

Summary of data from preclinical and human studies

SGLT-2 inhibitors and heart failure

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Summary

The sodium-glucose co-transporter 2 inhibitors have become an integral part of the treatment of patients with high cardiovascular risk or established cardiovascular disease. In the present review, we summarise the available data from preclinical and human studies on the mechanisms underlying the beneficial effects of sodium-glucose co-transporter 2 inhibitors in patients with cardiac dysfunction and heart failure, we discuss the data from clinical trials on the prevention and treatment of heart failure, and we present the recommendations of the most recent international guidelines regarding the use of sodium-glucose co-transporter 2 inhibitors in this context.

Introduction

Within a very short time, the sodium-glucose co-transporter 2 inhibitors (SGLT2i) have become an important part of the medical treatment armamentarium for patients with type 2 diabetes (T2DM) and high cardiovascular risk or established cardiovascular disease, in particular patients at risk for heart failure and patients with established heart failure with or without T2DM. The present review article provides a brief overview of the putative mechanisms underlying the only recently detected dramatic clinical effects of SGLT2i in heart failure patients, the key data from mechanistic human studies and clinical trials, and the current role of SGLT2i in the clinical management of patients with or at risk for heart failure. Parts of the content of this article have been presented in the form of a talk at the 2021 meeting of the Swiss Society of Cardiology in June 2021 (held in a fully digital format). In the meantime, additional important data have been published, and this information has also been included.

Mechanisms

Although the mechanism of the hypoglycaemic effect of SGLT2i is relatively clear, the exact way these drugs confer their cardiovascular benefits is still incompletely understood. Most data on SGLT2i and heart failure are derived from preclinical experiments, and information from mechanistic studies in humans with heart failure is still limited. The clinical effect of SGLT2i regarding heart failure prevention and therapy and its magnitude came as a big surprise. Therefore, intense research in the underlying mechanisms started only

when the compelling data from clinical trials were already available. Still, for didactic reasons, we first discuss basics and mechanistic studies before addressing the clinical trials in more detail.

In patients with T2DM, the SGLT2i are used to improve glycaemic control by increased renal glucose elimination (enhanced glycosuria) [1]. Under physiological circumstances, glucose is filtered by the renal glomeruli and fully reabsorbed by the tubules. Reabsorption is predominantly (90%) mediated by the sodium-glucose co-transporter 2, which is located in the first segment of proximal convoluted tubule. There is also sodium-glucose cotransporter 1, which is located in the distal tubule and accounts for the remaining 10% of glucose reabsorption. In contrast to the sodium-glucose cotransporter 1, which is also expressed in extrarenal organs and transports two sodium molecules per molecule of glucose, the sodium-glucose cotransporter 2 is nearly almost expressed in the kidneys (notably, not expressed in the heart), and transports one sodium molecule per molecule of glucose. Accordingly, the SGLT2i reduce tubular glucose reabsorption by inhibition of the cellular uptake of glucose and sodium. This process depends on renal function (decreased in patients with estimated glomerular filtration rate <45 ml/min/1.73 m²) and the plasma glucose concentration [1]. In patients with T2DM, there is glomerular hyperfiltration, and glycosuria occurs if blood glucose exceeds a threshold concentration of approximately 11 mmol/l. In this situation, SGLT2i substantially reduce glycaemia and enhance glycosuria. In people without hyperglycaemia, this effect is attenuated, which explains the low risk of hypoglycaemia with SGLT2i. Accordingly, SGLT2i have a diuretic effect, which could explain the clinical benefit of these drugs in heart failure and subclinical left ventricular dysfunction. However, given that this effect should theoretically depend on renal function and diabetes status, which is not the case in clinical studies, a number of additional hypotheses for important SGLT2i-mediated effects have been put forward, including but certainly not restricted to the following ones (table 1). First, the SGLT2i are thought to cross-react not only with the renal sodium-hydrogen exchanger (NHE) 3 in the kidney (co-localised with the sodium-glucose cotransporter 2) and thereby further enhancing natriuresis, but also with the cardiac NHE isoform 1. Although the sodium-glu-

Table 1: Putative mechanisms of the beneficial effect of sodium glucose co-transporter 2 inhibitors in patients with heart and subclinical left ventricular dysfunction (for details please see text).

Diuretic effect (synergistic with loop diuretic)
Cross-reaction with the cardiac sodium-hydrogen exchanger 1 with increase in mitochondrial calcium and improved cardiac function
Switch of myocardial substrate utilisation from glucose toward free fatty acids, ketone bodies, and branched amino acids
Lipolysis and reduction of pericardial adipose tissue with attenuation of adipokine signalling and thereby attenuation of pro-inflammatory and pro-fibrotic mechanisms
Improved vascular function with improved ventriculo-vascular coupling
Erythropoietin stimulation

cose cotransporter 2 is not expressed in the heart, cross-reaction between SGLT2i and the NHE1 may reduce cytoplasmic sodium and calcium and increase mitochondrial calcium, which may directly reduce myocardial injury and attenuate hypertrophy and fibrosis (attenuation of fibroblast activation and extracellular matrix remodelling). Second, the loss of calories through glycosuria may result in a state of perceived starvation with subsequent activation of nutrient deprivation signalling pathways with a switch of myocardial substrate utilisation from glucose toward the more efficient oxidation of free fatty acids, ketone bodies, and branched amino acids. Third, loss of glucose with a negative net energy balance may result in lipolysis and reduction of lipid deposits, in particular pericardial adipose tissue, which via attenuation of the paracrine effects of adipokines and other cytokines may attenuate pro-inflammatory and pro-fibrotic

A number of hypotheses for important SGLT2i-mediated effects in heart failure have been put forward.

mechanisms in the heart. Fourth, such effects may not be restricted to the heart but may also affect the vasculature with a favourable impact of ventriculo-vascular coupling (consistent with the blood pressure lowering effect of SGLT2i). Fifth, SGLT2i seem to stimulate erythropoietin production, which in combination with the diuretic effect of SGLT2i may lead to the haemoconcentration seen in clinical studies [1–3].

A number of mechanistic studies investigating the effects of dapagliflozin and empagliflozin on cardiac function in patients with or at risk of heart failure have recently been published (table 2) [4–17]. Among patients with heart failure with a reduced ejection fraction (HFrEF), randomised studies comparing empagliflozin and placebo found a reduction in left ventricular end-diastolic [4, 7] and end-systolic [4, 7] volume index and left atrial volume index [7]. Studies were not consistent with regard to changes in left ventricular ejection fraction (LVEF): a study using cardiac magnetic resonance

imaging (MRI) reported an improvement in LVEF [5], whereas an echocardiographic [4] and MRI study found no significant change [7]. A placebo-controlled MRI study in HFrEF patients also demonstrated that empagliflozin led to a reduction in epicardial adipose tissue [6], which may be an important mechanism, by modulation of paracrine signalling on the one hand (as discussed above) and reduction of pericardial restraint on the other hand [18]. In one study, a reduction in left ventricular and left atrial volumes over 12 weeks following empagliflozin treatment was not associated with a reduction in N-terminal-pro-B-type natriuretic peptide (NT-proBNP) [9], whereas in a 36-week treatment study, empagliflozin resulted in a significant reduction in NT-proBNP compared with placebo, which paralleled reductions in left ventricular volumes [4]. In the meantime, data on NT-proBNP from the large clinical HFrEF studies have become available, and treatment with both dapagliflozin and empagliflozin have been shown to result in a significant, albeit modest, reduction in NT-proBNP [19–21]. In patients with preserved LVEF and left ventricular hypertrophy but no overt heart failure, dapagliflozin treatment for 12 months lead to a reduction in LV mass (by MRI) [11] and an improvement in global longitudinal strain (by echocardiography) compared with placebo [12]. A study in patients with coronary artery disease and a broad spectrum of LVEF (mainly >50%) but no overt heart failure also reported a reduction in left ventricular mass [14] and extracellular volume [22] (by MRI). A placebo-controlled haemodynamic study using exercise right heart catheterization in HFrEF patients revealed a reduction in mean pulmonary artery wedge pressure during exercise and a rightward shift of the left ventricular end-diastolic pressure volume relationship following empagliflozin treatment for 12 weeks [8]. This suggests an improvement in left ventricular diastolic function, whereas a study in the setting of preserved LVEF (but no overt heart failure) found no change in left ventricular diastolic function parameters [12]. In an uncontrolled case series among HFrEF patients with an implanted pulmonary artery pressure sensor, a reduc-

tion in the mean pulmonary pressure 7 days after initiation of dapagliflozin therapy was observed [10]. In a larger placebo-controlled study using empagliflozin and a treatment duration of 12 weeks in patients with T2DM and heart failure with a broad LVEF spectrum (HFrEF and heart failure with preserved ejection fraction [HFpEF]), there was a small but significant reduc-

tion (between group difference -1.7 mm Hg) in the diastolic pulmonary artery pressure in the SGLT2i group compared with the placebo group [13]. In all these studies, efforts were made to include stable patients on guideline-directed therapy with unchanged medication during the study, in particular diuretics, in order to minimise confounding effects. Figure 1 is a prelimi-

Table 2: Mechanistic studies evaluating the cardiac effects of sodium glucose co-transporter 2 inhibitors in humans with structural heart disease.

	Study population	Intervention/investigation	Main findings
Reduced LVEF			
Lee et al. 2021 [4]	105 patients with HFrEF, mean LVEF 33% (all $\leq 40\%$), T2DM/prediabetes, median NT-proBNP 466 ng/l	Randomisation to EMPA 10 mg versus placebo for 36 weeks; assessment of LV volumes by cardiac MRI	Reduction in LV end-systolic and end-diastolic volume index as well as NT-proBNP, but not global longitudinal strain and LVEF, with EMPA
Santos-Gallego et al. 2021 [5]	84 patients with HFrEF, LVEF 36%, (all $\leq 50\%$), no diabetes	Randomisation to EMPA 10 mg versus placebo for 6 months; assessment of LV volumes by cardiac MRI	Reduction in LV end-diastolic and end-systolic volume and LV mass, and increase in LVEF, peak oxygen consumption and 6 minute walking distance with EMPA
Requena-Ibanez et al. 2021 [6]	84 patients with HFrEF (all $\leq 50\%$), no diabetes	Randomisation to EMPA 10 mg versus placebo for 6 months; assessment by cardiac MRI	Reduction in epicardial adipose tissue, subcutaneous adipose tissue, extracellular volume, matrix volume, cardiomyocyte volume and aortic stiffness with EMPA
Jensen et al. 2020 [9]	70 patients with HFrEF (LVEF $\leq 40\%$) with or without T2DM	Randomisation to EMPA 10 mg versus placebo for 12 weeks. Measurement of NT-proBNP at baseline and after 12 weeks.	No effect on NT-proBNP
Omar et al. 2020 [8]	70 patients with HFrEF (LVEF $\leq 40\%$) with or without T2DM	Randomisation to EMPA 10 mg versus placebo for 12 weeks. Exercise right heart catheterisation at baseline and after 12 weeks.	Reduction in mean pulmonary artery wedge pressure during exercise with EMPA, no effect on cardiac index
Omar et al. 2021 [7]	186 patients with HFrEF (LVEF $\leq 40\%$) with or without T2DM	Randomisation to EMPA 10 mg versus placebo for 12 weeks. Echocardiography at baseline and after 12 weeks.	Reduction in LV end-diastolic and end-systolic volume index and left atrial volume index with EMPA, no effect on LVEF
Mullens et al. 2020 [10]	9 patients with HFrEF	Treatment with DAPA, no control group; all patients had an implanted PAP sensor	Reduction in mean PAP from 42 to 38 mm Hg within 7 days
Preserved LVEF			
Brown et al. 2020 [11]	66 patients, T2DM, no HF, LV hypertrophy (LV mass index >115 g/m ² in men and >95 g/m ² in women), good blood pressure control ($<145/90$ mm Hg)	Randomisation to DAPA 10 mg versus placebo for 12 months; assessment of LV mass by cardiac MRI	Reduction in LV mass with DAPA; reduction in systolic blood pressure, body weight, adipose tissue and insulin resistance
Brown et al. 2021 [12]	47 patients, T2DM, no HF, LV hypertrophy (LV mass index >115 g/m ² in men and >95 g/m ² in women), good blood pressure control ($<145/90$ mm Hg)	Randomisation to DAPA 10 mg versus placebo for 12 months; assessment of LV global longitudinal strain by echocardiography	Improvement in global longitudinal strain with DAPA, no effect on e' and E/e'
Reduced or preserved LVEF			
Nassif et al. 2021 [13]	65 patients with HF: LVEF 44%, 52% T2DM, median NT-proBNP 637 ng/l	Randomisation to EMPA 10 mg versus placebo for 12 weeks; all patients had an implanted PAP sensor	Baseline diastolic PAP 22 mm Hg; at 12 weeks: diastolic PAP 1.7 mm Hg lower in EMPA group despite absence of a difference in loop diuretic dose
Verma et al. 2019 [14]	90 patients with coronary artery disease and T2DM, mean LVEF $\approx 57\%$ (all $\geq 30\%$), most without HF	Randomisation to EMPA 10 mg versus placebo for 6 months; assessment by cardiac MRI	Reduction in LV mass index and systolic and diastolic blood pressure, and increase in haematocrit with EMPA
Mason et al. 2021 [17]	74 patients with coronary artery disease and T2DM, LVEF $\approx 57\%$ (all $\geq 30\%$), most without HF	Randomisation to EMPA 10 mg versus placebo for 6 months; assessment by cardiac MRI	Reduction in extracellular volume with EMPA
Mazer et al. 2019 [15]	80 patients with coronary artery disease and T2DM, LVEF mainly $>50\%$ (all $\geq 30\%$), most without HF	Randomisation to EMPA 10 mg versus placebo for 6 months, blood samples at baseline, 1 month, and 6 months	Increase in erythropoietin at 1 month (not significant at 6 months) and haemoglobin, and decrease in ferritin with EMPA
Sarak et al. 2021 [16]	90 patients with coronary artery disease and T2DM, LVEF mainly $\approx 57\%$ (all $\geq 30\%$), most without HF	Randomisation to EMPA 10 mg versus placebo for 6 months; assessment by cardiac MRI	No effect by EMPA on RV mass, RV volumes and RV ejection fraction

DAPA: dapagliflozin; EMPA: empagliflozin; e' : peak early mitral annular velocity; E/e' : ratio of the peak early transmitral velocity to the peak early mitral annular velocity; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; LV: left ventricular; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; NT-proBNP: N-terminal-pro-B-type natriuretic peptide; PAP: pulmonary artery pressure; T2DM: type 2 diabetes mellitus; RV: right ventricular.

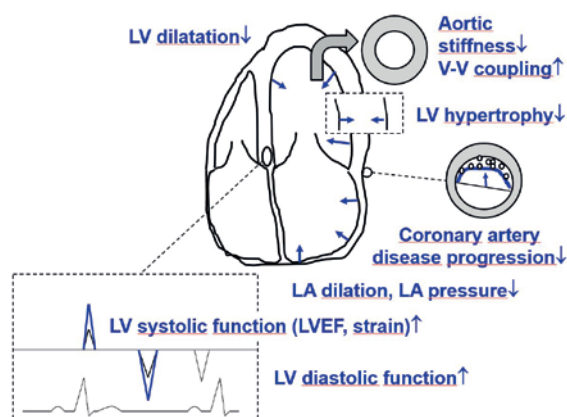


Figure 1: Schematic representation of the cardiac effects of sodium-glucose co-transporter 2 inhibitors in patients with cardiac dysfunction and/or heart failure. Please see also text and table 1. LA: left atrial; LV: left ventricular; LVEF: left ventricular ejection fraction; V-V coupling: ventriculo-vascular coupling

nary summary of these effects. It has to be realised, however, that data were collected in different settings (reduced versus preserved LVEF, heart failure versus asymptomatic left ventricular dysfunction) and are at least partially contradictory.

Collectively, these data point to a clinically relevant diuretic effect of SGLT2i in patients with left ventricular dysfunction and/or heart failure. Importantly, SGLT2i not only reduce the intravascular volume but also the interstitial volume (decongestion of the interstitium), which may explain changes in left ventricular dimension, in particular left ventricular mass, and finally left ventricular compliance [2, 23]. Given that the reduction in left ventricular mass by SGLT2i occurs very fast (i.e., within months, see table 1) compared with the effect of afterload reduction on myocardial fibrosis, this could be an important mechanism of the effect of SGLT2i on cardiac structure and function [23]. However, the data on the exact diuretic effect of SGLT2i in heart failure patients are inconsistent. A randomised placebo-controlled cross-over study in patients with chronic heart failure (45% HFrEF), T2DM and stable drug therapy found an increase in natriuresis following initiation of empagliflozin (as a monotherapy) and a synergistic effect after administration of intravenous bumetanide [24]. Thus, these results are in line with the expected effect of sodium-glucose co-transporter 2 inhibition. In contrast, in another study in stable HFrEF patients, treatment with empagliflozin in addition to a stable dose of a loop diuretic resulted in an increase in 24-hour urine volume and weight loss, but without an increase in urinary sodium compared with placebo after 6 weeks [25]. Similar data have been obtained in patients with acute decompensated

heart failure [26]. The lack of an increased 24-hour urinary sodium excretion is unexpected in view of the mechanism of action of SGLT2i and suggests compensatory sodium reabsorption in the distal nephron [23]. The SGLT2i are considered “smart osmotic diuretics”: their diuretic effect is not mediated via increased natriuresis but by increased osmotic diuresis due to glycosuria [23]. The natriuretic response seems to vary, probably depending on the patient population studied. In any case, SGLT2i are free of some potentially deleterious effects of classical loop diuretics: there is no effect on serum potassium, there is not stimulation of the sympathetic nervous system, and there is hypouricaemia rather than hyperuricaemia [24, 27].

SGLT2i and heart failure prevention

Interest in SGLT2i in the context of heart failure began with the results of the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME; $n = 7020$). This study in patients with T2DM and established cardiovascular disease not only revealed a reduced risk (14% relative risk reduction) of the primary endpoint (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) in patients treated with empagliflozin compared with placebo but also a 35% relative reduction of hospitalisations for heart failure [28]. Subsequent trials with different SGLT2i confirmed this unexpected finding: the Canagliflozin Cardiovascular Assessment Study (CANVAS; $n = 10,142$) in patients with T2DM and high cardiovascular risk reported a 14% relative risk reduction for the same primary endpoint and a 33% relative risk reduction for heart failure hospitali-

EMPA-REG OUTCOME study revealed a reduced risk of the primary endpoint but also a 35% relative reduction of hospitalisations for heart failure.

sations [29]. In a second trial with canagliflozin in patients with T2DM and chronic kidney disease with albuminuria (estimated glomerular filtration rate [eGFR] 30–89 ml/min/1.73 m²; CREDENCE: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation), not only were the renal endpoints improved with SGLT2i but there was also a 39% relative risk reduction in heart failure hospitalisations [30]. The Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58; $n = 17,160$) in patients with established atherosclerotic disease (41%) or high cardiovascular risk (59%) found a significant 17% relative risk reduction for the

co-primary endpoint of cardiovascular death and heart failure hospitalisation with dapagliflozin versus placebo, which was driven by the reduction in heart failure hospitalisation [31]. In the Cardiovascular Outcomes following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants with Vascular Disease (VERTIS-CV) trial in patients with T2DM and established cardiovascular disease, ertugliflozin did not reduce major cardiovascular events but reduced heart failure hospitalisations [32]. In the Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment who are at cardiovascular Risk (SCORE) trial in patients with T2DM, chronic kidney disease with eGFR 25–60 ml/min/1.73 m², and increased cardiovascular risk, sotagliflozin (also inhibits the gastrointestinal sodium-glucose cotransporter 1; more diarrhoea in the sotagliflozin group) reduced the primary endpoint of cardiovascular

known reduced LVEF and patients without heart failure. Cardiovascular death (and all cause mortality) was reduced by dapagliflozin only in patients with HFrEF and not in those without HFrEF [34]. All these SGLT2i are now recommended for the prevention of heart failure hospitalisations in patients with high cardiovascular risk [35]. The intriguing and overall consistent findings of these trials regarding heart failure endpoints led to the design of large-scale true heart failure trials, importantly including patients with and without T2DM.

Heart failure with reduced ejection fraction

Two large randomised trials have specifically tested the effects of SGLT2i in patients with HFrEF: the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) [19] and the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR reduced) [20] trials. In DAPA-HF (n = 4474), treatment with dapagliflozin 10 mg/d versus placebo led to a 26% relative risk reduction of the primary endpoint of cardiovascular death and “worsening heart failure” (heart failure hospitalisation or urgent outpatient heart failure visit) [19]. The number needed to treat to prevent one event was 20 for a median trial duration of 18 months. In EMPEROR reduced (n = 3730) comparing empagliflozin 10 mg versus placebo, a similar effect on the primary endpoint of cardiovascular death or heart failure hospitalisation was observed: a 25% relative risk reduction, number needed to treat to prevent one event of 19 for a median trial duration of 16 months [20]. These results were obtained on good background therapy except for the relatively low proportion of patients with a defibrillator although more than 50% of patients had ischaemic heart failure aetiology in both studies. Both trials in-

These findings were not easy to understand because baseline information regarding heart failure and the exact nature of the heart failure events was limited.

death and heart failure hospitalisations [33]. This trial was terminated prematurely because the sponsor stopped funding, which led to the change of the initial planned primary endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) and to the use of investigator-reported endpoints rather than adjudication of endpoints as planned by study design [33].

These findings were not easy to understand because baseline information regarding heart failure and the exact nature of the heart failure events was limited. It was unclear whether heart failure events represented worsening of pre-existing heart failure / left ventricular dysfunction or were the result of the progression of atherosclerotic disease with an atherothrombotic event leading to de novo heart failure. Relevant information in this regard comes from the DECLARE-TIMI 58 trial, where information on heart failure at baseline was collected in all patients, and information on LVEF was available from approximately 5000 out of 17,160 patients: 3.9% of all patients had HFrEF (defined as LVEF <45%), 7.7% had heart failure without a known reduced LVEF (i.e., documented LVEF ≥45% or no documented LVEF), and 88.4% had no history of heart failure. Dapagliflozin reduced the primary endpoint of cardiovascular death and heart failure hospitalisation more in patients with HFrEF than in patients without HFrEF, in whom the treatment effect was similar in patients with heart failure without a

Both trials included a substantial number of patients without diabetes, and importantly, the effect of SGLT2i on the primary endpoint was independent of diabetes status.

cluded a substantial number of patients without diabetes (58% in DAPA-HF, 50% in EMPEROR reduced), and importantly, the effect of SGLT2i on the primary endpoint was independent of diabetes status [19, 20]. There were no relevant differences in adverse events between SGLT2i and placebo except for the well known SGLT2i-associated risk of genitourinary infections. Despite overall consistent findings, there were differences between the trials (table 3) [19–21, 36]. EMPEROR re-

duced included patients with more severe heart failure (lower LVEF, higher NT-proBNP). Background therapy was similar in the two trials with the exception of the higher proportion of patients on sacubitril/valsartan, which is probably explained by the fact that the DAPA-HF trial started to include patients earlier. In addition, in EMPEROR reduced, there was no information on diuretic therapy at baseline in the original paper, which may be relevant with regard to baseline NT-proBNP and the effect of empagliflozin (according to a sub-

study approximately 84% patients were on a loop diuretic [21], compared with 94% in DAPA-HF [19]). A pre-specified analysis of EMPEROR reduced has revealed that baseline NT-proBNP quartile was a strong predictor of the primary endpoint, that empagliflozin was similarly effective across all NT-proBNP quartiles, that empagliflozin led to a stronger reduction in NT-proBNP than placebo and, notably, that the NT-proBNP value at 12 weeks was a better prognostic predictor than the baseline value [21]. The effect on heart failure hospitali-

Table 3: Comparison of the DAPA-HF [19] and EMPEROR [20] reduced studies.

	DAPA-HF		EMPEROR reduced	
	Dapagliflozin (n = 2373)	Placebo (n = 2371)	Empagliflozin (n = 1863)	Placebo (n = 1867)
Baseline characteristics				
Age (years)	66 ± 11	67 ± 11	67 ± 11	67 ± 11
Female sex (%)	24	23	24	24
Body mass index (kg/m ²)	28 ± 6	28 ± 6	28 ± 6	28 ± 5
Diabetes (%)	42	42	50	50
LVEF (%)	31 ± 7	31 ± 7	28 ± 6	27 ± 6
NT-proBNP (ng/l)	1428 (857–2655)	1446 (857–2641)	1887 (1077–3429)	1926 (1153–3525)
Systolic blood pressure (mm Hg)	122 ± 16	122 ± 16	123 ± 16	121 ± 15
Atrial fibrillation (%)	39	38	36	38
eGFR (ml/min/1.73 m ²)	66 ± 20	66 ± 19	62 ± 22	62 ± 22
Baseline therapy				
Diuretic (%)	93	94	NA [§]	NA [§]
ACEi (%)	56	56	47	45
ARB (%)	28	27	24	25
ARNi (%)	11	11	18	21
Beta-blocker (%)	96	96	95	95
MRA (%)	72	71	70	73
Digitalis (%)	19	19	NA	NA
Cardiac resynchronisation therapy (%)	8	7	12	12
Defibrillator (%)	26	26	31	32
Study endpoints				
Primary endpoint*				
– %	16.3	21.2	19.4	24.7
– Events/100 patients years	11.6	15.6	15.8	21.0
– HR (95% CI)	0.74 (0.65–0.85)		0.75 (0.65–0.86)	
– Number needed to treat	21 (18 months)		19 (16 months)	
Cardiovascular death				
– %	9.6	11.5	10.0	10.8
– Events/100 patients years	6.5	7.9	7.6	8.1
– HR (95% CI)	0.82 (0.69–0.98)		0.92 (0.75–1.12)	
HF hospitalisations				
– %	9.7	13.4	13.2	18.3
– Events/100 patients years	6.9	9.8	10.7	15.5
– HR (95% CI)	0.70 (0.59–0.83)		0.69 (0.59–0.81)	

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNi: angiotensin receptor neprilysin inhibitor; eGFR: estimated glomerular filtration rate; HF: heart failure; HR (95% CI): hazard ratio and 95% confidence interval; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NT-proBNP: N-terminal-pro-B-type natriuretic peptide
For detailed discussion and acronyms please see text. * DAPA-HF: composite of cardiovascular death and worsening HF (HF hospitalisation or urgent outpatient visit for HF); EMPEROR reduced: composite of cardiovascular death and hospitalisation for HF. [§] data not reported in the original report [20]. Information was provided in a pre-specified subanalysis [21], see text.

	HFrEF	HFmrEF	HFpEF
Loop diuretic	I	I	I
ACEI /ARB	I	IIb	
Betablocker	I	IIb	
MRA	I	IIb	
ARNI (replacement for ACEI)	I	IIb	
ARNI (first line)	IIb	IIb	
Dapagliflozin (+/- T2DM)	I	DELIVER: ?	
Empagliflozin (+/- T2DM)	I	EMPEROR preserved: +	
Sotagliflozin (+T2DM)	I		
Ivabradin	IIa		
Vericiguat	IIb		
Digoxin (sinus rhythm)	IIb		
Iron carboxymaltose	IIa	IIa	

Figure 2: Role of sodium-glucose co-transporter 2 inhibitors for the treatment of heart failure according to the recommendations of the 2021 guidelines of the European Society of Cardiology. For detailed discussion, please see text. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; DELIVER: Dapagliflozin Evaluation to Improve the LIVES of Patients With Preserved Ejection Fraction Heart Failure; EMPEROR preserved: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; MRA: mineralocorticoid receptor antagonist; T2DM: type 2 diabetes mellitus. +: the trial has been published and has been positive. ?: the trial has not been published yet

sations was very similar in both trials (30% and 31% relative risk reduction) whereas the effect on cardiovascular mortality differed numerically (DAPA-HF: 18%; EMPEROR reduced: 8%). A meta-analysis of the two trials, however, revealed no statistical heterogeneity with regard to this endpoint [36]. In the prevention trials, the opposite situation was observed: empagliflozin reduced mortality in EMPAREG outcome [28], whereas dapagliflozin in DECLARE did not [31].

These convincing data resulted in a class I indication for the treatment of HFrEF in the recently published guidelines of the European Society of Cardiology (ESC) [35]. The SGLT2i dapagliflozin and empagliflozin are now part of the standard “quadruple therapy” (angiotensin converting enzyme inhibitor [ACEi] / angiotensin neprilysin inhibitor [ARNi], beta-blocker, mineralocorticoid receptor antagonist [MRA]) [37], which is indicated for every HFrEF patient independent of diabetes status [35] (fig. 2). Importantly, there is no evidence (but the opposite is true) that SGLT2i are not effective on the background of the second newest HFrEF drug, namely the ARNi [38]. Exactly when to introduce a SGLT2i is not clearly defined, however. Several experts propose the “rapid sequence initiation” of this therapy: starting with a SGLT2i in a standard dose at

day 1 (simultaneously with low dose ARNi, beta-blocker and MRA), followed by a stepwise up-titration of the three other drugs within 1.5 months [37, 39]. The ESC guidelines state that “dapagliflozin or empagliflozin are recommended, in addition to optimal medical therapy with an ACEi/ARNi, a beta-blocker and an MRA for patients with HFrEF regardless of diabetes status” [35]. Thus, physicians are left with some flexibility as to when exactly to introduce which drug. The big advantage of SGLT2i is the ease of their use (no titration, no clinically relevant effect on blood pressure, no requirement to check potassium, etc.), and therefore a quick adoption of these drugs can be expected. Still, the complexity of the treatment of HFrEF is increasing, and clinicians have to be aware of the diuretic effect of SGLT2i as discussed above and the potential need to adjust loop diuretic dose in some patients. A DAPA-HF post-hoc study has shown, however, that dapagliflozin is effective independently of the baseline diuretic dose, and that changes in diuretic dose were rare throughout the trial [40].

A third SGLT2i, sotagliflozin, has been studied in patients with heart failure but in a different setting from the DAPA-HF and EMPEROR reduced studies: in the Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial, patients with T2DM and a recent hospitalisation for worsening heart failure (independent of LVEF; 79% had LVEF <50%) sotagliflozin treatment resulted in a lower number of cardiovascular deaths, heart failure hospitalizations, and urgent heart failure visits (primary endpoint; 33% relative risk reduction) [41]. This trial was terminated prematurely because the sponsor stopped funding, which led to the change of the initial planned primary endpoint (cardiovascular death, heart failure hospitalisations) and to the use of investigator-reported endpoints rather than adjudication of endpoints as planned by study design. Still, the 2021 ESC guidelines issued a class I indication for sotagliflozin for the treatment of patients with HFrEF but only if they also have T2DM (fig. 2).

Heart failure with preserved ejection fraction

Given the many effects of SGLT2i that could potentially have favourable effects in HFpEF, including anti-inflammatory and anti-fibrotic properties and salutary effects on blood pressure and renal function, trials evaluating SGLT2i for the treatment of patients with HFpEF were launched in parallel with the HFrEF trials [42, 43]. The first of these trials, the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with

Preserved Ejection Fraction (EMPEROR preserved) trial, was published in 2021 [22]: the study included 5988 patients with LVEF >40% and NT-proBNP >300 ng/l (for patients with atrial fibrillation: >900 ng/l) randomised to empagliflozin 10 mg versus placebo. Patients treated with empagliflozin had a 21% lower relative risk of experiencing the primary endpoint of cardiovascular death or heart failure hospitalisation (number needed to treat to prevent one event: 31 for a median trial dura-

The EMPEROR preserved trial has been labelled as “first positive trial in HFpEF”, but cautious interpretation of these findings is still required.

tion of 26 months). The study included 49% patients with T2DM, and there was no interaction of diabetes status with the effect of empagliflozin on the primary endpoint. Importantly, the result for the primary endpoint was driven by the reduction in heart failure hospitalisation (hazard ratio 0.71, 95% confidence interval 0.60–0.83). Adverse events were similarly common in the empagliflozin and placebo groups with the exception of a higher incidence of genitourinary infections and hypotension with empagliflozin [22]. This trial has been labelled as “first positive trial in HFpEF” [44], but cautious interpretation of these findings is still required for a number of reasons. First, EMPEROR preserved was not a pure HFpEF trial (ESC guidelines 2021: HFpEF: LVEF $\geq$ 50% [35] but by design also included patients with heart failure with mildly reduced LVEF (HFmrEF; defined as LVEF 41–49% according to the 2021 ESC guidelines [35], which is very similar to most recent “HFpEF trials” including CHARM-preserved [45], TOPCAT [46], and PARAGON-HF [47]. In EMPEROR preserved, the proportions of patients with LVEF 41–49%, 50–59% and $\geq$ 60% were 33%, 34% and 33%, respectively [22]. Although the pre-specified subgroup analysis did not reveal a true interaction between LVEF stratum and the impact of empagliflozin on the primary endpoint, there was at least a certain attenuation of the effect with increasing LVEF (hazard ratios 0.71, 0.80 and 0.87). Second, empagliflozin had no significant effect on cardiovascular mortality (hazard ratio 0.91, 95% confidence interval 0.76–1.09), and there was no signal for a reduction in total mortality (hazard ratio 1.0) [22]. Third, in contrast to the SGLT2i trials in HFrEF there was no significant effect on the composite renal endpoint either, although the rate of decline in eGFR was reported to be slower in the empa-

gliflozin group [48]. Thus, empagliflozin seems to be very effective in reducing heart failure hospitalizations in patients with HFmrEF and HFpEF, but there is still no drug that improves mortality in HFpEF. In the 2021 ESC guidelines, the results of EMPEROR preserved are not reflected yet, because the trial was published simultaneously with the release of the guidelines (fig. 2). The guidelines now give a class I indication for diuretics for HFpEF and HFmrEF and a class IIb indication for ACEi / angiotensin receptor blockers, ARNi, beta-blockers, and MRA for HFmrEF (based on post hoc analysis of “HFpEF trials” also including HFmrEF patients as mentioned above) [35]. In SOLOIST-WHF, only 21% of patients had HFpEF [41]. The effect in HFpEF was at least as strong as for HFrEF + HFmrEF (hazard ratio 0.48 versus LVEF <50%: 0.72%) [41], but given the small number of HFpEF patients in this trial no recommendation was given for HFpEF [35]. In SOLOIST-WHF, the HFmrEF group was not separated [41], and there is no recommendation for sotagliflozin for HFmrEF either [35]. To better understand the role of SGLT2i in HFpEF (and HFmrEF) and as a basis for recommendations for the use of SGLT2i in HFpEF and HFmrEF, the results of the Dapagliflozin Evaluation to Improve the LIVES of Patients With PReserved Ejection Fraction Heart Failure (DELIVER) study evaluating the effect of dapagliflozin versus placebo on the primary endpoint of cardiovascular death and a worsening heart failure event (same

To better understand the role of SGLT2i in HFpEF and as a basis for recommendations for the use of SGLT2i in HFpEF and HFmrEF, the results DELIVER study will be important.

endpoint as in DAPA-HF) in patients with LVEF >40% and NT-proBNP >300 ng/l (>600 ng/l for patients with atrial fibrillation) will be important [43] (fig. 2). Very recently, the PRESERVED-HF study has revealed an interesting result: an improvement in quality of life and six-minute walking distance in patients with HFpEF (and HFmrEF; LVEF $\geq$ 45% required for inclusion) [49].

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References

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