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Outcomes with empagliflozin in heart failure with preserved ejection fraction using DELIVER-like endpoint definitions

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Aims

To report data from EMPEROR-Preserved according to prespecified endpoints of DELIVER.

Methods and results

In order to assess the impact of DELIVER-like definition on EMPEROR-Preserved outcomes, the following differences were reconciled: (1) the primary outcome in DELIVER added urgent heart failure (HF) visits to cardiovascular death or HF hospitalizations; (2) the EMPEROR-Preserved trial did not require documentation of physical findings or laboratory tests for confirming a HF hospitalization and it included events of 12–24 h if intensification of treatment was not only oral diuretics; (3) DELIVER excluded undetermined causes of deaths from the primary endpoint; (4) the composite renal endpoint in DELIVER included a sustained $\geq 50\%$ decline in estimated glomerular filtration rate and incorporated renal death; and (5) DELIVER will assess outcomes in the overall population and in patients with ejection fraction (EF) $< 60\%$ separately. Using the endpoint definitions from DELIVER, the primary outcome overall occurred in 13.1% in the empagliflozin and 16.8% in the placebo group (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.67–0.87; $p < 0.0001$). The relative risk reduction (RRR) changed from 21% to 24% when urgent HF visits were added, and undetermined death was eliminated. Compared to overall population RRR of 24%, it was 28% in patients with EF $< 60\%$. Death from cardiovascular causes excluding undetermined causes occurred in 6.2% in the empagliflozin and in 7.1% in the placebo group (HR 0.88, 95% CI 0.73–1.07). The RRR for the composite renal endpoint changed from 22% in the overall population (HR 0.78, 95% CI 0.54–1.13) to 40% when patients with EF $< 60\%$ were assessed ($p = 0.037$).

Conclusion

Findings from EMPEROR-Preserved were modestly altered when analysed using cardiovascular trial endpoint definitions of the DELIVER trial. For the composite renal endpoint, the effect of empagliflozin became statistically significant in patients with EF $< 60\%$ using the DELIVER definition.

Keywords

EMPEROR-Preserved • Heart Failure with preserved ejection fraction • Empagliflozin • Outcomes • DELIVER

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Introduction

The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) trial was the first published outcome trial specifically designed to assess the effect of sodium–glucose co-transporter 2 (SGLT2) inhibitors on cardiovascular and renal outcomes in patients with heart failure (HF) and preserved ejection fraction (HFpEF).¹ It showed that empagliflozin significantly reduced the risk of cardiovascular death or hospitalization for HF in these patients. The ongoing DELIVER (Dapagliflozin Evaluation to Improve the LIVES of Patients with Preserved Ejection Fraction Heart Failure) trial was designed to study the effect of dapagliflozin in the same target population.² Taken together, the results of these two trials may increase our understanding of the effect of SGLT2 inhibition in patients with HFpEF. However, the definition of endpoints in both trials have several meaningful differences, potentially making comparison of the results difficult. Thus, we report data from the EMPEROR-Preserved trial according to prespecified endpoints of the DELIVER trial.

Methods

Study design and patient population

The design for the EMPEROR-Preserved trial has been described previously.³ In brief, the EMPEROR-Preserved trial was a phase 3, placebo-controlled trial that enrolled adult patients who have chronic HF with New York Heart Association (NYHA) functional class II–IV symptoms and a left ventricular ejection fraction (LVEF) of >40% with no prior measurement of ≤40%. Patients were also required to have elevated N-terminal pro-hormone B-type natriuretic peptide (NT-proBNP) levels (>900 or >300 pg/ml in patients with and without atrial fibrillation, respectively) and a documented hospitalization for HF within 12 months prior to enrolment or evidence of structural heart disease. Patients were randomized to receive either placebo or empagliflozin 10 mg once daily.

Trial outcomes

The outcomes of the EMPEROR-Preserved trial have been described and reported in detail previously.^{1,3} In brief, the primary outcome was the composite of cardiovascular death or hospitalization for HF. Secondary outcomes included a composite renal endpoint (sustained ≥40% decline in estimated glomerular filtration rate [eGFR] or end-stage kidney disease or need for renal replacement therapy). The investigation conforms with the principles outlined in the Declaration of Helsinki. The ethics committee at each participating centre approved the trial, and all patients provided written informed consent.

Using the endpoint definitions similar to DELIVER, the outcomes for this analysis included the primary outcome of cardiovascular death or worsening HF events (consisting of adjudicated hospitalization for HF [following Hicks criteria]⁴ or investigator-reported urgent care or emergency room visit for HF requiring intravenous therapy) and secondary outcomes included time to worsening HF event, cardiovascular death, and composite renal endpoint (sustained ≥50% decline in eGFR or end-stage kidney disease or renal death or need for renal replacement therapy).

In summary, outcomes in the EMPEROR-Preserved and DELIVER trials differ in five ways. First, the primary composite outcome in EMPEROR-Preserved was cardiovascular death or hospitalizations for HF, whereas DELIVER also included urgent HF visits requiring evidence of HF therapy other than only use of oral diuretics. Second, because it was based on the Hicks criteria, DELIVER required patients to have an unscheduled hospital admission for a primary diagnosis of HF with a length of stay that exceeds 24 h and have signs, symptoms, and diagnostic testing results consistent with the diagnosis of HF to fulfil the criteria for hospitalization for HF.⁴ In addition, patients were required to receive treatment specifically directed at HF. In contrast, EMPEROR-Preserved did not require documentation of worsening physical findings or worsening laboratory tests for confirming a HF hospitalization and it included events of 12–24 h if intensification of treatment was not only based on the use of oral diuretics. Third, EMPEROR-Preserved included undetermined causes of deaths in the category of cardiovascular death, while DELIVER will not. Fourth, as for the renal composite endpoints, EMPEROR-Preserved included a sustained ≥40% decline in eGFR and did not include renal death, while DELIVER will include a sustained ≥50% decline in eGFR and incorporate renal death; both definitions included the development of end-stage kidney disease as a renal event. Lastly, DELIVER will assess outcomes in the total population and in those with ejection fraction <60% separately.

Statistical analysis

Like DELIVER, the primary endpoint was assessed in a dual primary analysis – the full population and in those with left ventricular ejection fraction (LVEF) <60%. This was also done for the other prespecified endpoints. All endpoints were analysed using Cox regression model. Models were adjusted for baseline covariates of sex, age, eGFR, LVEF, region and diabetes.

Results

Patient characteristics

From 27 March 2017 to 13 April 2020, a total of 5988 patients were randomly assigned to receive either empagliflozin or matching placebo at 622 centres in 23 countries. Baseline characteristics and HF therapies were well balanced between the two treatment groups and have been reported in detail previously. The median duration of follow-up was 26.2 months (interquartile range 18.1–33.1).

Outcomes

Using the endpoint definitions in DELIVER, the primary composite outcome of cardiovascular death or worsening HF event occurred in 394 of 2997 patients (13.1%) in the empagliflozin group and in 502 of 2991 patients (16.8%) in the placebo group (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.67–0.87; $p < 0.0001$) (Figure 1 and Table 1). Compared to the overall population (relative risk reduction [RRR] 24%), the RRR in patients with LVEF <60% changed to 28% (HR 0.72, 95% CI 0.61–0.84; $p < 0.0001$). A worsening HF event occurred in 263 patients (8.8%) in the empagliflozin group and in 366 (12.2%) in the placebo group (HR

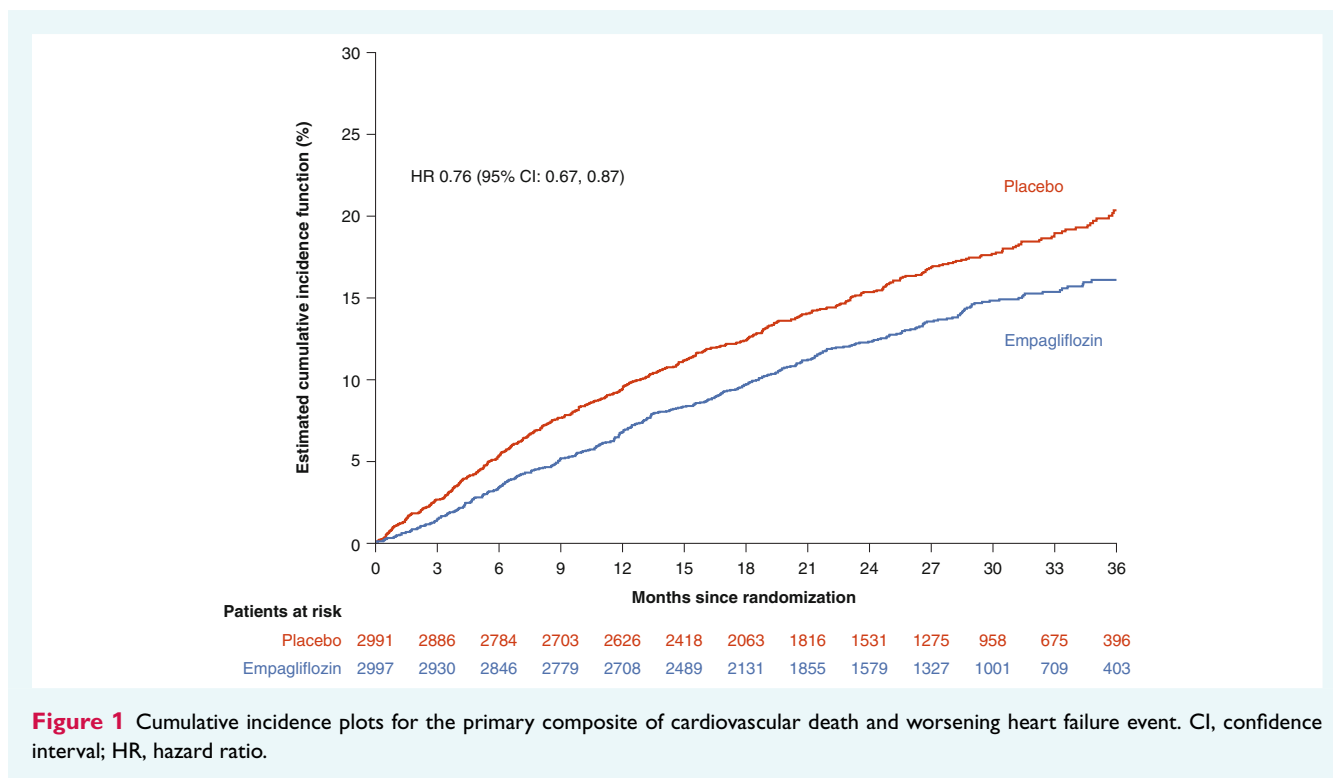


Figure 1 Cumulative incidence plots for the primary composite of cardiovascular death and worsening heart failure event. CI, confidence interval; HR, hazard ratio.

0.69, 95% CI 0.59–0.81; $p < 0.0001$) (Figure 2A). Death from cardiovascular causes occurred in 186 patients (6.2%) who received empagliflozin and in 213 (7.1%) who received placebo (HR 0.88, 95% CI 0.73–1.07) (Figure 2B). When only patients with LVEF $<60\%$ were considered, the RRR increased from 31% to 37% for worsening HF events (HR 0.63, 95% CI 0.51–0.76) and from 12% to 15% for death from cardiovascular cause (HR 0.85, 95% CI 0.67–1.07).

In the overall population, there was a total of 50 and 62 composite renal endpoints (HR 0.78, 95% CI 0.54–1.13) (Table 1) in the empagliflozin and placebo groups, respectively. In patients with LVEF $<60\%$, the RRR in patients with LVEF $<60\%$ increased to 40% (HR 0.60, 95% CI 0.37–0.97; $p = 0.0371$).

Discussion

In this analysis we evaluated data from the EMPEROR-Preserved trial using endpoint definitions from DELIVER and show several key findings. The risk of the primary composite outcome of cardiovascular death or worsening HF event (hospitalization for HF or an urgent HF visit requiring intravenous therapy) was significantly lower in the empagliflozin group than in the placebo group. This benefit numerically increased when only patients with LVEF $<60\%$ were analysed. The effects on the primary endpoint were seen consistently across all prespecified subgroups, including patients with and without diabetes. Empagliflozin also reduced the time to first worsening HF event. This pattern of benefit was similar to those reported using the original endpoint definitions of the EMPEROR-Preserved trial.

When urgent HF visits were added and undetermined death as part of cardiovascular death was eliminated from the primary

composite endpoint, there was a modest impact on the effect size, with the RRR changing from 21% to 24%. Although the event rates decreased for cardiovascular death after excluding undetermined causes of death, a similar increase in RRR was noticed (i.e. from 9% to 12%). Undetermined causes of death are widely assumed to be due to sudden cardiac death and are generally incorporated into the definition of cardiovascular death; however, in HFpEF, undetermined causes of death are not well defined. Compared to the overall population, the RRR for the primary endpoint in patients with LVEF $<60\%$ increased from 24% to 28%.

It is particularly noteworthy that the RRR for the composite renal endpoint increased considerably (to a 40% reduction in risk) and became nominally significant when a threshold change of a $\geq 50\%$ decrease in eGFR and renal death were included in the analysis and when the analysis was confined to patients with ejection fraction $<60\%$. These findings are the first to suggest a significant treatment benefit on hard kidney outcomes in patients with HFpEF with LVEF $<60\%$. This observation extends our previous finding of a 50% reduction in the risk of a renal event with empagliflozin in patients with HF and an ejection fraction of $\leq 40\%$, which was reported in the EMPEROR-Reduced trial.

The EMPEROR-Preserved trial varied from the strict Hicks criteria of defining HF hospitalizations since, in many global trials, the documentation of physical findings or testing for laboratory abnormalities that are required to meet all criteria are often missing. In EMPEROR-Preserved, the clinical events committees were instructed to use their best judgement about the occurrence of a HF hospitalization if patients had worsening symptoms and required intensification of treatment for HF.

Table 1 Primary and secondary cardiovascular outcomes according to different definitions

Definition from trial	Endpoint	Empagliflozin (n = 2997)		Placebo (n = 2991)		Hazard ratio (95% CI)	p-value
		N (%)	Events/100 patient-years	N (%)	Events/100 patient-years		
EMPEROR-Preserved	Cardiovascular death or HHF	415 (13.8)	6.9	511 (17.1)	8.7	0.79 (0.69–0.90)	0.0003
	Cardiovascular death or HHF ^a	394 (13.1)	6.5	485 (16.2)	8.2	0.79 (0.69–0.90)	0.0005
	Cardiovascular death ^b or HHF ^a	369 (12.3)	6.1	461 (15.4)	7.8	0.78 (0.68–0.89)	0.0003
DELIVER definitions applied to EMPEROR-Preserved	Cardiovascular death ^b or worsening HF ^c in the overall population	394 (13.1)	6.5	502 (16.8)	8.5	0.76 (0.67–0.87)	<0.0001
DELIVER definitions applied to EMPEROR-Preserved	Cardiovascular death ^b or worsening HF ^c in patients with LVEF <60%	263/2023 (13.0)	6.4	357/2018 (17.7)	9.0	0.72 (0.61–0.84)	<0.0001
EMPEROR-Preserved	Time to first HHF	259 (8.6)	4.3	352 (11.8)	6.0	0.71 (0.60–0.83)	<0.0001
DELIVER definitions applied to EMPEROR-Preserved	Time to worsening HF ^c in the overall population	263 (8.8)	4.4	366 (12.2)	6.2	0.69 (0.59–0.81)	<0.0001
DELIVER definitions applied to EMPEROR-Preserved	Time to worsening HF ^c in patients with LVEF <60%	165/2023 (8.2)	4.0	257/2018 (12.7)	6.5	0.63 (0.51–0.76)	<0.0001
EMPEROR-Preserved	Cardiovascular death	219 (7.3)	3.4	244 (8.2)	3.8	0.91 (0.76–1.09)	0.295
DELIVER definitions applied to EMPEROR-Preserved	Cardiovascular death ^b in the overall population	186 (6.2)	2.9	213 (7.1)	3.3	0.88 (0.73–1.07)	0.214
DELIVER definitions applied to EMPEROR-Preserved	Cardiovascular death ^b in patients with LVEF <60%	132/2023 (6.5)	3.1	158/2018 (7.8)	3.6	0.85 (0.67–1.07)	0.163
EMPEROR-Preserved	Composite renal endpoint (sustained ≥40% decline in eGFR and ESKD)	108 (3.6)	2.1	112 (3.7)	2.2	0.95 (0.73–1.24)	0.724
DELIVER definitions applied to EMPEROR-Preserved	Composite renal endpoint (sustained ≥50% decline in eGFR, ESKD and renal death) in the overall population	50 (1.7)	1.0	62 (2.1)	1.2	0.78 (0.54–1.13)	0.193
DELIVER definitions applied to EMPEROR-Preserved	Composite renal endpoint (sustained ≥50% decline in eGFR, ESKD and renal death) in patients with LVEF <60%	27 (1.3)	0.8	45 (2.2)	1.3	0.60 (0.37–0.97)	0.0371

CI, confidence interval; DELIVER, Dapagliflozin Evaluation to Improve the LVEs of Patients with Preserved Ejection Fraction Heart Failure; eGFR, estimated glomerular filtration rate; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; ESKD, end-stage kidney disease (sustained eGFR <15 ml/min/1.73 m² [for patients with baseline eGFR ≥30 ml/min/1.73 m²] or sustained eGFR <10 ml/min/1.73 m² [for patients with baseline eGFR <30 ml/min/1.73 m²] or chronic dialysis or renal transplant); HF, heart failure; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction.

^aFollowing Hicks criteria.⁴

^bExcluding undetermined death.

^cWorsening HF means HHF (Hicks criteria) or urgent visit for HF requiring intravenous therapy.

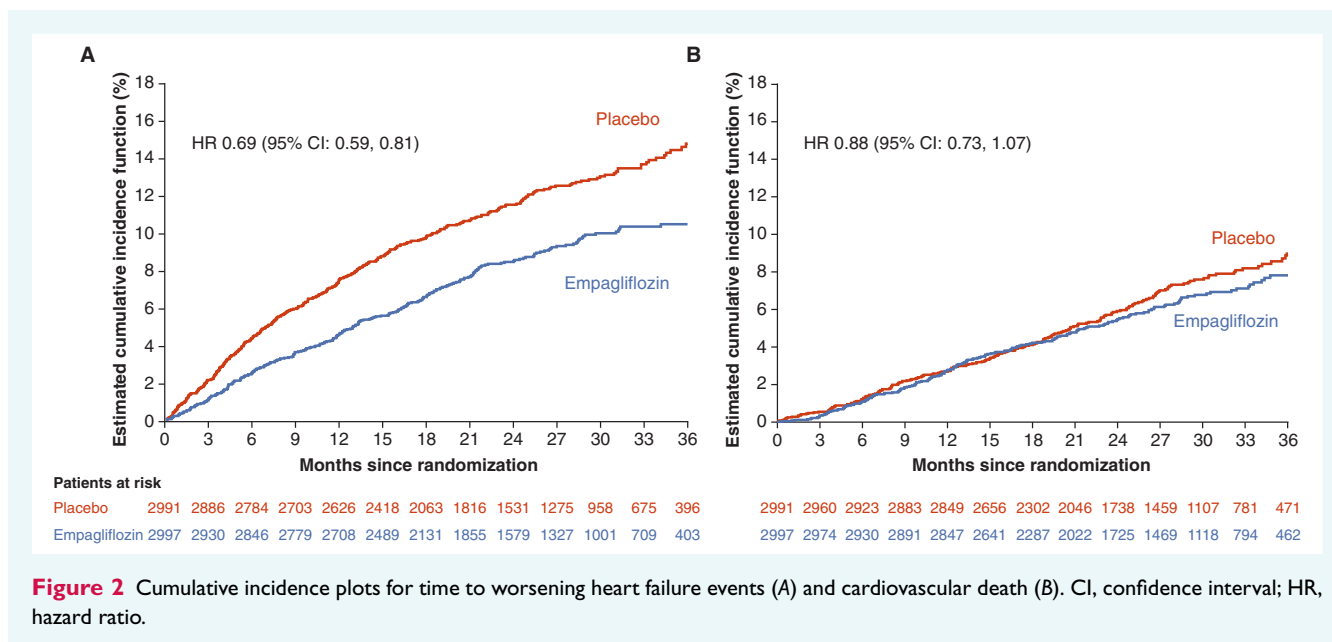


Figure 2 Cumulative incidence plots for time to worsening heart failure events (A) and cardiovascular death (B). CI, confidence interval; HR, hazard ratio.

The findings of this study should be interpreted in the context of potential limitations. This analysis was performed using endpoints not prespecified for EMPEROR-Preserved. The statistical model applied to the DELIVER trial were those prespecified in the EMPEROR trials. Emergency room and urgent care visits for HF were not adjudicated. DELIVER will also include patients recently hospitalized and those with improved LVEF, while EMPEROR did not. Of note, compared to EMPEROR-Preserved, DELIVER had more patients at baseline with history of HF hospitalization (23% within the prior 12 months in EMPEROR-Preserved vs. 26% in DELIVER), more patients with coronary artery disease (35% vs. 50.5%), and fewer patients in NYHA class II (82% vs. 75%), suggesting that patients enrolled in DELIVER were possibly somewhat sicker. A recent press release on DELIVER highlighted that dapagliflozin achieved the primary endpoint in patients with HFpEF.⁵ A detailed outline of its findings will help us to understand the effect of dapagliflozin on clinical outcomes in this population.

In conclusion, using the alternative endpoint definitions of the DELIVER trial, treatment with empagliflozin reduced the risk for cardiovascular death or worsening HF events in patients with HFpEF and this benefit was consistent across pre-specified subgroups. For cardiovascular events, the pattern of benefit was like that reported using the original endpoint definitions of the EMPEROR-Preserved trial. However, using the DELIVER criteria, the magnitude of the effect of empagliflozin to reduce the risk of a major renal event increased meaningfully and became statistically significant when patients with LVEF $\geq 60\%$ were removed from the analysis.

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