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REVIEW

Emerging concepts in heart failure management and treatment: focus on SGLT2 inhibitors in heart failure with preserved ejection fraction

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Abstract

The role of sodium–glucose cotransporter 2 inhibitors (SLTG2i), developed initially as glucose-lowering agents, has represented a novelty in patients with heart failure (HF) and reduced ejection fraction (HFrEF) since dapagliflozin (DAPA-HF study) and empagliflozin (EMPEROR-Reduced study) were able to reduce morbidity and mortality in this setting regardless of the presence or absence of diabetes. In previous large clinical trials (EMPA-REG OUTCOME study, CANVAS, DECLARE-TIMI 58), SGLT2i have been shown to attenuate HF progression expressed by reducing the risk of HF hospitalizations in patients with type 2 diabetes mellitus mostly without HF at baseline. This benefit was then corroborated with positive results in HF outcomes (cardiovascular mortality and HF hospitalizations) in patients with HF with preserved ejection fraction (HFpEF) in the EMPEROR-Preserved (empagliflozin) and DELIVER (dapagliflozin) trials. Several biological mechanisms apart from the glycosuria are attributed to these agents in this last context, including anti-inflammatory effects, reduction of fibrosis and apoptosis, improvement of myocardial metabolism, mitochondrial function optimization, and oxidative stress protection. Moreover, SGLT2i can also improve ventricular loading conditions by forcing diuresis and natriuresis, and by enhancing vascular and renal function. In addition, SGLT2i can reduce myocardial passive stiffness (diastolic function) by enforcing the phosphorylation of myofilament modulatory proteins. This article provided an overview of the main pathophysiological characteristics of HFpEF and of the diverse mechanisms of action of SGLT2i in this setting. The supporting clinical evidence of SGLT2i in HFpEF (EMPEROR-Preserved and DELIVER trials) is also reviewed.

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Introduction

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) were originally developed as hypoglycaemic agents in the treatment of type 2 diabetes mellitus (T2DM) based on their potent glycosuric effects.[1,2] Subsequently, their benefits were demonstrated in terms of reducing morbidity and mortality in very different clinical scenarios, for example, heart failure (HF) with reduced ejection fraction (HFrEF); however, in this case, the benefits were due to a multiplicity of biological effects.[3,4] In this setting, the composite of death from cardiovascular (CV) causes or worsening HF was significantly reduced (*versus* placebo) by dapagliflozin, as observed in the DAPA-HF trial (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), and by empagliflozin in a similar combined outcome (CV death or HF hospitalization (HFH)), as observed in the EMPEROR-Reduced trial (Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure), in both cases in both patients with diabetes and in those without.[3,4]

More recently, the EMPEROR-Preserved (Empagliflozin in Heart Failure with a Preserved Ejection Fraction) trial showed, for the first time, that the use of a pharmacological agent (empagliflozin) was able to reduce (independent of the presence of T2DM) the combined risk of CV death or HFH in patients with HF and preserved ejection fraction (HFpEF).[5] Much more recently, in the DELIVER (Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction) trial, another SGLT2i (dapagliflozin) was also shown to reduce the combined risk of worsening HF or CV death in patients with HF and mildly reduced or preserved ejection fraction.[6]

This article provides an overview of the main pathophysiological characteristics of HFpEF, the considered diverse biological effects of SGLT2i in this context and the supporting clinical evidence of SGLT2i in patients with HFpEF focused on the EMPEROR-Preserved and DELIVER trials.

Review

HFpEF

In 2020, a writing committee comprised of members of the Heart Failure Society of America, the Heart Failure Association of the European Society of Cardiology and the Japanese Heart Failure Society introduced a new and revised classification of HF phenotypes by left ventricular ejection fraction (LVEF). Consequently, HFpEF should be considered in patients with symptomatic HF and LVEF ≥50%, HFrEF when LVEF is ≤40%, whereas individuals with an LVEF between 41% and 49% should be diagnosed as HF with mildly reduced ejection fraction (HFmrEF).[7]

Patients with HFpEF are estimated to account for approximately half of all patients with HF and common factors, such as advanced age, obesity, metabolic syndrome, hypertension, diabetes, renal dysfunction, non-alcoholic fatty liver disease, coronary artery disease, or atrial fibrillation, are associated with and favour its development; therefore, future incidence of HFpEF is expected to increase, particularly in relation to a progressively longer life expectancy.[1,8] HFpEF syndrome consists of several different phenotypes but with a common pathophysiology that determines a progressive deterioration in autonomy and quality of life. Clinically, it is characterized by functional limitation, dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea and even peripheral oedema, which ultimately results in increased morbidity and mortality due to HF.[8,9]

Characteristically, diastolic relaxation is impaired in patients with HFpEF whilst LVEF remains normal, resulting in decreased diastolic ventricular compliance and impaired ventricular filling. Consequently, filling pressures must increase to maintain an adequate stroke volume, and this condition is especially marked during exercise, when the cardiac cycle is shortened at the expense of

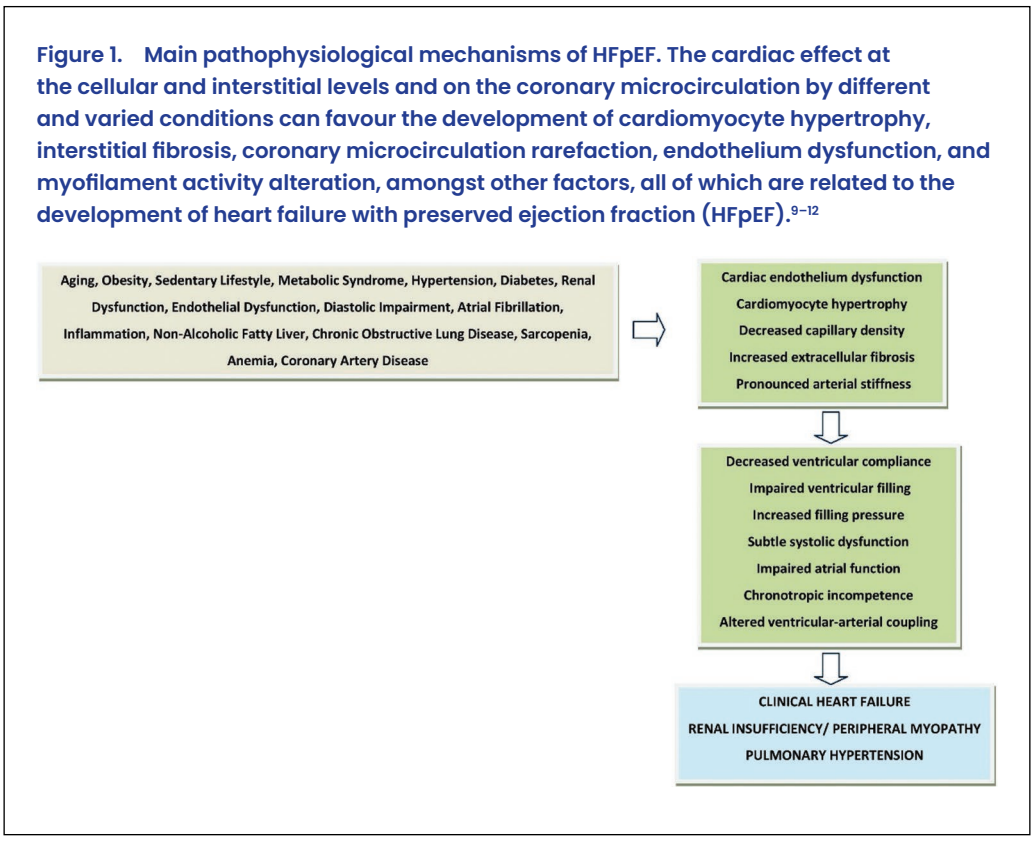


Figure 1. Main pathophysiological mechanisms of HFpEF. The cardiac effect at the cellular and interstitial levels and on the coronary microcirculation by different and varied conditions can favour the development of cardiomyocyte hypertrophy, interstitial fibrosis, coronary microcirculation rarefaction, endothelium dysfunction, and myofilament activity alteration, amongst other factors, all of which are related to the development of heart failure with preserved ejection fraction (HFpEF).[9–12]

diastolic duration.[9] Despite the fact that LVEF remains within a normal range, patients with HFpEF usually have some subtle systolic dysfunction that is expressed as a lower increase in LVEF during exertion. On the other hand, these patients may also present with other cardiac abnormalities, such as impaired atrial function and/or chronotropic incompetence.[10]

The pathophysiology of this entity is still not fully elucidated since many underlying mechanisms are involved in its development and in its different phenotypes (Figure 1). In this scenario, it is considered that progressive endothelial dysfunction as a consequence of a systemic pro-inflammatory state (multiple risk factors and comorbidities) would be responsible for various subsequent pathophysiological abnormalities that include the heart, blood vessels and other organs.[9,11] Dysfunction of the cardiac endothelium (inflammatory cytokines, production of reactive oxygen species and decreased bioavailability of nitric oxide) would trigger the typical features of HFpEF, including cardiomyocyte hypertrophy, decreased capillary density, increased extracellular fibrosis, pronounced arterial stiffness (preserved vasodilatation reduction) and an altered ventricular–arterial coupling.[11,12] On the other hand, the general compromise of endothelial dysfunction would also be responsible for other phenomena such as remodelling of the pulmonary arteries (pulmonary hypertension) and the decrease in capillary density in both skeletal muscle (peripheral myopathy) and renal tissue (renal dysfunction).[11,12] In addition, HFpEF also shows overactivation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS), resulting in tachycardia, vasoconstriction, renal retention of salt and volume, ventricular remodelling (pro-hypertrophic and pro-fibrotic effects), and increased oncostatic pressures (pulmonary and peripheral).[9,13,14]

Historically, HFpEF has been characterized as having no specific effective treatment since multiple large controlled clinical trials based on diverse and very different study drugs failed to find it and, in this context, the only available resources were diuretics for patients with congestive symptoms and the adequate control (if necessary) of arterial hypertension, atrial fibrillation, or coronary artery disease.[15] Despite therapeutic limitations, some discreet or modest benefits (certain subgroups of patients) were found with the use of mineralocorticoid receptor antagonists or an angiotensin receptor blocker/neprilysin inhibitor (ARNI).[16–18] This situation has positively changed with the results of the EMPEROR-Preserved and DELIVER trials, which have opened the perspectives for a widespread and necessary use of SGLT2i in patients with HFpEF.[5,6]

SGLT2i and risk of HF development

Large-scale clinical trials (Table 1) revealed that SGLT2i use, in addition to standard care, was associated with a consistent decrease in HFH risk amongst patients with T2DM but who were likely to develop HF, as these populations met many conditions (apart from diabetes) associated with its development, including obesity, hypertension and CV disease. The primary goals of these trials were to determine the effects of SGLT2i (*versus* placebo) on major CV adverse events (MACE) such as CV death, non-fatal myocardial infarction, or non-fatal stroke; of note, most of the included patients did not present baseline HF (only 10–15%).[19–22]

In the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes study (EMPA-REG OUTCOME study),[19] 7020 patients with T2DM and established CV disease were randomized to placebo or empagliflozin 10 or 25 mg. The rate of CV mortality or HFH was significantly lower in the active arm (5.7% *versus* 8.5%; HR 0.66, 95% CI 0.55–0.79; $p<0.001$). In the case of patients with HF at baseline ($n=706$; 10.1%), empagliflozin also reduced both HFH rate (10.4% *versus* 12.4%; HR 0.75, 95% CI 0.48–1.19) and CV mortality (8.2% *versus* 11.1%; HR 0.71, 95% CI 0.43–1.16), though CV mortality did not reach statistical significance.[19,20] The Canagliflozin Cardiovascular Assessment Study (CANVAS) Program[23] integrated data from two trials involving a total of 10,142 participants with T2DM and high CV risk. Besides its positive effect on the primary outcome (MACE), canagliflozin also significantly diminished HFH compared to placebo (HR 0.68; 95% CI 0.51–0.90; $p=0.91$) but without a significant difference regarding overall and CV mortality.[21] The Dapaglifozin and Cardiovascular Outcomes in Type 2 Diabetes study (DECLARE-TIMI 58) evaluated the effect of dapagliflozin 10 mg/day (*versus* placebo) in >17,000 patients with T2DM and established CV disease (or multiple CV risk factors). This trial (mean follow-up was 4.2 years) had two primary efficacy objectives: MACE and a composite of CV death or HFH. Dapagliflozin was non-inferior (*versus* placebo) in MACE reduction and CV mortality reduction was also non-significant (HR 0.98, 95% CI 0.82–1.17). However, the combined endpoint of CV death or HFH was significantly reduced (4.9% *versus* 5.8%; HR 0.83, 95% CI 0.73–0.95; $p=0.005$) mainly due to a decline in HFH (HR 0.73; 95% CI 0.61–0.88), which was consistent amongst different subgroups, including either presence or absence of established CV disease.[22] In a systematic review of these three trials, Kluge et al. showed that the relative risk (RR) reduction in the case of HFH was 27% in the DECLARE-TIMI 58 study ($p=0.0008$), 33% in the CANVAS Program ($p=0.02$) and 35% in the EMPA-REG trial ($p=0.002$). Regarding HFH or CV death, the values were 17% in the DECLARE-TIMI 58 study ($p=0.005$), 22% in the CANVAS Program ($p=0.0015$) and 34% in the EMPA-REG trial ($p<0.001$).[24,25] Therefore, in patients with T2DM and established CV or with the presence of multiple CV risk factors, SGLT2i combined with standard treatment showed a marked decrease in the rates of CV death

Table 1. Comparative features of cardiovascular safety studies of SGLT2 inhibitors in patients with T2DM population.

	EMPA-REG	CANVAS Program	DECLARE-TIMI 58
Intervention	Empagliflozin 10 mg/20 mg	Canagliflozin 100 mg/300 mg	Dapagliflozin 10 mg
Population (*n*)	7020	10.142	17.160
Entry criteria	T2DM + CVD	T2DM + CVD or ≥2 CV RF	T2DM + CVD or multiple CV RF
- T2DM	100%	100%	100%
- History of CVD	99%	65.6%	40.5%
- Age ≥65 years old	44.6%	33.8%	46.1%
- Women	28.5%	35.8%	37.4%
- BMI ≥30	51.3%	89.9%	59.4%
- Hypertension	96%	87%	87.7%
- Atrial fibrillation	5.5%	5.9%	6%
- History of HF	10.1%	14.4%	10.0%
- Known HFpEF	3.3%	4.8%	7.7%
Median follow-up, years	3.1	2.4	4.2
MACE (primary outcome), HR (95% CI)	0.86 (0.74–0.79)	0.86 (0.75–0.97)	0.93 (0,84–1.03)
CV death, HR (95% CI)	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.81–1.17)
HFH, HR (95% CI)	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.73 (0.61–0.88)

Regardless of the positive effects on the primary endpoint (MACE), these studies demonstrated a significant effect on HFH in a population that was largely unaffected by HF but with a notable presence of HFpEF-associated risk factors/comorbidities.
CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; HFH, hospitalization for heart failure; HFpEF, heart failure with preserved ejection fraction; MACE, major adverse cardiovascular event; RF, risk factors.
Data retrieved from Zinman et al. (EMPA-REG OUTCOME™),[19] Carbone et al. (CANVAS Program)[21] and Wiviott et al. (DECLARE-TIMI 58).[22]

and, especially, HFH; this benefit was consistent in patients with and without baseline HF.[19,22]

SGLT2i in HFpEF

EMPEROR-Preserved

The EMPEROR-Preserved trial was a randomized, double-blind, parallel-group, placebo-controlled, event-driven trial that studied the effect of empagliflozin (10 mg/day) in patients with HFpEF.[5] Major entry criteria included LVEF >40%, NYHA functional class II–IV (NYHA), body mass index <45 kg/m^2 and pro N-terminal B-type natriuretic peptide (NT-proBNP) levels >300 pg/mL (>900 pg/mL if atrial fibrillation); patients with an estimated glomerular filtration rate (eGFR) <20 ml/min/1.73 m^2 were excluded. The primary outcome was a composite of CV death or HFH, analysed as time to first event, whilst the secondary outcomes were the occurrence of all assigned HFHs (initial and recurrent events) and the rate of decline in eGFR. A total of 5988 patients (2997 empagliflozin; 2991 placebo) were included and the median duration of follow-up was 26.2 months.[5] The median LVEF was 54%, though one-third of patients had an LVEF between 40% and 49% (HFmrEF); thus, only two-thirds of cases were strictly HFpEF[5] (Table 2).

The primary composite outcome was significantly reduced (RR 17%) by empagliflozin (13.8% *versus* 17.1%; HR 0.79, 95% CI 0.69–0.90; $p<0.001$) and this result was mainly based on the decrease in HFH (8.6% *versus* 11.8%; HR 0.71, 95% CI 0.60–0.83) since CV death was not significantly affected (7.3 % *versus* 8.2%; HR 0.91, 95% CI 0.76–1.09) (Table 3). This positive impact on HFH was detected as early as 1 month after randomization and was generally consistent across different prespecified subgroups, including patients with and without diabetes at baseline. However, baseline LVEF spectral analysis showed some loss of efficacy as LVEF increased, with doubtful impact at values ≥60%. In this last case, the clinical impact was not statistically significant (HR 0.87, 95% CI 0.69–1.10), whilst there was marginal statistical significance in the

Table 2. Comparative baseline characteristics of EMPEROR-Preserved and DELIVER trials (active arms).

	EMPEROR-Preserved	DELIVER trial
Intervention	Empagliflozin 10 mg	Dapagliflozin 10 mg
Comparator	Placebo	placebo
Total population (*n*)	5988	6263
Active arm		
Total patients	2997	3131
Age (years)	71.8±9.3	71.8±9.6
Women	44.6%	43.6%
T2DM	48.9%	44.7%
Hypertension	90.8%	88.0%
History of AF	51.5%	56.7%
NYHA II/III/IV	81.1%/18.4%/0.3%	73.9%/25.8%/0.3%
Median NT-proBNP (interquartile range), pg/ml	994 (501–1740)	1.011 (623–1751)
LVEF <50%[a]	33.2%	34.1%
LVEF ≥50% to <60%[b]	34.2%	36.2%
LVEF ≥60%[c]	32.5%	29.7%
Mean eGFR, ml/min/1.73 m^2	60.6±19.8	61±19

Both trials were similar and well balanced in terms of demographic characteristics but it should be noted that around one-third of patients had LVEF <50%, currently considered as heart failure with mildly reduced ejection fraction.

AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNB, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; T2DM, type 2 diabetes mellitus. In DELIVER trial: [a]LVEF ≤49%; [b]LVEF 50–59%; [c]LVEF ≥60%.

Data retrieved from Anker et al. (EMPEROR-Preserved)[5] and Solomon et al. (DELIVER).[6]

subgroup with LVEF between ≥50% and <60% (HR 0.80, 95% CI 0.64–0.99) (Table 4).[5]

Regarding secondary outcomes, the rate of decline in the mean eGFR slope/year was slower in the empagliflozin arm (–1.25 ml/min/1.73 m² *versus* 2.62 ml/min/1.73 m²; $p<0.001$) even though the composite renal outcome was similar (3.6% *versus* 3.7%; $p>0.05$). Total hospitalizations were lesser in the active arm (407 *versus* 541; $p<0.001$) and there were no significant changes regarding all-cause mortality (13.4% *versus* 14.2%; HR 0.92, 95% CI 0.77–1.10; $p>0.05$) and in the Clinical Summary Score of the Kansas City Cardiomyopathy Questionnaire (CSS KCCQ). Subgroup analysis showed that patients >70 years old, LVEF <50, eGFR <60 ml/min/1.73 m², NYHA II and a previous treatment with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers or ARNIs were the most benefited.[4] Adverse effects leading to discontinuation of treatment occurred in 571 (19.1%) patients in the empagliflozin group and in 551 (18.4%) patients in the placebo group and, in this setting, uncomplicated genital and urinary tract infections and hypotension were more common in patients treated with empagliflozin.[5]

DELIVER trial

The recently published DELIVER trial, which was a phase III randomized, double-blind, parallel-group, placebo-controlled, event-based trial, randomized 6263 people with the objective of evaluating the efficacy of dapagliflozin (*versus* placebo) in the treatment of patients with HF and LVEF ≥40% (with or without T2DM). The main admission criteria were age ≥40 years, LVEF ≥40% with evidence of structural heart disease [left atrial enlargement or left ventricular (LV) hypertrophy] and NT-proBNP levels of ≥300 pg/mL (≥600 pg/mL in case of atrial fibrillation or atrial flutter).[6] Both outpatients and inpatients were eligible for enrolment and dapagliflozin was given once daily in addition to standard therapy; the main baseline demographic characteristics are shown in Table 2. The primary endpoint was time to first occurrence of CV death, HFH, or HF urgent visit, whilst secondary endpoints included total number of HF events (HFH or HF urgent visit), CV death, change from baseline in KCCQ total symptom score (at 8 months), time to occurrence of CV death, and time to occurrence of death from any cause.[6]

During a median of 2.3 years, the primary outcome was documented in 512 (16.4%) of 3131 patients in the dapagliflozin group and in 610 (19.5%) of 3132 patients in the placebo group (HR 0.82, 95% CI 0.73–0.92; $p>0.001$). This result was based more on the reduction in events of worsening HF that occurred in 368 (11.8%) patients in the dapagliflozin group *versus* in 455 (14.5%) patients in the placebo group (HR 0.79, 95% CI 0.69–0.91), whilst CV death affected 231 (7.4%) patients in the active group and 261 (8.3%) patients in the placebo group (HR 0.88, 95% CI 0.74–1.05). The number of CV deaths and first and recurrent worsening HF events were lower in the dapagliflozin group than in the placebo group in the overall population (RR 0.77, 95% CI 0.67–0.89; $p<0.001$) and total events and symptom burden were also lower in the dapagliflozin group. KCCQ total symptom score (baseline-month 8) also favoured dapagliflozin *versus* placebo (win ratio 1.11, 95% CI 1.03–1.21; $p=0.009$) (Table 3).[6] The effect of dapagliflozin on the primary outcome was consistent amongst subgroups with LFVEF ≥60% or ≤60% (Table 4), patients with or without T2DM, enrolment that occurred during or

Table 3. Primary and secondary outcomes in EMPEROR-Preserved and DELIVER trial.

EMPEROR-Preserved outcomes	**Empagliflozin *n*=2997**	**Placebo *n*=2991**	**HR (95% CI)**	***p* value**
Primary composite outcome events, *n* (%)	415 (13.8)	511 (17.1)	0.79 (0.69–0.90)	<0.001
HF hospitalization	259 (8.6)	352 (11.8)	0.73 (0.60–0.88)	
CV death	219 (7.3)	244 (8.2)	0.91 (0.76–1.09)	
Secondary outcomes				
Total HF hospitalizations, *n*	407	541	0.73 (0.61–0.88)	<0.001
eGFR mean slope change per year, ml/min/1.73 m^2	-1.25±0.11	-2.62±0.11	1.36 (1.06–1.66)	<0.001
Other prespecified analyses				
Change in KCCQ clinical summary score (52 weeks)	4.51±0.31	3.18±0.31	1.32 (0.45–2.19)	
Total hospitalizations for any cause, *n*	2566	2769	0.93 (0.85–1.01)	
Death for any cause, *n* (%)	422 (14.1)	427 (14.3)	1.00 (0.87–1.15)	
DELIVER Trial outcomes	**Dapagliflozin *n*=3131**	**Placebo *n*=3132**	**HR (95% CI)**	***p* value**
Primary composite outcome events, *n* (%)	512 (16.4)	610 (19.5)	0.82 (0.73–0.92)	<0.001
HF hospitalization/urgent visit for HF	368 (11.8)	455 (14.5)	0.79 (0.69–0.91)	
HF hospitalization	329 (10.5)	418 (13.3)	0.77 (0.67–089)	
Urgent visit for HF	60 (1.9)	78 (2.5)	0.76 (0.55–1.07)	
CV death	231 (7.4)	261 (8.3)	0.88 (0.74–1.05)	
Secondary outcomes				
Total number or worsening HF events and CV deaths, *n*	815	1057	0.77 (0.67–089)	<0.001
Change in KCCQ clinical summary score (month 8)	—	—	1.11 (1.03–1.21)	0.009
Mean change in KCCQ clinical summary score (month 8)[a]	—	—	2.4 (1.5–3.4)	
Death from any cause, *n* (%)	497 (15.9)	526 (16.8)	0.94 (0.83–1.07)	

The primary composite outcome event reduction showed a benefit in favour of both empagliflozin and dapagliflozin.
CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire. [a]In survivors.
Data retrieved from Anker et al. (EMPEROR-Preserved)[5] and Solomon et al. (DELIVER).[6]

within 30 days of a HFH (*versus* not occurring during or within that time), and the presence or absence of a previous LVEF ≤40% that improved to >40% by the time of enrolment. The overall rate of adverse events was similar in both groups whilst a total of serious adverse events (including death) were reported in 1361 (43.5%) patients in the dapagliflozin group and in 1423 (45.5%) patients in the placebo group. Dapagliflozin had to be withdrawn due to some adverse event in 182 (5.8%) patients whilst placebo was withdrawn in 181 (5.8%) patients.[6]

Possible mechanisms of action of SGLT2i in HFpEF

The biological mechanisms responsible for the clinical benefits provided by SGLT2i to HFpEF are not yet fully

Table 4. Primary composite outcome according LVEF at enrolment in EMPEROR-Preserved and DELIVER trial.

EMPEROR-Preserved	Empagliflozin	Placebo		DELIVER trial	Dapagliflozin	Placebo	
LVEF at baseline	Number of patients with events/total number of patients	Number of patients with events/ total number of patients	Hazard ratio (95% CI)	LVEF at baseline	Number of patients with events/total number of patients	Number of patients with events/ total number of patients	Hazard ratio (95% CI)
<50%	145/995	193/998	0.71 (0.57–0.88)	≤49%	207/1067	229/1049	0.87 (0.72–1.04)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)	50–59%	174/1133	211/1123	0.79 (0.65–0.97)
≥60%	132/974	145/973	0.87 (0.69–1.10)	≥60%	131/931	170/960	0.78 (0.62–0.98)

In EMPEROR-Preserved, spectral analysis of the baseline left ventricular ejection fraction (LVEF) showed a loss of efficacy (relative to the combined primary outcome) as the LVEF increased. The impact was doubtful at values ≥60% (not statistically significant), whilst the statistical significance was marginal in the subgroup with LVEF between ≥50% and <60%. In the DELIVER trial, the results regarding the combined primary endpoint were similarly positive in all the LVEF subgroups analysed (there was no loss of efficacy in patients with LVEF >60%). It should be noted that around one-third of patients have a LVEF <50%, currently considered as heart failure with mildly reduced ejection fraction.
Data retrieved from Anker et al. (EMPEROR-Preserved)[5] and Solomon et al. (DELIVER trial).[6]

elucidated and possibly many of them are also considered beneficial in the field of HFrEF. The main biological and cellular mechanisms in this context are described below (Figure 2).

Myocardial oedema reduction

From a haemodynamic perspective, SGLT2 inhibition exerts simultaneous glycosuric, natriuretic and diuretic (osmotic and non-osmotic) action. The direct effect against glucose reuptake (renal proximal convoluted tubule) promotes glycosuria, natriuresis and osmotic diuresis as glucose is excreted along with sodium and chloride, whilst indirectly also inducing natriuresis and osmotic diuresis by decreasing sodium reuptake (loop of Henle) through inhibition of the activity of the renal sodium–hydrogen exchanger (NHE3 isoform).[26,27] It has been suggested that SGLT2i-induced osmotic diuresis (loss of free water) would eject myocardial interstitial fluid into the vascular space, resulting in improved diastolic function and reduced filling pressures.[28,29]

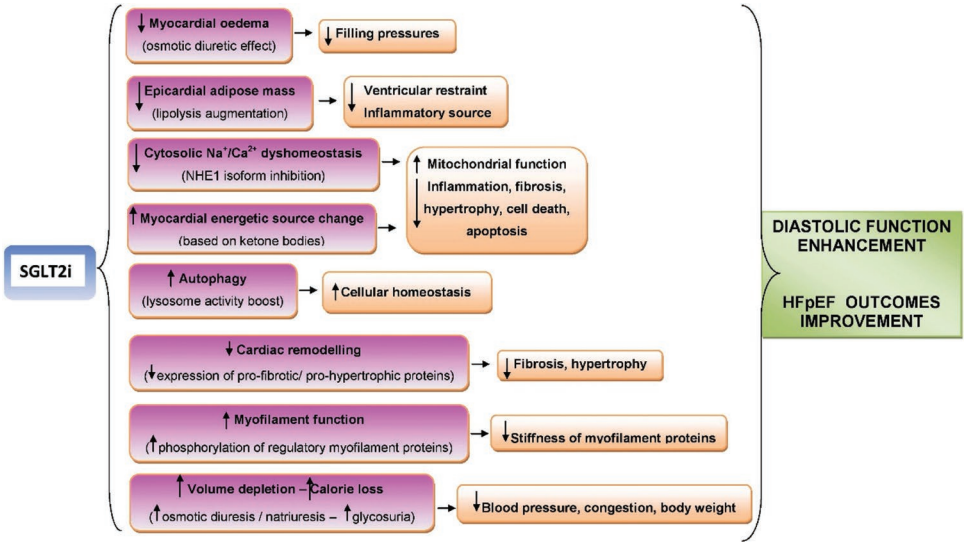
Epicardial adipose tissue mass decrease

The excessive renal elimination of glucose promoted by SGLT2i (preventing its renal reuptake) secondarily causes a decrease in plasma insulin levels and an increase in glucagon levels. This whole metabolic effect favours lipolysis with the consequent reduction of visceral adipose tissue, including epicardial adipose tissue.[27,30] Decreasing epicardial fat improves diastolic function by relieving ventricular restraint and, on the other hand, reduces the magnitude of an important source of pro-inflammatory and pro-fibrotic cytokines that closely surrounds cardiac tissue.[31,32]

Cytosolic sodium and calcium dyshomeostasis correction

The failing heart has a marked overexpression of the myocardial sodium–hydrogen exchanger (NHE1 isoform) that induces myocardial cell damage by causing an abnormal increase in intracellular sodium and calcium concentrations (dyshomeostasis).[33] NHE1 hyperactivation leads to an increase in intracellular calcium concentration (through increased sodium uptake), which apart from being arrhythmogenic, causes cardiomyocyte damage, necrosis and apoptosis.[33,34] For its part, intracellular sodium overload alters the Krebs cycle and the energy production chain by facilitating mitochondrial calcium depletion. On the other hand, pathological overexpression of NH1 activates the calcium-dependent calcineurin signalling pathway, leading to additional sodium and calcium overload, promoting oxidative damage, impaired excitation–contraction coupling, fibrosis, hypertrophy, tissue damage and cell death.[35] By inhibiting the activity of this enzyme, SGLT2i exert a homeostatic function, normalizing intracellular sodium and calcium levels and, secondarily, favouring the availability of calcium for mitochondrial function and myocardial contractility; chronic NHE1 suppression in animals has been shown to reduce oxidative stress, myocardial hypertrophy and fibrosis, improve diastolic function, and prevent cardiac remodelling.[23,36]

Figure 2. Proposed cardioprotective effect of SGLT2i HFpEF.



Sodium–glucose cotransporter 2 (SGLT2) inhibition promotes caloric loss (weight reduction) because of increased glycosuria and, at the same time, exerts a clearly positive haemodynamic effect (volume depletion through natriuresis and osmotic diuresis). Moreover, SGLT2 inhibitors (SGLT2i) act independently on metabolic, molecular and biological pathways preventing cardiac functional derangement through direct cytoplasmic Na^+ and Ca^{2+} lowering actions and attenuating the remodelling process (fibrosis, necrosis, apoptosis) related to inflammation and augmented oxidative stress. In addition, SGLT2i improve myocardial energetic supply, boost intracellular autophagy, reduce myocardial oedema, reduce epicardial fat mass, and enhance myocardial mitochondrial turnover and myofilament function.[1,30,60,84] The relevance of all these effects can explain the benefits of SGLT2i in heart failure with preserved ejection fraction (HFpEF). NHE1 isoform, cardiac sodium–hydrogen exchanger.

Myocardial energetic improvement

The use of SGLT2i improves the naturally inefficient energy supply mechanism in failing myocardium by changing its main fuel source (fat and glucose oxidation) to a more effective one (ketone bodies) with intrinsic anti-inflammatory and antiremodelling effects.[37] SGLT2i augment the production of ketone bodies, mainly ββ-hydroxybutyrate (ββ-OHB), which is attributed to an increased production of glucagon secondary to glycosuria and lipolysis and to a reduced urinary excretion of ketones since a high concentration of tubular sodium (positive ion) would attract electrically negative ketone bodies.[37,38] On the other hand, the increase in levels of ββ-OHB would inhibit class I histone deacetylase, which blunts pro-hypertrophic transcription pathways in HF[39,40] and, in addition, an increase in ββ-OHB could mitigate inflammation and the harmful hyperacetylation of mitochondrial enzymes, which results in an improvement in mitochondrial energy production.[41]

Another hypothesis suggests that SGLT2i induces the degradation of the aberrant branched-chain amino acids in the failing myocardium as an alternative source of fuel[25] and, in addition, that ketone bodies may exert an anti-inflammatory role by suppressing the activation of the P3 receptor inflammasome (NLRP3).[42] In any case, the change in cardiac fuel for one based on ketone bodies promoted by SGLT2i improves metabolism of the failing myocardium and, at the same time, mitigates the processes of inflammation, hypertrophy and fibrosis, thereby attenuating remodelling of ventricular function and enhancing cardiac output and diastolic function.[41,43,44]

Autophagy stimulation

Autophagy is an intracellular homeostatic process by which the cell eliminates organelle debris and other potentially inflammatory and damaging cellular fragments for cardiomyocytes and coronary microcirculation, leading to oxidative stress and cell death.[45] It has been documented that SGLT2i induce autophagy in dysfunctional intracellular organelles by the activation of adenosine monophosphate-activated protein kinase (AMPK), sirtuin 1 (SIRT1) and/or hypoxia-inducible factors 1α/2α that are stimulant mediators of

lysosome-mediated autophagy and, therefore, of the maintenance of cellular homeostasis.[46,47]

Antifibrotic and antihypertrophic effects

Increased interstitial fibrosis and cardiomyocyte hypertrophy are common elements in HFpEF and both are related to impaired diastolic function. Both processes (fibrosis and hypertrophy) augment myocardial stiffness and modify ventricular geometry, which alters ventricular filling and increases filling pressure.[11,12] In an animal model of HFpEF (hypertensive), treatment with empagliflozin was associated with decreased development of myocardial fibrosis and less cardiac remodelling.[48] In an animal model of myocardial infarction, the use of dapagliflozin reduced fibroblastic infiltration and, therefore, the development of fibrosis.[49] A lower fibrotic content was also observed following dapagliflozin treatment in a further animal model of HFrEF induced by increased afterload.[50] The possible antifibrotic mechanism of SGLT2i would be linked to an increase in AMPK phosphorylation.[51] The activation of this metabolic pathway favours a lower formation of reactive oxygen species and attenuates the resulting pro-inflammatory and pro-apoptotic response.[52]

In the case of myocardial hypertrophy, ipragliflozin (another SGLT2i) reduced LV mass and interventricular septal thickness (echocardiography), whilst also attenuating the progression of cardiomyocyte hypertrophy and interstitial fibrosis (histopathological examination) in a non-diabetic obese rat model of cardiomyopathy.[53] In a female rodent model of diabetes, empagliflozin improved cardiac diastolic function (measured by the tissue Doppler-derived E'/A' ratio), which was accompanied by a reduction in the expression of pro-fibrotic/pro-hypertrophic proteins and attenuation of interstitial fibrosis and LV hypertrophy, explained by a reduction in the cross-sectional area of cardiomyocytes.[54] The DAPA-LVH study was a single-centre, double-blind, placebo-controlled trial designed to evaluate the effect of dapagliflozin 10 mg once daily (*versus* placebo) on LV hypertrophy in normotensive patients (n=66) with T2DM and LV hypertrophy (dapagliflozin arm: 32 patients). After 12 months, LV mass as assessed by cardiac magnetic resonance imaging was significantly reduced (primary outcome) with dapagliflozin (*versus* placebo) with a mean absolute change of −2.82 g (p=0.018). In addition, dapagliflozin also significantly reduced the secondary endpoints of body weight (p<0.001), visceral adipose tissue (p<0.001), subcutaneous adipose tissue (p=0.001), 24-hour ambulatory systolic blood pressure (p=0.012), nocturnal systolic blood pressure (p=0.017), insulin resistance (p=0.017) and high-sensitivity C-reactive protein (p=0.049), which may be involved in the pathophysiology of LV hypertrophy.[55]

Myofilament function enhancement

Myofilament stiffness is abnormally increased in patients with HFpEF[56] because of a profound disturbance of the phosphorylation process of titin[57] and other regulatory myofilament proteins such as myosin-binding protein C and troponin I.[58,59] Pabel et al. found that empagliflozin effectively decreased the diastolic pressure of isolated ventricular trabeculae from patients with end-stage HFrEF, whilst their systolic force was not affected. The basis for this mechanism was further elucidated when myocardial fibres from patients and rats with HFpEF were exposed to empagliflozin, and it was found that passive myofilament stiffness was decreased by increasing the level of phosphorylation of myofilament regulatory proteins. On the other hand, intravenous injection of empagliflozin in HFpEF-anesthetized rats significantly improved diastolic function whilst systolic contractility was unchanged (echocardiography).[60] Apparently, this improvement in diastolic function would be secondary to an improvement in myocardial cyclic guanosine monophosphate (cGMP)-dependent protein kinase (PKG) signalling, which is usually reduced in HFpEF.[61] In this context, empagliflozin increases PKG-dependent phosphorylation and consequently reduces the stiffness of myofilament proteins.[62]

Inflammation and oxidative stress attenuation

As previously mentioned, increased oxidative stress and inflammation are strongly associated with the development of HFpEF and its linked comorbidities.[9–11] In this context, empagliflozin was found to strongly decrease levels of pro-inflammatory markers (ICAM1, VCAM1, TNF and IL-6), and to attenuate pathological oxidative parameters (H_2O_2, 3-nitrotyrosine, GSH, peroxidation of lipids), consequently improving the relaxation of myocardial fibres in obese murine rats and in patients with HFpEF.[62,63] For its part, an improvement effect on diastolic dysfunction and a reduction in associated inflammation was also documented with dapagliflozin in a rat model of HFpEF.[64]

It is considered that the processes of fibrosis or hypertrophy development may be secondary to an underlying factor of inflammation or increased oxidative stress. Therefore, by exerting an anti-inflammatory effect, SGLT2i would favour the improvement of diastolic function and attenuate remodelling.[65]

Improvement of renal outcomes: importance in HFpEF

The presence of renal dysfunction in terms of reduced eGFR or increased albuminuria is very common in patients with HFpEF and frequently related to adverse cardiac remodelling and subtle systolic dysfunction.[66] In this context, renal dysfunction is considered a consequence of a complex combination of haemodynamic factors

that include neurohormonal activation and systemic congestion and other phenomena, such as inflammation and endothelial dysfunction, all of which are commonly present in HFpEF.[67]

SGLT2i were initially introduced as antihyperglycaemic drugs based on their main mechanism of action, which is the blockade of SGLT2 channels in the renal proximal convoluted tubule (S1 and S2 segments), where the greatest reabsorption of filtered glucose occurs (approximately 90%).[6] Consequently, prevention of urinary glucose reuptake reduces its blood levels and those of glycosylated haemoglobin, resulting in decreased glucotoxicity and improvement in both pancreatic β-cell function and insulin sensitivity, in turn clinically accompanied by a decrease in body weight.[6,68,69] In this setting, it should be noted that excess adipose tissue (particularly in patients with T2DM) acts as systemic chronic inflammatory stimuli that interfere with insulin signalling (pro-inflammatory cytokine synthesis)[31,32] and, in this context, SGLT2i exert a helpful effect by inducing lipolysis, adipose tissue reduction and weight loss.[27,30] From a haemodynamic perspective, SGLT2 inhibition also exerts a simultaneous diuretic and natriuretic effect since glucose is excreted coupled with sodium and chloride as its tubular reabsorption is suppressed. These diuretic and natriuretic effects are initially produced by osmotic diuresis (proximal tubules) but, later and more importantly, through decreased sodium reuptake in the loop of Henle via inhibition of the activity of the renal sodium–hydrogen exchanger (NHE3 isoform).[9,26,27]

Aside from their metabolic and haemodynamic actions, SGLT2i exert different nephroprotective actions important for patients with HF, for example, by regulating renal haemodynamics, SGLT2i can decrease hypertension and glomerular hyperfiltration, hyperalbuminuria and chronic hypoxia, all important mechanisms implicated in the development of chronic kidney disease.[70] By blocking the reabsorption of sodium in the proximal tubule, its distal availability in the macula densa is increased. Consequently, aberrant tubular-glomerular feedback is restored, causing vasodilation of the afferent arterioles and vasoconstriction of the efferent arterioles that contribute to reducing glomerular hyperfiltration and intra-glomerular pressure (involved in glomerular fibrosis) without increasing renal vascular resistance.[71] On the other hand, SGLT2i reduce the increase in albumin excretion by restoring the glomerular filtration barrier, reducing proteinuria and optimizing the function of podocytes.[72] Additionally, and by blocking sodium reuptake, SGLT2i increase renal oxygen availability and thus glomerular oxygen tension, favouring glomerular preservation.[73] On the other hand, the inhibition of SGLT2 promotes tubular protection by reducing various inflammatory and pro-fibrotic stimuli in proximal tubular cells.[9,26,27] In this context, it should be highlighted that, by blocking glucose reuptake, renal protein glycosylation is reduced as is the generation of advanced glycation end products that promote mitochondrial dysfunction, oxidative stress, inflammation and apoptosis (linked to the development of chronic diabetic kidney disease).[74] On the other hand, the abnormal reabsorption in proximal tubules of fatty acids present in patients with diabetes (elevated circulating fatty acids) causes oxidative stress, tubulointerstitial inflammation and fibrosis (renal dysfunction) that could be mitigated by SGLT2i-induced fatty acid oxidation.[75] Finally, elevated uric acid levels have been associated with increased renal inflammation and oxidative stress and, in this context, SGLT2i would promote an increased glycosuria-associated uricosuric action.[76]

From a clinical perspective, the glomerular effects secondary to the introduction of SGLT2i can result in an initial increase in albuminuria and a transient fall in eGFR.[77,78] This drop usually lasts for 4 weeks after the start of an SGLT2i and then stabilizes, showing a slower decline in renal function (*versus* placebo) in the long term accompanied by a reduction in albuminuria (30–50%).[79] In patients with T2DM, these effects are independent of blood pressure, glycaemic control or presence of diabetic kidney disease,[79] whilst they have also been observed in HF patients (with or without T2DM).[3–6]

Discussion

Considering the classification of HF phenotype according LVEF, HFpEF should be diagnosed in symptomatic patients with LVEF ≥50%.[7] From a pathophysiological perspective, HFpEF is characterized by altered diastolic properties, higher filing pressures and a conserved LVEF; the main histological features include myocardial cell hypertrophy, interstitial fibrosis, coronary microcirculatory rarefaction and vascular stiffness promoted by progressive vascular endothelial dysfunction (systemic chronic pro-inflammatory setting). In this context, HFpEF is clinically mostly exhibited by older patients and in several inflammatory conditions such as obesity, hypertension and T2DM.[9–11] Clinical randomized trials have demonstrated that various neurohormonal antagonists and, more recently, SGLT2i can reduce morbidity and mortality in patients with HFrEF (LEVF ≤40%) but, apart from SGLT2i,[80] those same agents (beta blockers, angiotensin II receptor blockers, mineralocorticoid receptor antagonists and ARNIs) have failed to demonstrate consistent benefits in patients with a LVEF ≥50%.[81–83]

SGLT2i have shown clear clinical benefits in patients prone to the development of HF,[19–22,24] in patients with

HFrEF,[3,4] and in patients with HFmrEF and HFpEF.[5,6] In a HF setting, SGLT2 inhibition results in a clear positive haemodynamic effect since both ventricular preload (via natriuresis and osmotic diuresis) and afterload (via blood pressure reduction and vascular function improvement) are reduced.[60] In addition, SGLT2i act independently on metabolic, molecular and biological pathways known to be involved in the development of HF and are thus able to prevent cardiac functional derangement through direct cytoplasmic sodium and calcium lowering actions, attenuate the remodelling process (fibrosis, necrosis, apoptosis), mitigate involved pro-inflammatory and oxidative stress processes, improve myocardial energetic supply, enhance myocardial mitochondrial turnover and myofilament function,[1,84] and improve renal outcomes.[70] The relevance of these direct cardiac effects may justify the important clinical benefit provided by SGLT2i since, despite being volume depleting, they did not substantially modify (pre/post) haematocrit, body weight, or NT-proBNP levels in patients with HFrEF,[80,85,86] whilst, on the other hand, patients with HFpEF had lower baseline NT-proBNP values (*versus* HFrEF) with similar positive results post SGLT2i introduction.[5,6]

In any case, EMPEROR-Preserved was the first study to demonstrate clinical benefits in patients with HFpEF after a long and frustrating history of failed clinical trials given that empagliflozin significantly reduced the combined risk of CV death or HFH, regardless of the presence or absence of diabetes. This study exhibited satisfactory safety results but left certain doubts regarding patients with LVEF >60%, in which empagliflozin was less effective.[5] This last effect was not observed in the population with HFpEF included in the DELIVER trial where the reduction of the primary combined endpoint significantly affected the entire spectrum of LVEF studied.[6] The pharmacological basis for these benefits are not fully understood, but it could most likely lay in the intrinsic direct pleiotropic properties of SGLT2i, resulting in improved diastolic function.[84] In conclusion, the clinical benefits (morbidity and mortality) seen in the prevention of HF development (EMPA-REG, CANVAS, DECLARE-TIMI 58 trials) in the treatment of HFrEF (DAPA-HF and EMPEROR-reduced) and HFpEF (EMPEROR-preserved, DELIVER) are probably highly related to the multiple direct pleiotropic effects of SGLT2i.[31]

Conclusion

Patients with HFpEF are estimated to represent at least half of the whole HF population, and this situation is expected to increase in the near future due to the aging population and a progressively increasing incidence of several related comorbidities such as T2DM, hypertension and obesity, amongst others. The EMPEROR-Preserved and DELIVER trials demonstrated, for the first time, clinical benefits of reduced morbidity and mortality in this group of patients regardless of the presence or absence of T2DM. The pharmacological basis for these benefits is not fully understood, but it could most likely lay in the intrinsic direct pleiotropic properties of SGLT2i, resulting in improved diastolic function.

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