manzano L, McMurray JJ, Ruschitzka F, Van Veldhuisen DJ, Von Lueder TG. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: An individual patient-level analysis of double-blind randomized trials. *Eur Heart J* 2018; **39**: 26–35.
19. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, Swedberg K, Yusuf S, Granger CB, Pfeffer MA, McMurray JJ. Heart failure with mid-range ejection fraction in CHARM: Characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur J Heart Fail* 2018; **20**: 1230–1239.
20. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, O'meara E, Shah SJ, McKinlay S, Fleg JL, Sopko G. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J* 2016; **37**: 455–462.
21. Solomon SD, Vaduganathan ML, Claggett B, Packer M, Zile M, Swedberg K, Rouleau JA, Pfeffer M, Desai AH, Lund L, Kober L. Sacubitril/valsartan across the spectrum of ejection fraction

in heart failure. *Circulation* 2020; **141**: 352–361.
22. Savarese G, Uijl A, Lund LH, Anker SD, Asselbergs FW, Fitchett D, Inzucchi SE, Koudstaal S, Ofstad AP, Schrage B, Vedin O. Empagliflozin in heart failure with predicted preserved versus reduced ejection fraction: Data from the EMPA-REG OUTCOME trial. *J Card Fail* 2021; **27**: 888–895.
23. Savarese G, Settergren C, Schrage B, Thorvaldsen T, Löfman I, Sartipy U, Mellbin L, Meyers A, Farsani SF, Brueckmann M, Brodovicz KG. Comorbidities and cause-specific outcomes in heart failure across the ejection fraction spectrum: A blueprint for clinical trial design. *Int J Cardiol* 2020; **313**: 76–82.
24. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: An analysis of the ESC heart failure long-term registry. *Eur J Heart Fail* 2017; **19**: 1574–1585.
25. Rickenbacher P, Kaufmann BA, Maeder MT, Bernheim A, Goetschalckx K, Pfister O, Pfisterer M, Brunner-La Rocca HP, TIME-CHF Investigators. Heart failure with mid-range ejection fraction: A distinct clinical entity? Insights from the trial of intensified versus standard medical therapy in elderly patients with congestive heart failure (TIME-CHF). *Eur J Heart Fail* 2017; **19**: 1586–1596.
26. Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, Devore AD, Yancy CW, Fonarow GC. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *J Am Coll Cardiol* 2017; **70**: 2476–2486.
27. Ibrahim NE, Song Y, Cannon CP, Doros G, Russo P, Ponirakis A, Alexanian C, Januzzi JL Jr. Heart failure with mid-range ejection fraction: Characterization of patients from the PINNACLE Registry®. *ESC Heart Fail* 2019; **6**: 784–792.
28. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, Jackson R, Rahneva T, Wage R, Smith G, Venneri L. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): An open-label, pilot, randomised trial. *Lancet* 2019; **393**: 61–73.
29. Garg SK, Henry RR, Banks P, Buse JB, Davies MJ, Fulcher GR, Pozzilli P, Gesty-Palmer D, Lapuerta P, Simó R, Danne T. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. *N Engl J Med* 2017; **377**: 2337–2348.
30. Abdul-Ghani MA, DeFronzo RA, Norton L. Novel hypothesis to explain why SGLT2 inhibitors inhibit only 30–50% of filtered glucose load in humans. *Diabetes* 2013; **62**: 3324–3328.
31. Zambrowicz B, Freiman J, Brown PM, Frazier KS, Turnage A, Bronner J, Ruff D, Shadoan M, Banks P, Mseeh F, Rawlins DB. LX4211, a dual SGLT1/SGLT2 inhibitor, improved glycemic control in patients with type 2 diabetes in a randomized, placebo-controlled trial. *Clin Pharmacol Therap* 2012; **92**: 158–169.
32. Dobbins RL, Greenway FL, Chen L, Liu Y, Breed SL, Andrews SM, Wald JA, Walker A, Smith CD. Selective sodium-dependent glucose transporter 1 inhibitors block glucose absorption and impair glucose-dependent insulinotropic peptide release. *Am J Physiol Gastrointest Liver Physiol* 2015; **308**: G946–G954.
33. Powell DR, Smith M, Greer J, Harris A, Zhao S, DaCosta C, Mseeh F, Shadoan MK, Sands A, Zambrowicz B, Ding ZM. LX4211 increases serum glucagon-like peptide 1 and peptide YY levels by reducing sodium/glucose cotransporter 1 (SGLT1)-mediated absorption of intestinal glucose. *J Pharmacol Exp Ther* 2013; **345**: 250–259.
34. (a)Rodbard HW, Giaccari A, Lajara R, Stewart J, Strumph PS, Oliveira J, Lapuerta P, Castro R. Sotagliflozin added to optimized insulin therapy leads to HbA1c reduction without weight gain in adults with type 1 diabetes: A pooled analysis of inTandem1 and inTandem2. *Diabetes Obes Metab*. 2020; **22**: 2089–2096.
(b)Sands AT, Zambrowicz BP, Rosenstock J, Lapuerta P, Bode BW, Garg SK, Buse JB, Banks P, Heptulla R, Rendell M, Cefalu WT. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes. *Diabetes Care* 2015; **38**: 1181–1188.
35. Seidelmann SB, Feofanova E, Yu B, Franceschini N, Claggett B, Kuokkanen M, Puolijoki H, Ebeling T, Perola M, Salomaa V, Shah A. Genetic variants in SGLT1, glucose tolerance, and cardiometabolic risk. *J Am Coll Cardiol* 2018; **72**: 1763–1773.
36. Borghi C, Bragagni A. The new type 2 diabetes mellitus therapy: Comparison between the two classes of drugs GLPR (glucagon-like peptide receptor) agonists and SGLT2 (sodium–glucose cotransporter 2) inhibitors. *Eur Heart J Suppl* 2020; **22**: L28–L32.
37. Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; **377**: 644–657.
38. Volpe M, Patrono C. Do VERTIS-CV trial results question a class-effect of cardiovascular protection with sodium-glucose cotransporter 2 inhibitors? *Eur Heart J* 2020; **41**: 4232–4233.
39. McMurray JJ, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; **381**: 1995–2008.
40. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Voors AA, Metra M, Lund LH. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021; **384**: 117–128.
41. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, Carson P, Anand I, Doehner W, Haass M, Komajda M. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: The EMPEROR-reduced trial. *Circulation* 2021; **143**: 326–336.
42. Bivol E, Grib L, Cazac N, Cernei I. Prevalence of renal changes in patients with heart failure with mid-range and reduced ejection fraction. *Romanian J Cardiol* 2018; **28**: 23–29.
43. Li N, Lv D, Zhu X, Wei P, Gui Y, Liu S, Zhou E, Zheng M, Zhou D, Zhang L. Effects of SGLT2 inhibitors on renal outcomes in patients with chronic kidney disease: A meta-analysis. *Front Med* 2021; **8**.
44. Omar M, Jensen J, Ali M, Frederiksen PH, Kistorp C, Videbæk L, Poulsen MK, Tuxen CD, Möller S, Gustafsson F, Køber L. Associations of Empagliflozin with left ventricular volumes, mass, and function in patients with heart failure and reduced ejection fraction: A substudy of the empire HF randomized clinical trial. *JAMA Cardiol* 2021; **77**: 243–255.
45. Lee MM, Brooksbank KJ, Wetherall K, Mangion K, Roditi G, Campbell RT, Berry C, Chong V, Coyle L, Docherty KF, Dreisbach JG. Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). *Circulation* 2021; **143**: 516–525.
46. Díaz-Rodríguez E, Agra RM, Fernández ÁL, Adrio B, García-Caballero T, González-Juanatey JR, Eiras S. Effects of dapagliflozin on human epicardial adipose tissue: Modulation of insulin resistance, inflammatory chemokine production, and differentiation ability. *Cardiovasc Res* 2018; **114**: 336–346.
47. Schwartzenberg S, Redfield MM, From AM, Sorajja P, Nishimura RA, Borlaug BA. Effects of vasodilation in heart failure with preserved or reduced ejection fraction: Implications of distinct pathophysiologies on response to therapy. *J Am Coll Cardiol* 2012; **59**: 442–451.
48. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP, PARAGON-HF In-

vestigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019; **381**: 1609–1620.
49. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner–la Rocca HP, Choi D-J, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; **385**: 1451–1461.
50. Solomon SD, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CS, Martinez F, Shah SJ, Lindholm D, Wilderäng U. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: Rationale and design of the DELIVER trial. *Eur J Heart Fail* 2021; **29**: 1217–1225.
51. Writing Committee, Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, Fonarow GC, Ibrahim NE, Lindenfeld J, Masoudi FA, Motiwala SR, Oliveros E, Patterson JH, Walsh MN, Wasserman A, Yancy CW, Youmans QR. 2021 update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: Answers to 10 pivotal issues about heart failure with reduced ejection fraction: A report of the American College of Cardiology Solution set Oversight Committee. *J Am Coll Cardiol* 2021; **77**: 772–810.
52. Rosano GMC, Moura B, Metra M, Böhm M, Bauersachs J, Ben Gal T, Adamopoulos S, Abdelhamid M, Bistola V, Čelutkienė J, Chioncel O, Farmakis D, Ferrari R, Filippatos G, Hill L, Jankowska EA, Jaarsma T, Jhund P, Lainscak M, Lopatin Y, Lund LH, Milicic D, Mullens W, Pinto F, Ponikowski P, Savarese G, Thum T, Volterrani M, Anker SD, Seferovic PM, Coats AJS. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the heart failure Association of the European Society of cardiology. *Eur J Heart Fail* 2021; **23**: 872–881.
53. U.S. Food and Drug Administration. FDA approves treatment for wider range of patients with heart failure. https://www.fda.gov/news-events/press-announcements/fda-approves-treatment-wider-range-patients-heart-failure. Accessed April 2022.
54. European Medicines Agency. Jardiance: EPAR – Summary for the public. https://www.ema.europa.eu/en/documents/overview/jardiance-epar-summary-public_en.pdf. Accessed April 2022.
55. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; **380**: 347–357.
56. Food and Drug Administration (FDA). FDA approves new treatment for a type of heart failure. 2020. https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-type-heart-failure. Accessed January 2022.
57. European Medicines Agency. Forxiga (dapagliflozin): EU summary of product characteristics. 2021. https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information_en.pdf. Accessed January 2022.
58. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, Khariton Y, Malik AO, Khumri T, Umpierrez G, Lamba S. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: A multicenter randomized trial. *Nat Med* 2021; **27**: 1954–1960.
59. Anker SD, Ponikowski P, Wanner C, Pfarr E, Hauske S, Peil B, Salsali A, Ritter I, Koitka-Weber A, Brueckmann M, Lindenfeld J, Abraham WT, EMPERIAL Investigators and National Coordinators. Kidney function after initiation and discontinuation of Empagliflozin in patients with heart failure with and without type 2 diabetes: Insights from the EMPERIAL trials. *Circulation* 2021; **144**: 1265–1267.
60. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RH, Kuder J, Murphy SA, Bhatt DL, Leiter LA, McGuire DK. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation* 2019; **139**: 2528–2536.
61. Packer M, Butler J, Zannad F, Filippatos G, Ferreira JP, Pocock SJ, Carson P, Anand I, Doehner W, Haass M, Komajda M, Miller A, Pehrson S, Teerlink JR, Schnaidt S, Zeller C, Schnee JM, Anker SD, EMPEROR-Preserved Trial Study Group. Effect of empagliflozin on worsening heart failure events in patients with heart failure and preserved ejection fraction. *Circulation* 2021; **144**: 1284–1294.
62. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W, Packer M. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: A metaanalysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020; **396**: 819–829.
63. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RH, Bhatt DL. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019; **393**: 31–39.
64. Brosius FC, Vandvik PO. Cardioprotection with yet another SGLT2 inhibitor—An embarrassment of riches. *N Engl J Med* 2021; **384**: 179–181.
65. Cefalo CM, Cinti F, Moffa S, Impronta F, Sorice GP, Mezza T, Pontecorvi A, Giaccari A. Sotagliflozin, the first dual SGLT inhibitor: Current outlook and perspectives. *Cardiovasc Diabetol* 2019; **18**: 1–4.
66. Kashiwagi Y, Nagoshi T, Yoshino T, Tanaka TD, Ito K, Harada T, Takahashi H, Ikegami M, Anzawa R, Yoshimura M. Expression of SGLT1 in human hearts and impairment of cardiac glucose uptake by phlorizin during ischemia-reperfusion injury in mice. *PLoS ONE* 2015; **10**: e0130605.
67. Ramratnam M, Sharma RK, D'Auria S, Lee SJ, Wang D, Huang XY, Ahmad F. Transgenic knockdown of cardiac sodium/glucose cotransporter 1 (SGLT 1) attenuates PRKAG 2 cardiomyopathy, whereas transgenic overexpression of cardiac SGLT 1 causes pathologic hypertrophy and dysfunction in mice. *J Am Heart Assoc* 2014; **3**: e000899.
68. Eleftheriadou I, Grigoropoulou P, Liberopoulos E, Liatis S, Kokkinos A, Tentolouris N. Update on cardiovascular effects of older and newer anti-diabetic medications. *Curr Med Chem* 2018; **25**: 1549–1566.
69. Hallow KM, Helmlinger G, Greasley PJ, McMurray JJ, Boulton DW. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. *Diabetes Obes Metab* 2018; **20**: 479–487.
70. Santos-Ferreira D, Gonçalves-Teixeira P, Fontes-Carvalho R. SGLT-2 inhibitors in heart failure and type-2 diabetes: Hitting two birds with one stone? *Cardiology* 2020; **145**: 311–320.
71. Dekkers CC, Sjöström CD, Greasley PJ, Cain V, Boulton DW, Heerspink HJ. Effects of the sodium-glucose co-transporter-2 inhibitor dapagliflozin on estimated plasma volume in patients with type 2 diabetes. *Diabetes Obes Metab* 2019; **21**: 2667.
72. Matsutani D, Sakamoto M, Kayama Y, Takeda N, Horiuchi R, Utsunomiya K. Effect of canagliflozin on left ventricular diastolic function in patients with type 2 diabetes. *Cardiovasc Diabetol* 2018; **17**: 1–2.
73. Pabel S, Hamdani N, Luedde M, Sossalla S. SGLT2 inhibitors and their mode of action in heart failure—Has the mystery been Unravelled? *Curr Heart Fail Rep* 2021; **18**: 315–328.
74. Packer M. SGLT2 inhibitors produce cardiorenal benefits by promoting adaptive cellular reprogramming to induce a state of fasting mimicry: A paradigm shift in understanding their mechanism of action. *Diabetes Care* 2020; **43**: 508–511.
75. Inoue MK, Matsunaga Y, Nakatsu Y, Yamamotoya T, Ueda K, Kushiyama A,

Sakoda H, Fujishiro M, Ono H, Iwashita M, Sano T. Possible involvement of normalized Pin1 expression level and AMPK activation in the molecular mechanisms underlying renal protective effects of SGLT2 inhibitors in mice. *Diabetol Metab Syndr* 2019; **11**: 1–11.
76. Avogaro A, Fadini GP, Del Prato S. Reinterpreting cardiorenal protection of renal sodium–glucose cotransporter 2 inhibitors via cellular life history programming. *Diabetes Care* 2020; **43**: 501–507.
77. Baartscheer A, Schumacher CA, Wüst RC, Fiolet JW, Stienen GJ, Coronel R, Zuurbier CJ. Empagliflozin decreases myocardial cytoplasmic Na+ through inhibition of the cardiac Na+/H+ exchanger in rats and rabbits. *Diabetologia* 2017; **60**: 568–573.
78. Packer M, Anker SD, Butler J, Filippatos G, Zannad F. Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart failure: Proposal of a novel mechanism of action. *JAMA Cardiol* 2017; **2**: 1025–1029 PMID: 28768320. Accessed Janurary 2022.
79. Mudaliar S, Alloju S, Henry RR. Can a shift in fuel energetics explain the beneficial cardiorenal outcomes in the EMPA-REG OUTCOME study? A unifying hypothesis. *Diabetes Care* 2016; **39**: 1115–1122.
80. Hwang IC, Cho GY, Yoon YE, Park JJ, Park JB, Lee SP, Kim HK, Kim YJ, Sohn DW. Different effects of SGLT2 inhibitors according to the presence and types of heart failure in type 2 diabetic patients. *Cardiovasc Diabetol* 2020; **19**: 1–2.
81. Crawford PA. Refueling the failing heart: A case for sodium-glucose cotransporter 2 inhibition in cardiac energy homeostasis. *JACC: Basic Transl Sci* 2018; **3**: 588–590.
82. Ahmad Y, Madhavan MV, Stone GW, Francis DP, Makkar R, Bhatt DL, Howard JP. Sodium-glucose cotransporter 2 inhibitors in patients with heart failure: A systematic review and meta-analysis of randomized trials. *Eur Heart J Qual Care Clin Outcomes* 2021.
83. Shoar S, Shah AA, Ikram W, Farooq N, Udoh A, Tabibzadeh E, Khavandi S, Khavandi S. Cardiovascular benefits of SGLT2 inhibitors in patients with heart failure: A meta-analysis of small and large randomized controlled trials. *Am J Cardiov Dis* 2021; **11**: 262.
84. Teo YH, Teo YN, Syn NL, Kow CS, Yoong CS, Tan BY, Yeo TC, Lee CH, Lin W, Sia CH. Effects of sodium/glucose cotransporter 2 (SGLT2) inhibitors on cardiovascular and metabolic outcomes in patients without diabetes mellitus: A systematic review and meta-analysis of randomized-controlled trials. *J Am Heart Assoc* 2021; **10**: e019463.