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EDITORIAL COMMENT

Empagliflozin in heart failure with preserved and mildly reduced ejection fraction: prognostic benefit confirmed with different endpoint definitions

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This article refers to 'Outcomes with empagliflozin in heart failure with preserved ejection fraction using DELIVER-like endpoint definitions' by S.D. Anker *et al.*, published in this issue on pages 1400–1405.

'Although phlorizin was first isolated from the bark of the apple tree by Petersen in 1835, it was not until a half century later that it was discovered by von Mering to have glucosuric properties …'.
Eugene Braunwald[1]

A very recent review by Prof. Braunwald told the amazing story of sodium–glucose cotransporter 2 inhibitors (SGLT2i), from the discovery of their glycosuric properties in the late 19th century to the characterization of the mechanism of glycosuria (1980s), the development of the first synthetic SGLT2i (1990s), the evaluation of SGLT2i as antidiabetic drugs, and finally the unexpected finding of their great efficacy in patients with heart failure (HF).[1] The emerging paradigm is that SGLT2i are effective across the whole spectrum of HF: indeed, a prognostic benefit from SGLT2i has been observed in patients with chronic HF with reduced ejection fraction (HFrEF) or preserved/mildly reduced ejection fraction (HFmrEF/HFpEF), and also in those with acute HF. The great survival benefit from SGLT2i is likely unrelated to their diuretic effect (which is mild) and also to glycosuria (given their efficacy in both diabetic and non-diabetic patients).[1–3] Other positive effects have then been searched, and may include a modulation of cardiac metabolism and the epicardial adipose tissue phenotype, a relief from oxidative stress and inflammation, blunted sympathetic nerve activity, and the induction of a more favourable haemodynamic profile.[1] The combination of these effects might explain the survival benefit from SGLT2i even in the challenging scenario of HFpEF,

Table 1 Main patient features at baseline in DELIVER and EMPEROR-Preserved

	DELIVER	EMPEROR-Preserved
Patients randomized	6263	5988
Age (years)	72 ± 10	72 ± 9
Women	44%	45%
NYHA class		
II	75%	82%
III	25%	18%
IV	0.3%	0.3%
Hypertension	89%	90%
Diabetes	45%	49%
Obesity	45%	45%
COPD	11%	13%
Smoker	8%	7%
History of MI	26%	29%
CAD	51%	35%
History of AF/flutter	56%	52%
AF/flutter at screening	42%	35%
Prior HF hospitalization	26% (within 12 months), 40% (any prior hospitalization), 10% (subacute)	23% (within 12 months)
Mean LVEF (%)	54	54
LVEF ≥50%	66%	67%
Mean eGFR (ml/min/1.73 m^2)	61	61
Median NT-proBNP (ng/L)	1011	974
ACEi/ARB/ARNI	72%	81%
Beta-blockers	76%	86%
MRA	39%	37%
ICD	2%	4%

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

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Table 2 Main characteristics of trial design in DELIVER and EMPEREOR-Preserved

	DELIVER	EMPEROR-Preserved
Main inclusion criteria	Male or female patients aged **≥40 years**	Male or female patients aged **≥18 years** at screening (Japan: ≥20 years)
	Symptomatic HF (NYHA class II–IV) at enrolment, typical symptoms/signs of HF for ≥6 weeks, at least intermittent need for diuretics LVEF >40%, evidence of structural heart disease NT-proBNP ≥300 ng/L (≥600 ng/L if AF/flutter)	• Chronic HF, NYHA class II–IV, LVEF >40%, NT-proBNP >300 ng/L (>900 ng/L if AF/flutter) • Structural heart disease or documented HF hospitalization <12 months
	Both ambulatory and hospitalized patients may be enrolled and randomized. Patients currently hospitalized for HF must be off intravenous HF medications for ≥24 h before randomization	Stable dose of oral diuretics, if prescribed
Main exclusion criteria	Therapy with SGLT2i <4 weeks or previous intolerance to SGLT2i	• Current or prior use of SGLT2i or combined SGLT1 and two inhibitors • Known allergy or hypersensitivity to empagliflozin or other SGLT2i
	Type 1 diabetes	
	eGFR <25 ml/min/1.73 m^2	**eGFR <20 ml/min/1.73 m^2 or dialysis**
	SBP <95 mmHg	Symptomatic hypotension and/or SBP <100 mmHg
	SBP ≥160 mmHg (if not on treatment) or ≥180 mmHg	SBP ≥180 mmHg
	MI, unstable angina, coronary revascularization, ablation of AF/flutter, valve repair/replacement <12 weeks	MI, CABG or other major cardiovascular surgery, stroke or TIA <90 days
	Planned coronary revascularization, ablation of AF/flutter or valve repair/replacement	
	Stroke or TIA <12 weeks	
	Probable alternative or concomitant diagnoses which could account for HF symptoms and signs	
	BMI >50 kg/m^2	BMI ≥45 kg/m^2
	Severe impairment of liver function	Liver disease
	HF due to CMP or other specific aetiologies	HF due to CMP or other specific aetiologies
	Life expectancy <2 years	Life expectancy <1 year
		Acute HF
		Heart transplant recipient or listed for heart transplant
		History of ketoacidosis
Primary endpoint	Time to the first occurrence of any of the components of this composite: (i) CV death; (ii) HF hospitalization; (iii) **urgent HF visit** (e.g. emergency department or **outpatient visit**)	Time to first event of adjudicated CV death or adjudicated **HF hospitalization**
Endpoint adjudication	**Deaths with undetermined cause excluded from the primary endpoint**	**Deaths with undetermined cause included in the primary endpoint** **HF hospitalization events:** • **Physical findings or laboratory tests not needed to confirm the events** • **Events of 12–24 h admitted if intensification of treatment was not only oral diuretics**

Table 2 (Continued)

	DELIVER	EMPEROR-Preserved
Secondary endpoints	Total number of HF events (first and recurrent) and CV death	
		Occurrence of adjudicated HF hospitalization
	Change from baseline in KCCQ **total symptom score** at 8 months	Change from baseline in KCCQ **clinical summary score** at week 52
	Time to CV death	Time to CV death
	Time to all-cause death	Time to all-cause death
	Composite renal endpoint: sustained ≥50% reduction of eGFR or end-stage kidney disease or renal death or need for renal replacement therapy	Composite renal endpoint: sustained ≥40% reduction of eGFR or end-stage kidney disease or need for renal replacement therapy
		Time to first HF hospitalization
		All-cause hospitalization
		eGFR slope of change from baseline
		Time to onset of diabetes
Safety endpoints	Serious AEs, AEs leading to treatment discontinuation, amputations, AEs leading to amputation, and potential risk factor AEs for amputations affecting lower limbs	AEs, serious AEs, selected AEs of interest
Statistical analysis plan	Dual assessment of the primary endpoint in **both the full population, and in those with LVEF <60%**, then subsequent testing of secondary endpoints in the full population and in those with LVEF <60%	**'Standard' analysis of the primary endpoint in the full population** (plus subgroup analysis: LVEF <50%, 50–59%, ≥60%)

AE, adverse event; AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; CMP, cardiomyopathy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT1, sodium–glucose cotransporter 1; SGLT2i, sodium–glucose cotransporter 2 inhibitor; TIA, transient ischaemic attack.
The corresponding items (inclusion and exclusion criteria, etc.) are reported side by side. The main differences in the inclusion and exclusion criteria and statistical analysis plan are highlighted in bold.

where drugs targeting the neurohormonal axes or specific disease features (such as diastolic dysfunction or fibrosis) have consistently failed to improve clinical outcomes.[4]

The Empagliflozin Outcome Trial in Patients with Chronic HFpEF (EMPEROR-Preserved) trial provided the first demonstration of a prognostic benefit from empagliflozin in HFpEF (and HFmrEF).[5,6] This study randomized 5988 patients with New York Heart Association class II–IV HF, left ventricular ejection fraction (LVEF) >40% and elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) to empagliflozin 10 mg once daily or placebo, in addition to usual therapy. The main population characteristics are reported in *Table 1*. Over a median 26-month follow-up, 13.8% of patients in the empagliflozin group and 17.1% in the placebo group experienced the primary endpoint of cardiovascular death or first HF hospitalization (hazard ratio 0.79, 95% confidence interval 0.69–0.90; $p < 0.001$), with a number needed to treat of 31. Empagliflozin displayed a satisfactory safety profile.[5]

The Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction HF (DELIVER) trial has been recently completed. The design of the DELIVER trial had many similarities to that of EMPEROR-Preserved, but with some particularities in the inclusion and exclusion criteria and a more elaborate statistical analysis plan[7] (*Table 2*). DELIVER baseline patient characteristics have been presented and compared to the EMPEROR-Preserved and other HFpEF trials,[8] while the complete results are expected in the European Society of Cardiology meeting in August 2022.

In this issue of the Journal, Anker and colleagues reappraise the results from EMPEROR-Preserved on the light of the different definition of several endpoints in the DELIVER trial on dapagliflozin in HFpEF.[9] The differences between the two trials primarily relate to the inclusion of urgent HF clinic visits, requirement of laboratory testing, classification of death of unknown cause and incorporation of renal death in the renal endpoint[9] (*Table 2*). On top of that, DELIVER pre-specified an analysis of the primary endpoint in the subgroup of patients with LVEF <60%.[9] When using the DELIVER endpoint definition, most values of relative risk reduction became slightly greater than in EMPEROR-Preserved, and the renal endpoint was reached in patients with LVEF <60%.[9]

These findings are particularly meaningful from a trial science perspective. Indeed, this kind of analysis allows to learn about the impact of endpoint definitions on trial results, which is important to design future studies. Comparing the effects of slightly different inclusion and exclusion criteria on trial populations is similarly important. As recently reported,[8] the patient populations of EMPEROR-Preserved and DELIVER are remarkably similar despite some prominent differences in inclusion and exclusion criteria, such as the enrolment of both hospitalized and ambulatory patients in DELIVER, but not in EMPEROR-Preserved (*Table 2*). These

results suggest that a strict standardization of endpoint definitions and enrolment criteria is not required, at least in HFpEF trials. The proper definition of HFpEF is likely much more relevant, and should include preserved systolic function as well as the evidence of structural heart disease and elevated natriuretic peptides, to avoid misclassification of HFpEF, as likely occurred in Treatment of Preserved Cardiac Function HF With an Aldosterone Antagonist (TOPCAT)[10] and in other studies such as a sub-analysis of Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA).[11]

To summarize, considering the slightly different endpoint definitions employed in the DELIVER trial does not change the conclusions of the EMPEROR-Preserved trial. These findings add to the previous report that population characteristics are quite similar despite different inclusion and exclusion criteria, and will be likely instrumental to a head-to-head comparison between empagliflozin and dapagliflozin in HFpEF, as previously done in HFrEF.[12]

Conflict of interest: none declared.

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