Early Benefit with Empagliflozin in Heart Failure with Preserved Ejection Fraction

Insights from the EMPEROR-Preserved Trial

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ABSTRACT

Patients with chronic or worsening heart failure (HF) are at a high risk for morbidity, mortality and impaired health related quality of life (HRQoL). This risk is present in the short-term and increases significantly once hospitalized. Thus, it is crucial that HF therapies not only improve outcomes, but do so early post -initiation. The recent EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trial studied empagliflozin in patients with HFpEF and showed a significant reduction in the risk of cardiovascular death or HF hospitalization. This benefit also extended to health and functional status. We highlight that this benefit was early with Cox regression analysis achieved nominal statistical significance for separation between the empagliflozin and the placebo arms by day-18 for time to cardiovascular death or HF hospitalization (hazard ratio at 18 days, 0.41 [95% CI, 0.17-0.99]) and sustained for the rest of the trial period. A similar pattern of early and sustained benefit was seen for all domains of HRQoL scores and New York Heart Association functional class with significant improvement when first assessed at 3-months and 4 weeks, respectively. Our results reinforce the importance of early initiation of treatment in patients with HFpEF.

Patients with chronic heart failure (HF) are at a high risk for adverse outcomes and once hospitalized, the risk for readmission is ~20-25 at 1 month and ~50% at 6 months, with a one-year post-discharge mortality rate ranging between 20-30%. (1) Given the high risk of morbidity and mortality in both the chronic and the worsening HF settings, it is important to have therapies that not only improve overall outcomes, but that the onset of benefit is early post-initiation. This is important for not only the mortality and morbidity outcomes but for health status also, as HF patients suffer from significantly impaired health related quality of life (HRQoL).

Contemporary therapies for HF with reduced ejection fraction (HFrEF) provide early meaningful benefit. In-hospital initiation of sacubitril-valsartan therapy was associated with a lower rate of rehospitalization for HF at 8 weeks than enalapril therapy..(2) The DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, showed reduction in composite of cardiovascular death or worsening HF with dapagliflozin, with a sustained statistically significant benefit by 28 days after randomization (HR, 0.51 [95% CI, 0.28-0.94]). (3) Similarly, in the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) trial, empagliflozin showed a statistically significant 58% relative reduction in mortality, HF hospitalizations or urgent HF visit at 12 days after initiation. (4)

The clinical burden of HF with preserved ejection fraction (HFpEF) is similar to HFrEF, however, until now no trial had met its primary endpoint in a clinically meaningful and statistically significant manner for the overall study population. The recent EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trial studied empagliflozin in patients with HFpEF and a left ventricular ejection fraction >40% and showed a significant reduction in the risk of cardiovascular death or HF hospitalization. (5) This benefit was also seen for the two hierarchical endpoint including total (first and recurrent) HF hospitalization as well as renal function preservation, as assessed

by the deterioration of the rate of slope of estimated glomerular filtration rate. Health status, as measured by the KCCQ improved at all time points when assessed (3, 8, and 12 months) for all domains (total symptom score [TSS], clinical summary score [CSS], and the overall summary score [OSS]). (6)

As this was the first trial in patients with HFpEF that met its primary endpoint, there is interest in assessing how early the benefits were achieved. Overall, the patient population within the EMPEROR Preserved trial was a modest risk population. The event rate in the placebo arm for the primary endpoint of cardiovascular death or HF hospitalization was 8.7 per 100-person year, cardiovascular mortality 3.8 per 100-person year, ~30% of patients were not on loop diuretics, 81.6% of patients had New York Heart Association functional class I-II symptoms, and the mean (SD) KCCQ CSS score was 70.4 (21.2) at baseline.

Despite this, the benefits with the use of empagliflozin were seen early and consistently. The Cox regression analysis achieved nominal statistical significance for separation between the empagliflozin and the placebo arms by day-18 for time to cardiovascular death or HF hospitalization (hazard ratio at 18 days, 0.41 [95% CI, 0.17-0.99]), and the statistical significance of this benefit was sustained from there on after which boundary of the upper confidence interval remained below unity for the rest of the trial period. (**Figure 1**). (7)

A similar pattern of early and sustained benefit was seen for HRQoL scores as well. All three KCCQ domains, CSS, TSS, and OSS, were statistically significant improved when first assessed at 3 months, and these benefits were sustained when measured at 8 and 12 months (**Figure 2A**). In the responder analysis, the odds for 5, 10, and 15 points improvements were all significantly improved when first assessed at 3-months (**Figure 2B**). Patients treated with empagliflozin also had a ~20%-50% greater odds of having a less severe New York Heart Association functional class than patients on placebo; with the treatment difference statistically significant at all time points from week 12 through week 148 after randomization. While the KCCQ was first measured at 3 months, New York Heart Association functional class were first

assessed at 4-weeks and similar beneficial trend with empagliflozin were seen at the time point (**Table 1**).

Taken together these results reinforce early sustained clinical, health status, and quality of life benefits with empagliflozin in patients with HFpEF, underscoring the need for timely initiation of therapy. How these results replicate in a sicker population of patients with HFpEF needs further study.

DISCLOSURES

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Figure Legend

Figure 1: Effect of empagliflozin vs. placebo on for time to cardiovascular death or HF hospitalization.

HR, hazard ratio; CI, confidence interval.

*Adapted from: Packer M, Butler J, Zannad F, Filippatos G, Ferreira JP, Pocock SJ, Carson P, Anand I, Doehner W, Haass M, Komajda M, Miller A, Pehrson S, Teerlink JR, Schnaidt S, Zeller C, Schnee JM, Anker SD. Effect of Empagliflozin on Worsening Heart Failure Events in Patients With Heart Failure and Preserved Ejection Fraction: EMPEROR-Preserved Trial. Circulation. 2021 Oct 19;144(16):1284-1294.

Figure 2: Effects of empagliflozin vs. placebo on Kansas City Cardiomyopathy Questionnaire.

2A: Change in mean scores.

2B: Responder analysis. Multiple imputation was used to account for missing KCCQ values. Patients who died before respective week were counted as not improved/deteriorated. To account for ceiling/flooring effects, patients with a baseline KCCQ values of ≥95 or ≥90 or ≥85 or ≤5 points were considered to have 5- or 10- or 15-point improvement or ≥5 point deteriorated if their values remained ≥ 95 or 90 or 85 or ≤5 points

CI, confidence interval; CSS, clinical summary score; TSS, total summary score; OSS, overall summary score.

*****Figure from: Butler J, Filippatos G, Siddiqi TJ, Brueckmann M, Böhm M, Chopra VK, Ferreira JP, Januzzi JL, Kaul S, Piña IL, Ponikowski P, Shah SJ, Senni M, Vedin O, Verma S, Peil B, Pocock SJ, Zannad F, Packer M, Anker SD. Empagliflozin, Health Status, and Quality of Life in Patients with Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial. Epub ahead of print 10.1161/CIRCULATIONAHA.121.057812 1.

Table 1. Odds for less severe NYHA functional class at planned study visits with Empagliflozin [8]

	Empagliflozin (n=2997)	Placebo (n=2991)	Odds ratio (95% CI)	p-value
At 4 weeks	2967	2945	1.17 (0.99–1.37)	0.063
At 12 weeks	2924	2896	1.23 (1.07–1.41)	0.004
At 32 weeks	2792	2780	1.30 (1.14–1.49)	<0.0001
At 52 weeks	2689	2683	1.37 (1.20–1.57)	<0.0001
At 76 weeks	2390	2423	1.43 (1.24–1.64)	<0.0001
At 100 weeks	1833	1857	1.21 (1.04–1.41)	0.016
At 124 weeks	1319	1306	1.33 (1.11–1.60)	0.002
At 148 weeks	779	778	1.48 (1.17–1.88)	0.001

*Table from: Packer M, Butler J, Zannad F, Filippatos G, Ferreira JP, Pocock SJ, Carson P, Anand I, Doehner W, Haass M, Komajda M, Miller A, Pehrson S, Teerlink JR, Schnaidt S, Zeller C, Schnee JM, Anker SD. Effect of Empagliflozin on Worsening Heart Failure Events in Patients With Heart Failure and Preserved Ejection Fraction: EMPEROR-Preserved Trial. Circulation. 2021 Oct 19;144(16):1284-1294.

Figure 1

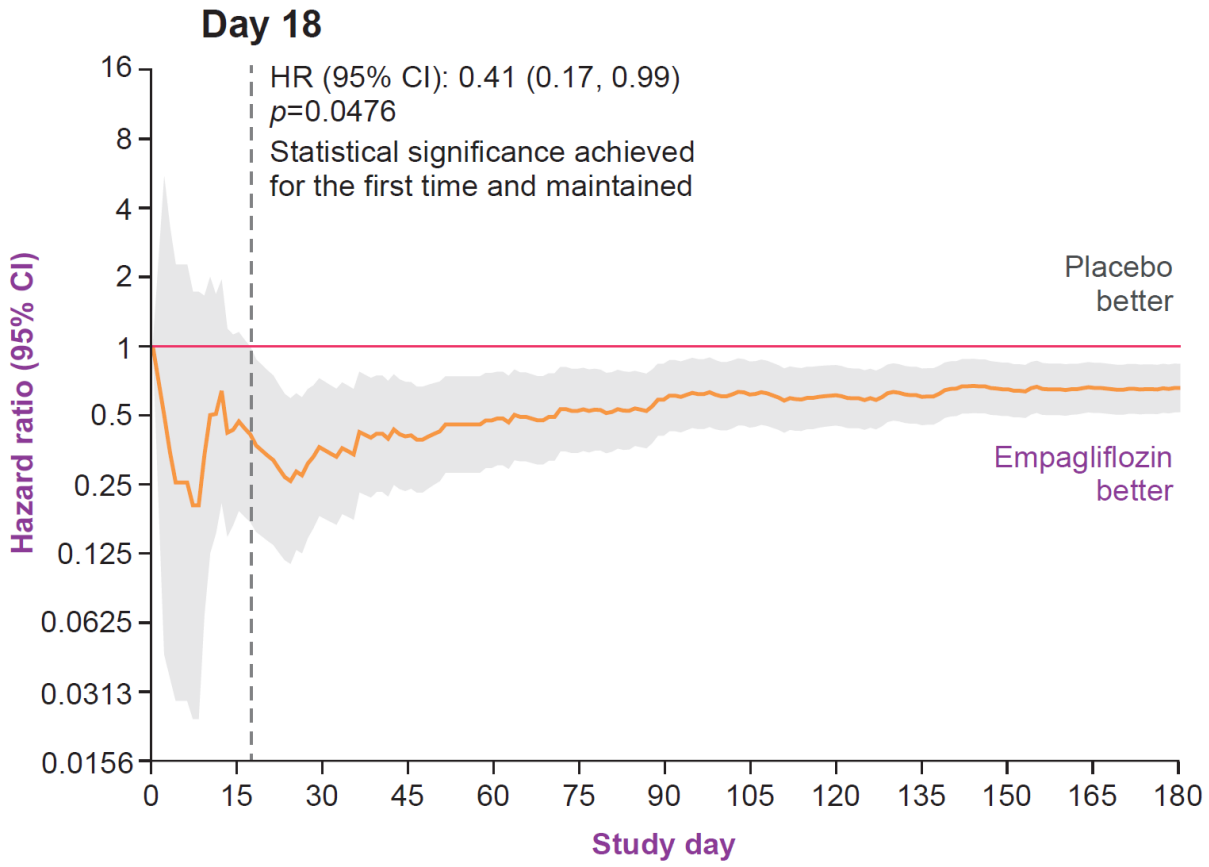
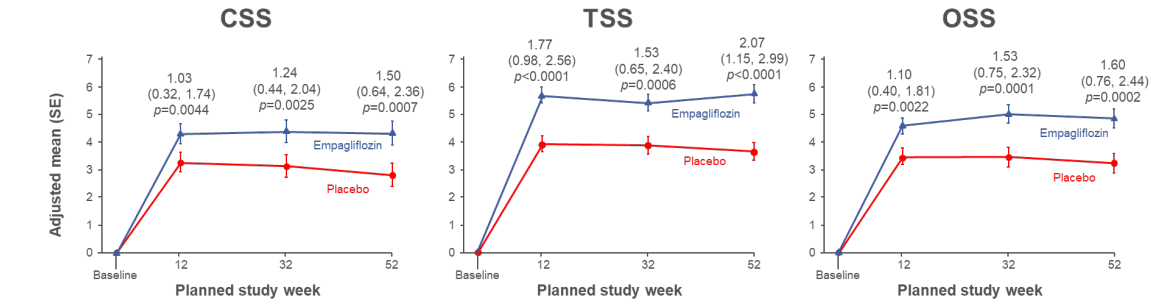


Figure 2A



No. with data at visit

Placebo	2867	2817	2576	2457	2867	2817	2575	2457	2867	2817	2576	2457
Empagliflozin	2884	2846	2616	2473	2884	2846	2616	2472	2884	2846	2616	2473

Figure 2B