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Early benefit with empagliflozin in heart failure with preserved ejection fraction: insights from the EMPEROR-Preserved trial

Javed Butler^{1*}, Tariq Jamal Siddiqi¹, Gerasimos Filippatos², João Pedro Ferreira³, Stuart J. Pocock⁴, Faiez Zannad⁵, and Stefan D. Anker⁶

¹Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA; ²National and Kapodistrian University of Athens School of Medicine, Athens University Hospital Attikon, Athens, Greece; ³Cardiovascular Research and Development Center, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Porto, Portugal; ⁴Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK; ⁵Université de Lorraine, Inserm, Centre d'Investigations Cliniques - Plurithématique 14-33, and Inserm U1116, CHRU, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France; and ⁶Department of Cardiology (CVK), and Berlin Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany

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 1-year post-discharge mortality rate ranging between 20% and 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

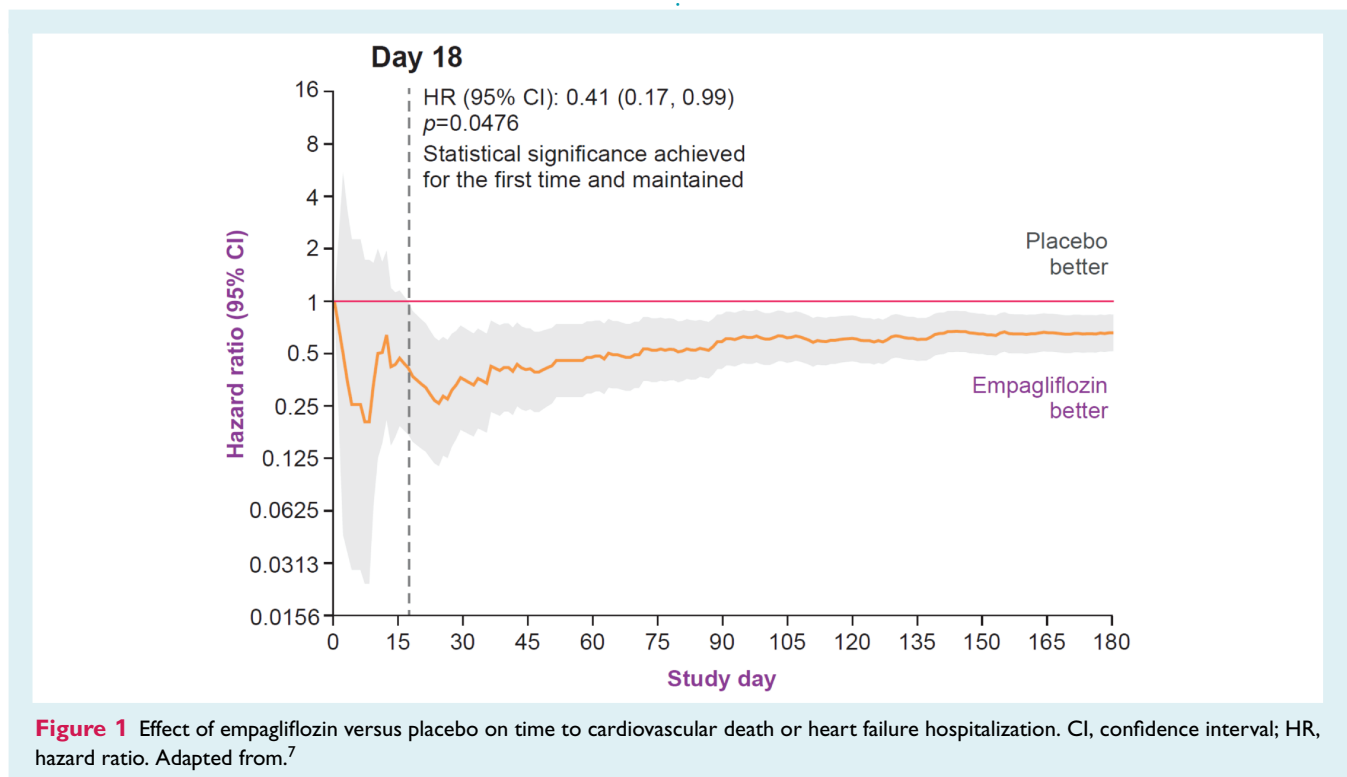


Figure 1 Effect of empagliflozin versus placebo on time to cardiovascular death or heart failure hospitalization. CI, confidence interval; HR, hazard ratio. Adapted from.⁷

*Corresponding author. University of Mississippi Medical Center, 2500 N. State Street, Jackson, MS 39216, USA. Tel: +1 601 984-5600, Fax: +1 601 984-5608, Email: jbutler4@umc.edu

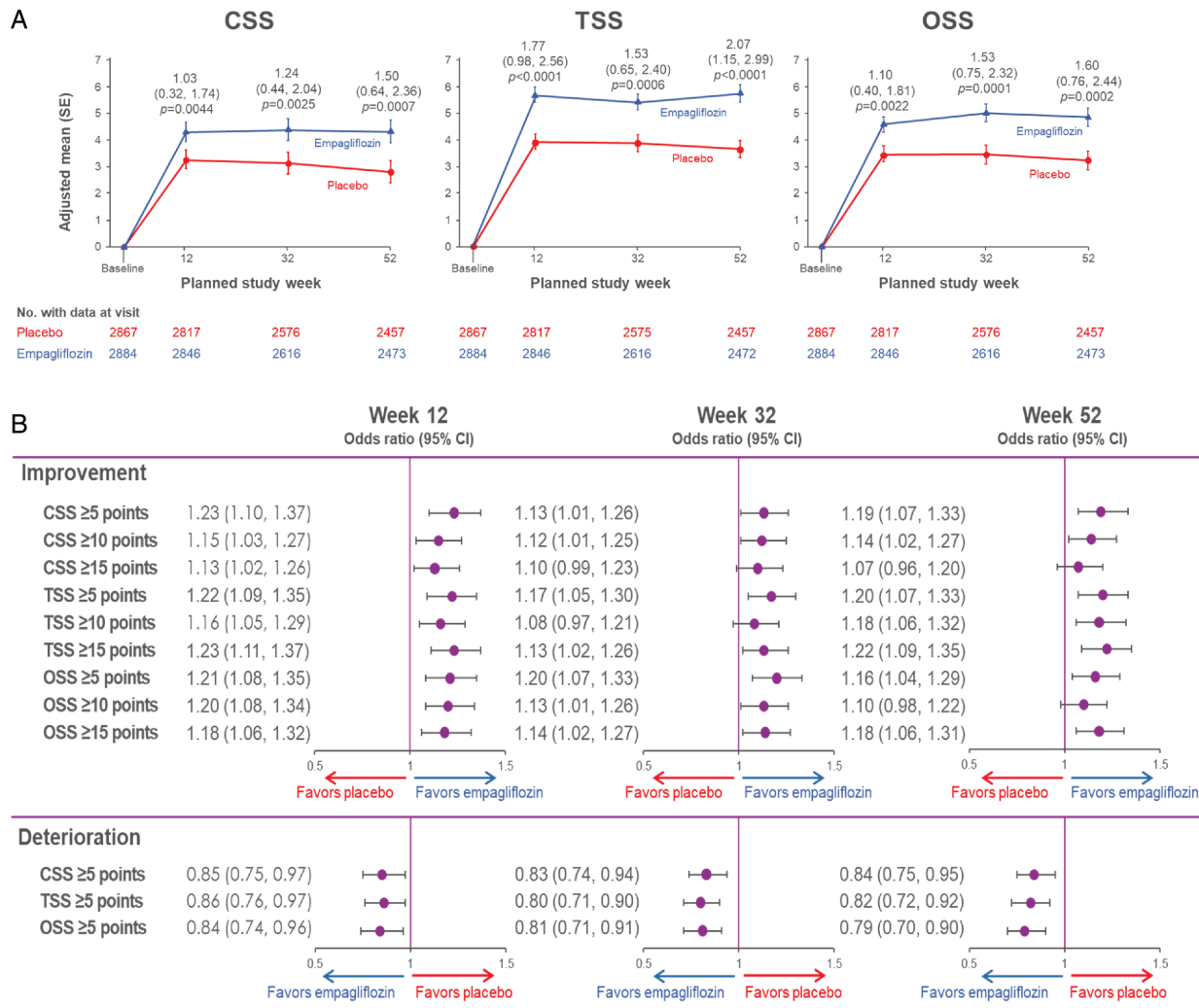


Figure 2 Effects of empagliflozin versus placebo on Kansas City Cardiomyopathy Questionnaire. (A) Change in mean scores. (B) Responder analysis. Multiple imputation was used to account for missing KCCQ values. Patients who died before respective week were counted as not improved/deteriorated. To account for ceiling/flooring effects, patients with a baseline KCCQ value 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; OSS, overall summary score; TSS, total summary score. Reproduced from.⁶

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 (hazard ratio 0.51, 95% confidence interval [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 endpoints 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 Kansas

Table 1 Odds for less severe New York Heart Association functional class at planned study visits with empagliflozin

	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

CI, confidence interval.
Reproduced from.⁷

City Cardiomyopathy Questionnaire (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 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 (standard deviation) 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 CI 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 significantly 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-point 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 was first assessed at 4 weeks and similar beneficial trends with empagliflozin were seen at the time points (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.

Conflict of interest: J.B. reports consulting fees from Boehringer Ingelheim, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, Sequana Medical, V-Wave Ltd, and Vifor. T.J.S. has no conflicts of interest to declare. G.F. reports lectures and/or Committee Member contributions in trials sponsored by Medtronic, Vifor, Servier, Novartis, Bayer, Amgen, and Boehringer Ingelheim. J.P.F. reports consulting fees from Boehringer Ingelheim during the conduct of the study. S.J.P. reports personal fees from Boehringer Ingelheim, during the conduct of the study. F.Z. reports personal fees from Boehringer Ingelheim during the conduct of the study; personal fees from Janssen, Novartis, Boston Scientific, Amgen, CVRx, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, Merck, Bayer, and Cellprothera outside of the submitted work; and other support from cardiovascular clinical trialists and Cardiorenal, outside of the submitted work. S.D.A. has received grants from Vifor; has received personal fees from Vifor, Bayer, Boehringer Ingelheim, Novartis, Servier, Impulse Dynamics, Cardiac Dimensions, and Thermo Fisher Scientific; and has received grants and personal fees from Abbott Vascular, outside the submitted work.

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