10.1161/CIRCULATIONAHA.121.057812

Empagliflozin, Health Status, and Quality of Life in Patients with Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial

Running title: *Butler et al.; Empagliflozin, health status and quality of life in HFpEF*

Javed Butler, MD[1]; Gerasimos Filippatos, MD, PhD[2]; Tariq Jamal Siddiqi, MBBS[1]; Martina Brueckmann, MD[3,4]; Michael Böhm, MD, PhD[5]; Vijay K. Chopra, MD[6]; João Pedro Ferreira, MD[7,8]; James L. Januzzi, MD[9]; Sanjay Kaul, MD[10]; Ileana L. Piña, MD[11]; Piotr Ponikowski, MD[12]; Sanjiv J. Shah, MD[13]; Michele Senni, MD[14]; Ola Vedin, MD, PhD[15]; Subodh Verma, MD[16]; Barbara Peil, Dr.sc.hum[17]; Stuart J. Pocock, MD[18]; Faiez Zannad, MD, PhD[7]; Milton Packer, MD[19,20]; Stefan D. Anker, MD, PhD[21]

[1]Department of Medicine, University of Mississippi School of Medicine, Jackson, MS; [2]National and Kapodistrian University of Athens School of Medicine, Athens University Hospital Attikon, Athens, Greece; [3]Boehringer Ingelheim International GmbH, Ingelheim, Germany; [4]Faculty of Medicine Mannheim, University of Heidelberg, Mannheim, Germany; [5]Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Saarland University, Homburg/Saar, Germany; [6]Max Superspeciality Hospital, Saket, New Delhi, India; [7]Université 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; [8]Cardiovascular Research and Development Center, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Porto, Portugal; [9]Massachusetts General Hospital and Baim Institute for Clinical Research, Boston, MA, USA; [10]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [11]Central Michigan University, Mount Pleasant, MI, USA; [12]Wroclaw Medical University, Wroclaw, Poland; [13]Northwestern University Feinberg School of Medicine, Chicago, IL; [14]Cardiovascular Department, Cardiology Division, Papa Giovanni XXIII Hospital, Bergamo, Italy; [15]Boehringer Ingelheim AB, Stockholm, Sweden; [16]Division of Cardiac Surgery, St. Michael's Hospital, University of Toronto, Toronto, Canada; [17]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; [18]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK; [19]Baylor

Heart and Vascular Institute, Baylor University Medical Center, Dallas, TX; [20]Imperial College, London UK; [21]Department 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

Address for Correspondence:

Javed Butler, MD MPH MBA
University of Mississippi Medical Center,
2500 N. State Street,
Jackson, MS 39216
Tel: 601 984-5600
Fax: 601 984-5608
Email address: jbutler4@umc.edu

**This work was presented AHA Scientific Sessions 2021, November 13-November 15, 2021.

Abstract

Background: Patients with heart failure and preserved ejection fraction (HFpEF) have significant impairment in health-related quality of life (HRQoL). In EMPEROR-Preserved, we evaluated the efficacy of empagliflozin on HRQoL in patients with HFpEF and whether the clinical benefit observed with empagliflozin varies according to baseline health status.
Methods: HRQoL was measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline, 12, 32 and 52 weeks. Patients were divided by baseline KCCQ Clinical Summary Score (CSS) tertiles and the effect of empagliflozin on outcomes were examined. The effect of empagliflozin on KCCQ-CSS, Total Symptom Score (TSS) and Overall Summary Score (OSS) were evaluated. Responder analyses were performed to compare the odds of improvement and deterioration in KCCQ related to treatment with empagliflozin.
Results: The effect of empagliflozin on reducing the risk of time to cardiovascular death or HF hospitalization was consistent across baseline KCCQ-CSS tertiles (HR 0.83 [0.69-1.00], HR 0.70 [0.55-0.88] and HR 0.82 [0.62-1.08] for scores <62.5, 62.5-83.3 and ≥83.3, respectively; P trend=0.77). Similar results were seen for total HF hospitalizations. Patients treated with empagliflozin had significant improvement in KCCQ-CSS versus placebo (+1.03, +1.24 and +1.50 at 12, 32 and 52 weeks, respectively P<0.01); similar results were seen for TSS and OSS. At 12 weeks, patients on empagliflozin had higher odds of improvement ≥5 points (OR 1.23; 95%CI 1.10, 1.37), ≥10 points (1.15; 95%CI 1.03, 1.27), and ≥15 points (1.13; 95%CI 1.02, 1.26) and lower odds of deterioration ≥5 points in KCCQ-CSS (0.85; 95%CI 0.75, 0.97). A similar pattern was seen at 32 and 52 weeks, and results were consistent for TSS and OSS.
Conclusions: In patients with HFpEF, empagliflozin reduced the risk for major HF outcomes across the range of baseline KCCQ scores. Empagliflozin improved HRQoL, an effect that appeared early and was sustained for at least one year.
Clinical Trial Registration: ClinicalTrials.gov number NCT03057951
https://clinicaltrials.gov/ct2/show/NCT03057951

Keywords: empagliflozin; heart failure with preserved ejection fraction; health status; quality of life

Non-standard Abbreviations and Acronyms

CI – confidence interval
CSS – Clinical Summary Score
CV – cardiovascular
eGFR – estimated glomerular filtration rate
EMPEROR-Preserved - Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction
HFpEF – Heart failure with preserved ejection fraction
HFrEF – Heart failure with reduced ejection fraction
HHF – Hospitalization for heart failure
HR – Hazard ratio
HRQoL – Health related Quality of Life
KCCQ – Kansas City Cardiomyopathy Questionnaire
LVEF – Left ventricular ejection fraction
NT-proBNP - N-terminal pro-hormone B-type natriuretic peptide
NYHA – New York Heart Association
OSS – Overall Summary Score
TSS – Total Symptom Score

Clinical Perspective

What is new?

- In EMPEROR-Preserved, baseline health status and quality of life did not influence the magnitude of the effect of empagliflozin on the risk of cardiovascular death or hospitalization for heart failure.
- Empagliflozin improved health status and quality of life, as assessed by the Kansas City Cardiomyopathy Questionnaire, across all domains and at all measured time points (12, 32 and 52 weeks).

What are the clinical implications?

- These findings indicate that the ability of SGLT2 inhibition with empagliflozin to improve health status and quality of life in patients with a reduced ejection fraction (previously demonstrated in the EMPEROR-Reduced trial) also extend to patients with a preserved ejection fraction.

Introduction

Approximately half of all patients with heart failure (HF) have preserved ejection fraction.[1 2] Patients with HF and preserved ejection (HFpEF) not only experience similar risk for adverse clinical outcomes compared to those with HF and reduced ejection fraction (HFrEF), but both HF phenotypes also have similarly impaired physical functioning and health-related quality of life (HRQoL).[3 4] While the overall burden of impaired HRQoL is similar in both HFrEF and HFpEF, most of the data related to health status in HF has been derived from patients with HFrEF.[5 6]

The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trial studied the sodium glucose co-transporter-2 (SGLT2) inhibitor empagliflozin in patients with HFpEF and a left ventricular ejection fraction (LVEF) >40% and showed a significant reduction in the risk of cardiovascular death or HF hospitalization.[7] The overall patient's health status, including HRQoL, in the EMPEROR Preserved trial was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ), this providing an opportunity to understand the impact of baseline HRQoL on clinical benefits with empagliflozin, and conversely, the effect of empagliflozin on HRQoL.

Methods

Study Design and Patient Population

The design and primary results of the EMPEROR-Preserved trial have been published previously.[6] In brief, the EMPEROR-Preserved trial was a phase III international, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial that enrolled adult patients who had chronic HF with New York Heart Association (NYHA) class II-IV symptoms for at

least 3 months and an LVEF of >40% with no prior measurement of ≤40% under stable conditions. Patients were required to have elevated N-terminal pro-hormone B-type natriuretic peptide (NT-proBNP) levels (>900 pg/mL or >300 pg/mL in patients with or without atrial fibrillation, respectively), and additionally, have evidence of structural heart disease (left ventricular hypertrophy or left atrial enlargement) or a documented hospitalization for HF within the 12 months prior to enrollment. The protocol was approved by the Ethical Committee of each of the 622 participating sites in 23 countries, and all patients gave written informed consent.

Quality of Life Outcome Assessment

HRQoL was assessed using KCCQ-23, which includes 23 items that map to 7 domains: symptom frequency; symptom burden and stability; physical limitations; social limitations; quality of life; and self-efficacy. The KCCQ scores are summarized as: (i) a total symptom score (TSS) which consists of symptom frequency and symptom burden domains; (ii) a clinical summary score (CSS) consisting of physical limitation and TSS; and (iii) an overall summary score (OSS) which is formed combining CSS, quality of life, and social limitation domains. The scores range from 0 to 100 with 100 being the best possible score. The KCCQ has been shown to be valid, reliable, and sensitive to clinical changes, and lower KCCQ scores are associated with higher risk of hospitalizations and mortality.[8 9 10] The KCCQ was completed by patients at baseline and at 12, 32 and 52 weeks following randomization to placebo or empagliflozin.

Statistical Analysis

Study participants were categorized according to tertiles of baseline KCCQ-CSS, TSS, OSS. Baseline characteristics were summarized as frequencies and percentages or means with standard deviation. The effect of empagliflozin in each tertile was assessed by hazard ratios (HR) with 95% confidence intervals (CIs) using a Cox proportional hazard model. accounting for non-CV

death as a competing risk. Additionally, the effect of empagliflozin on total (first and recurrent) hospitalizations for HF in KCCQ tertiles was analyzed by a joint frailty model with cardiovascular death as a competing risk.

To assess the impact of empagliflozin on HRQoL, differences between treatment groups in mean KCCQ-CSS, KCCQ-TSS, and KCCQ-OSS at 12, 32 and 52 weeks were calculated using a mixed model for repeated measures, and the least-squares mean difference between treatment groups was estimated following adjustment for baseline KCCQ score, eGFR, age, region, sex, diabetes status and LVEF. Responder analyses were performed to investigate the proportion of patients with an improvement or deterioration in KCCQ at 12, 32 and 52 weeks post-randomization; established clinically meaningful thresholds for changes in KCCQ (≥ 5, ≥10, and ≥15 points for improvement and ≥5 point for deterioration) were used for all responder analyses.

Multiple imputation was used to account for missing KCCQ values, and estimates were combined using Rubin's rules.[11] Odds ratios (OR) with 95% CI were calculated from a logistic regression model, which included baseline KCCQ score, estimated glomerular filtration rate, age, region, sex, diabetes status and ejection fraction as covariates. Patients who died before 12, 32 and 52 weeks were counted as not improved in the analyses of improvement and worse in the analyses of deterioration. To accommodate for the fact that patients with very high baseline KCCQ score are not able to experience certain numerical improvements, patients with a baseline KCCQ values of ≥95 or ≥90 or ≥85 points in KCCQ domains were considered to have 5- or 10- or 15-point improvement if their values remained ≥ 95 or 90 or 85. Similarly, patients with a KCCQ score ≤5 points at baseline were defined as deteriorated if their score remained ≤5 points. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Data Sharing

The sponsor of the EMPEROR-Preserved trial (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents, and patient level clinical study data. Researchers are invited to submit inquiries via the following website: https://trials.boehringer-ingelheim.com.

Results

Patient Population

Among the 5942 participants with a baseline KCCQ assessment, the mean (standard deviation [SD]) KCCQ-CSS, KCCQ-TSS and KCCQ-OSS scores were 70.4 (21.2), 73.5 (22.0) and 68.9 (21.1), respectively. Baseline characteristics of patients in KCCQ-CSS tertiles are shown in Table 1. Patients with lower KCCQ-CSS scores were more often female, White/Caucasian and enrolled in Europe, and were more likely to have worse NYHA class, higher body mass index and higher NT-proBNP levels, and a history of diabetes and atrial fibrillation. An overview of the availability of KCCQ-CSS data at each time point is shown in the Supplementary Figure I.

Effect of Baseline Health-Related Quality Of Life On Benefit With Empagliflozin

Empagliflozin reduced the primary outcome of time to cardiovascular death or HF hospitalization across the entire range of KCCQ-CSS (hazard ratio 0.83 [0.69-1.00], hazard ratio 0.70 [0.55-0.88] and hazard ratio 0.82 [0.62-1.08] for patients with baseline scores <62.5, 62.5-83.3 and ≥83.3, respectively; P -rend=0.77), Figure 1 and Supplementary Figure II. Similar results were observed for KCCQ-TSS and KCCQ-OSS scores. Empagliflozin reduced the total number of HF hospitalizations in each of the KCCQ-CSS tertiles (hazard ratio 0.82 (0.61-1.08];

hazard ratio 0.62 [0.44-0.88]; hazard ratio 0.70 [0.49-1.00] for scores <62.5, 62.5-83.3 and ≥83.3 respectively; P-trend=0.46). Results were similar for KCCQ-OSS and KCCQ-TSS (Figure 1).

Effect of Empagliflozin on Health-Related Quality of Life

The adjusted mean change in KCCQ-CSS, KCCQ-TSS and KCCQ-OSS by treatment arms over time are presented in Figure 2A-C. Compared to placebo, patients treated with empagliflozin had a significant improvement in mean KCCQ at 12, 32 and 52 weeks: CSS (1.03, 1.24 and 1.50 points), TSS (1.77, 1.53 and 2.07 points), and OSS (1.10, 1.53 and 1.60 points) respectively (P<0.01 for all, Figure 3). The effect of empagliflozin on KCCQ CSS, TSS and OSS by tertiles of baseline score at 12, 32 and 52 weeks is shown in Table 2.

At 12 weeks, patients in the empagliflozin arm were more likely to show meaningful improvements [≥ 5 point (51.6% vs. 46.5); ≥10 points (45.0% vs. 41.8%); ≥15 point (44.0% vs. 41.3%)] and less likely to show deterioration [≥5 points (21.6% vs. 24.4%)] in KCCQ-CSS. The odds ratios for the effect of empagliflozin vs. placebo at 12 weeks were 1.23 (95%CI 1.10, 1.37) with an NNT of 20 (95% CI 14-40) for a ≥5 point improvement; 1.15 (95%CI 1.03, 1.27) with an NNT of 31 (95% CI 18, 140) for a ≥10-point improvement; and 1.13 (95%CI 1.02, 1.26) with an NNT of 38 (95% CI 20, 708) for a ≥15-point improvement. The odds ratio for the effect of empagliflozin for a ≥5-point deterioration was 0.85 (95%CI 0.75, 0.97) with an NNT of 35 (95% CI 20, 138) . Similar trends were observed at 32 and 52 weeks, and results were generally consistent for KCCQ-TSS and KCCQ-OSS (Figure 4 and 5).

Discussion

In this pre-specified analysis of the EMPEROR-Preserved trial, we show two key findings. First, empagliflozin reduced the risk for major heart failure outcomes in patients with HFpEF across

the entire range of baseline HRQoL. Second, empagliflozin improved HRQoL, and the improvement was seen early and was sustained for at least one year. Patients treated with empagliflozin were more likely to show clinically meaningful improvement and less likely to experience clinically meaningful deterioration in health status, when compared with placebo. These findings are highly concordant with those reported with empagliflozin in patients with a reduced ejection fraction (40% or less) who were enrolled in the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction) trial.[12] Taken together, these data suggest that empagliflozin improves HRQoL across a broad range of patients with heart failure.

Several studies have assessed the effect of treatment on health status in patients with HFpEF.[13 14 15 16 17 18] The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial with 3,400 patients showed a baseline mean KCCQ OSS score of 54.8 and demonstrated 1.36 point improvement over placebo at 4 months.[13] The PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HFpEF) trial enrolled patients with similar baseline health status as EMPEROR-Preserved (mean KCCQ-CSS: 74.2) and showed an improvement in KCCQ-CSS with sacubitril/valsartan by 1.0 point compared with placebo at 8 months.[14] Several smaller trials have also assessed the effect of treatments on KCCQ in patients with HFpEF. The VITALITY-HFpEF (Patient-reported Outcomes in Vericiguat-treated Patients With HFpEF) trial showed no improvement in KCCQ with vericiguat.[15] In the NEAT-HFpEF (Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction) trial, treatment with isosorbide mononitrate showed numerically (although not statistically significant) unfavorable changes KCCQ scores.[16] The EMPERIAL-Preserved trial did not show a significant effect of empagliflozin on KCCQ-TSS in a 12-week

trial in approximately 300 mildly symptomatic patients with HFpEF.[18] In contrast, PRESERVED-HF (Dapagliflozin in PRESERVED Ejection Fraction Heart Failure) trial showed a significant improvement in the KCCQ CSS with dapagliflozin in patients with HfpEF;[17] the trial enrolled obese patients in the United States with over 40% having NYHA class III-IV symptoms.

The magnitude of the treatment effect on KCCQ health status seen in the EMPEROR-Preserved trial may appear to be modest (1.0 to 2.0 points), when compared with a change of 5.0 points, which is commonly regarded as representing a clinically meaningful shift in KCCQ scores. However, the 5-point threshold change has been identified as meaningful in individual patients rather than in populations of patients.[19] In population studies, it may be difficult to achieve a 5-point between-group difference, especially if the baseline KCCQ score is >70, indicative of a reasonably good quality of life and health status. Large between-group differences in KCCQ scores (e.g., 10-15 point treatment effects) have typically been observed only in patients who were severely compromised at baseline, and particularly in unblinded device trials, in which knowledge that a patient has received active therapy likely exaggerated changes in their perception of their own response to an experimental intervention.[20] Decisions about the handling of missing data and imputation methods may also amplify the size of a treatment difference. It is therefore noteworthy that the magnitude of the treatment effect in EMPEROR-Preserved is similar to that seen in other large-scale double-blind trials of drug therapies, particularly in patients with HFpEF (e.g., TOPCAT and PARAGON-HF).[13 14] Furthermore, our findings with respect to changes in KCCQ scores are concordant with favorable changes in NYHA functional class that we have previously reported in this trial.[21]

Our analyses and findings should be considered in light of certains strengths and limitations. The current study is the largest trial to evaluate the effect of any treatment on health status and quality of life, and our data were complete through one year in nearly 90% of patients. Longer-term data were not collected in this trial, but it is often difficult to interpret data beyond 12 months because of competing risks of deaths and other serious events. Furthermore, we studied stable patients who largely had functional class II symptoms, and treatment effects may have differed if we had enrolled patients with greater degrees of disability and limitation at the start of the trial. Finally, the current analysis did not evaluate the influence of ejection fraction or sex on the effect of empagliflozin on KCCQ scores, since these analyses are being presented fully in other publications. If brief, we previously reported an attenuated response for the effect of empagliflozin on heart failure hospitalizations in patients with ejection fractions ≥ 60-65%,[21] and we also noted an attenuated effect of empagliflozin on KCCQ scores in patients with the highest ejection fractions. By contrast, sex did not influence the effect of empagliflozin on KCCQ scores in the EMPEROR-Preserved trial, whereas in the PARAGON-HF trial, KCCQ scores in men responded significantly more favorably to sacubitril/valsartan than KCCQ scores in women.[22]

In conclusion, treatment with empagliflozin reduced the risk for cardiovascular death or HF hospitalization across the range of baseline HRQoL scores in patients with HFpEF. Empagliflozin also significantly improved HRQoL in patients with HFpEF, and this improvement was seen early and was sustained for at least one year.

Acknowledgments

The authors were fully responsible for all content and editorial decisions, were involved at all stages of development, and have approved the final version. Graphical assistance,supported financially by 7.4 Limited.

Sources of Funding

The EMPEROR-Preserved trial was supported by Boehringer Ingelheim and Eli Lilly and Company. (Trial registration: ClinicalTrials.gov Identifier: NCT03057951).

Disclosures

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. G.F. reports lectures and/or Committee Member contributions in trials sponsored by Medtronic, Vifor, Servier, Novartis, Bayer, Amgen, and Boehringer Ingelheim. T.J.S. has no conflicts of interest to declare. M.B., O.V., B.P are employees of Boehringer Ingelheim. M.B. is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation; TTR 219, project number 322900939) and reports personal fees from Abbott, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Medtronic, Novartis, Servier and Vifor during the conduct of the study. V.K.C. reports personal fees from AstraZeneca, Boehringer Ingelheim and Novartis. J.P.F. reports consulting fees from Boehringer Ingelheim during the conduct of the study. J.L.J. reports grant support, consulting income, and participation in clinical endpoint committees/data safety monitoring boards from Janssen, participation in clinical endpoint committees/data safety

monitoring boards from Boehringer Ingelheim, grant support from Novartis, Innolife, Applied Therapeutics, and Siemens Diagnostics, and consultancy fees from Novartis, Roche Diagnostics, and Abbott Diagnostics. S. K. reports personal fees from Boehringer Ingelheim, during the conduct of the study; personal fees from AstraZeneca, personal fees from Janssen Pharmaceuticals, personal fees from Merck, personal fees from Novo Nordisk, personal fees from GSK, personal fees from Abbott, personal fees from Amarin, personal fees from Novartis, outside the submitted work. I.L.P. reports personal fees from Boehringer Ingelheim. P.P. reports personal fees from Boehringer Ingelheim, Astra Zeneca, Servier, BMS, Amgen, Novartis, Merck, Pfizer, Berlin Chemie, and grants and personal fees from Vifor Pharma. S.J.S has received research grants from the National Institutes of Health (R01 HL107577, R01 HL127028, R01 HL140731, and R01 HL149423), the American Heart Association (#16SFRN28780016), Actelion, AstraZeneca, Corvia, Novartis and Pfizer; and consulting fees from Abbott, Actelion, AstraZeneca, Amgen, Axon Therapeutics, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Cardiora, CVRx, Cytokinetics, Eisai, GSK, Ionis, Ironwood, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Regeneron, Sanofi, Shifamed, Tenax and United Therapeutics. SK has received research grants from the American Heart Association (#19TPA34890060) and the National Institutes of Health (P30AG059988; P30DK092939). M.S. reports consultancy fees from Abbot, Bayer, Bayer Healthcare, Merck, Novartis and Vifor Pharma. S.V. holds a Tier 1 Canada Research Chair in Cardiovascular Surgery; and reports receiving research grants and honoraria from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, HLS Therapeutics, Janssen, Novartis, Novo Nordisk, PhaseBio and Pfizer; receiving honoraria from Sanofi, Sun Pharmaceuticals and the Toronto Knowledge Translation Working Group. He is a member of the scientific excellence committee of the EMPEROR-

Reduced trial and served as a national lead investigator of the DAPA-HF and EMPEROR-Reduced trials. He is the President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization. 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. M.P. reports personal fees from Boehringer Ingelheim, during the conduct of the study, and personal fees from Abbvie, Actavis, Amgen, Amarin, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Casana, CSL Behring, Cytokinetics, Johnson & Johnson, Lilly, Moderna, Novartis, ParatusRx, Pfizer, Relypsa, Salamandra, Synthetic Biologics, Theravance, outside 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.

Supplemental Material

Expanded methods for ‘Handling of missing data: Multiple Imputation’ and ‘Responder analysis with correction for ceiling effect and handling of death’

Supplemental Figures I-II

References

1. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. Circulation. 2021;143:e254-e743.
2. Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, Devore AD, Yancy CW, Fonarow GC. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. J Am Coll Cardiol. 2017;70:2476-2486.
3. Lewis EF, Lamas GA, O'Meara E, Granger CB, Dunlap ME, McKelvie RS, Probstfield JL, Young JB, Michelson EL, Halling K, et al; CHARM Investigators. Characterization of health-related quality of life in heart failure patients with preserved versus low ejection fraction in CHARM.Eur J Heart Fail. 2007; 9:83–91.
4. McMurray J, Ostergren J, Pfeffer M, Swedberg K, Granger C, Yusuf S, Held P, Michelson E, Olofsson B; CHARM committees and investigators. Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: baseline characteristics of patients in the Candesartan in Heart failure - Assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur J Heart Fail. 2003; 5:261–270.
5. Butler J, Anker SD, Filippatos G, Khan MS, Ferreira JP, Pocock SJ, Giannetti N, Januzzi JL, Piña IL, Lam CSP, et al; EMPEROR-Reduced Trial Committees and Investigators. Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-Reduced trial. Eur Heart J. 2021;42:1203-1212.
6. Anker SD, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, Kimura K, Zeller C, George J, Brueckmann M, et al; EMPEROR-Preserved Trial Committees and Investigators. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial. Eur J Heart Fail. 2019;21:1279-1287.
7. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385:1451-1461.
8. Johansson I, Joseph P, Balasubramanian K, McMurray JJV, Lund LH, Ezekowitz JA, Kamath D, Alhabib K, Bayes-Genis A, Budaj A, et al; G-CHF Investigators. Health-Related Quality of Life and Mortality in Heart Failure: The Global Congestive Heart Failure Study of 23 000 Patients From 40 Countries. Circulation. 2021;143:2129-2142.
9. Pokharel Y , Khariton Y , Tang Y , Nassif ME , Chan PS , Arnold SV , Jones SG , Spertus JA. Association of serial Kansas City cardiomyopathy questionnaire assessments with death and hospitalization in patients with heart failure with preserved and reduced ejection fraction: a secondary analysis of 2 randomized clinical trials. JAMA Cardiol. 2017;2:1315–1321.
10. Spertus JA , Jones PG. Development and validation of a short version of the Kansas City Cardiomyopathy Questionnaire. Circ Cardiovasc Qual Outcomes 2015;8:469–476.
11. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons; 2004.
12. Butler J, Anker SD, Filippatos G, Khan MS, Ferreira JP, Pocock SJ, Giannetti N, Januzzi JL, Piña IL, Lam CSP, et al; EMPEROR-Reduced Trial Committees and Investigators.

Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-Reduced trial. Eur Heart J. 2021;42:1203-1212.
13. Lewis EF, Kim HY, Claggett B, Spertus J, Heitner JF, Assmann SF, Kenwood CT, Solomon SD, Desai AS, Fang JC, et al; TOPCAT Investigators. Impact of Spironolactone on Longitudinal Changes in Health-Related Quality of Life in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial. Circ Heart Fail. 2016;9:e001937.
14. Chandra A, Vaduganathan M, Lewis EF, Claggett BL, Rizkala AR, Wang W, Lefkowitz MP, Shi VC, Anand IS, Ge J, et al; PARAGON-HF Investigators. Health-Related Quality of Life in Heart Failure With Preserved Ejection Fraction: The PARAGON-HF Trial. JACC Heart Fail. 2019;7:862-874.
15. Armstrong PW, Lam CSP, Anstrom KJ, Ezekowitz J, Hernandez AF, O'Connor CM, Pieske B, Ponikowski P, Shah SJ, Solomon SD, et al. Effect of Vericiguat vs Placebo on Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The VITALITY-HFpEF Randomized Clinical Trial. JAMA. 2020;324:1512–1521.
16. Redfield MM, Anstrom KJ, Levine JA, Koepp GA, Borlaug BA, Chen HH, LeWinter MM, Joseph SM, Shah SJ, Semigran MJ, et al; NHLBI Heart Failure Clinical Research Network. Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2015;373:2314-24.
17. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, Khariton Y, Malik AO, Khumri T, Umpierrez G et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med. 2021. doi: 10.1038/s41591-021-01536-x. [epub ahead of print].
18. Abraham WT, Lindenfeld J, Ponikowski P, Agostoni P, Butler J, Desai AS, Filippatos G, Gniot J, Fu M, Gullestad L, et al. Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes. Eur Heart J. 2021;42:700-710.
19. Butler J, Khan MS, Mori C, Filippatos GS, Ponikowski P, Comin-Colet J, Roubert B, Spertus JA, Anker SD. Minimal clinically important difference in quality of life scores for patients with heart failure and reduced ejection fraction. Eur J Heart Fail. 2020;22:999-1005.
20. Arnold SV, Chinnakondepalli KM, Spertus JA, Magnuson EA, Baron SJ, Kar S, Lim DS, Mishell JM, Abraham WT, Lindenfeld JA, et al; COAPT Investigators. Health Status After Transcatheter Mitral-Valve Repair in Heart Failure and Secondary Mitral Regurgitation: COAPT Trial. J Am Coll Cardiol. 2019;73:2123-2132.
21. Packer M, Butler J, Zannad F, Filippatos G, Ferreira JP, Pocock SJ, Carson P, Anand I, Doehner W, Haass M, et al. Effect of Empagliflozin on Worsening Heart Failure Events in Patients With Heart Failure and Preserved Ejection Fraction: EMPEROR-Preserved Trial. Circulation. 2021;144:1284-1294.
22. McMurray JJV, Jackson AM, Lam CSP, Redfield MM, Anand IS, Ge J, Lefkowitz MP, Maggioni AP, Martinez F, Packer M, et al. Effects of Sacubitril-Valsartan Versus Valsartan in Women Compared With Men With Heart Failure and Preserved Ejection Fraction: Insights From PARAGON-HF. Circulation. 2020;141:338-351.

Tables

Table 1: Baseline Characteristics According to Clinical Summary Score Scores at Baseline

	KCCQ-CSS			
	Tertile <62.5 (N=1956)	**Tertile 62.5-83.3 (N=1967)**	**Tertile ≥83.3 (N=2019)**	**P-Value**
Age, years	72.8 (9.5)	72.1 (9.4)	70.9 (9.2)	<0.001
Female	1136 (58.1%)	874 (44.4%)	645 (31.9%)	<0.001
Race				<0.001
Asian	96 (4.9%)	211 (10.7%)	489 (24.2%)	
Black OR African American	125 (6.4%)	66 (3.4%)	66 (3.3%)	
White	1632 (83.4%)	1581 (80.4)	1312 (65.0%)	
Other including mixed race	102 (5.2%)	109 (5.5%)	151 (7.5%)	
Missing	1 (0.1%)	0	1 (0.1%)	
Geographic region				<0.001
Asia	64 (3.3%)	175 (8.9%)	442 (21.9%)	
Europe	900 (46.0%)	979 (49.8%)	802 (39.7%)	
North America	292 (14.9%)	227 (11.5%)	196 (9.7%)	
Latin America	559 (28.6%)	475 (24.1%)	476 (23.6%)	
Other	141 (7.2%)	111 (5.6%)	103 (5.1%)	
HF hospitalization within 1 year	472 (24.1%)	439 (22.3%)	442 (21.9%)	0.093
BMI, kg/m^2	31.4 (6.0)	30.0 (5.7)	28.2 (5.4)	<0.001
Ejection fraction at screening, %	55.0 (8.7)	54.2 (8.6)	53.8 (8.9)	<0.001
New York Heart Association class II	1278 (65.3%)	1666 (84.7%)	1900 (94.1%)	<0.001
Systolic blood pressure, mm Hg	132.1 (16.9)	132.1 (15.0)	131.4 (15.0)	0.190
Heart rate, bpm	71.0 (12.1)	70.3 (11.9)	69.7 (11.6)	<0.001
Hypertension	1806 (92.3%)	1797 (91.4%)	1782 (88.3%)	<0.001
Diabetes mellitus	1026 (52.5%)	974 (49.5%)	911 (45.1%)	<0.001
Atrial fibrillation	1035 (52.9%)	1002 (50.9%)	1005 (49.8%)	0.045
Coronary artery disease	625 (32.0%)	704 (35.8%)	745 (36.9%)	<0.001
ACE-I, ARB, or ARNI	1542 (79.9%)	1619 (81.3%)	1166 (82.5%)	0.005
Diuretic*	1714 (87.6%)	1594 (81.0%)	1458 (72.2%)	<0.001
Beta-blocker	1688 (86.3%)	1716 (87.2%)	1736 (86.0%)	0.758
Mineralocorticoid receptor antagonist	761 (38.9%)	705 (35.8%)	756 (37.4%)	0.352
Statin	1331 (68.0%)	1347 (68.5%)	1416 (70.1%)	0.154
Hemoglobin, g/dL	13.1 (1.6)	13.4 (1.6)	13.6 (1.6)	<0.001
eGFR, ml/min/1.73 m^2				<0.001

<60	1139 (58.2%)	970 (49.3%)	855 (42.3%)	
≥60	817 (41.8%)	996 (50.6%)	1163 (57.6%)	
NT-proBNP (pg/mL)	1675.6 (2431.2)	1428.3 (1696.3)	1280.6 (1634.2)	<0.001

Data are mean (SD) or number (%). Race was self-reported. Those who identified with more than one race or with no race were classified as 'other'. Angiotensin receptor blocker is excluding valsartan when taken with sacubitril because sacubitril/valsartan is shown as angiotensin receptor neprilysin inhibitor.

KCCQ-CSS indicates Kansas City Cardiomyopathy Questionnaire-clinical summary score; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; GFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; IV, intravenous; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro−B-type natriuretic peptide.

* Excluding mineralocorticoid receptor antagonists.

Table 2: Effect of Empagliflozin on KCCQ Scores at 12-, 32-, and 52-weeks.

	12 weeks Placebo - adjusted mean change (95% CI)	**P - trend***	**32 weeks Placebo - adjusted mean change (95% CI)**	**P - trend***	**52 weeks Placebo - adjusted mean change (95% CI)**	**P - trend***
KCCQ-CSS						
Tertile 1 (<62.5)	1.49 (0.22 to 2.76)	0.446	1.28 (-0.16 to 2.72)	0.225	1.48 (-0.07 to 3.04)	0.200
Tertile 2 (62.5–83.3)	1.22 (-0.04 to 2.48)		2.12 (0.69 to 3.54)		2.48 (0.96 to 4.00)	
Tertile 3 (≥83.3)	0.39 (-0.85 to 1.63)		0.37 (-1.02 to 1.76)		0.54 (-0.94 to 2.02)	
KCCQ-TSS						
Tertile 1 (<66.7)	2.36 (0.93 to 3.79)	0.268	1.58 (0.01 to 3.16)	0.381	2.70 (1.03 to 4.37)	0.280
Tertile 2 (66.7–87.5)	2.69 (1.24 to 4.13)		2.71 (1.12 to 4.29)		3.14 (1.48 to 4.81)	
Tertile 3 (≥87.5)	1.14 (-0.23 to 2.51)		1.21 (-0.28 to 2.71)		1.36 (-0.21 to 2.94)	
KCCQ-OSS						
Tertile 1 (<61.2)	1.49 (0.24 to 2.75)	0.326	1.94 (0.53 to 3.34)	0.522	1.94 (0.43 to 3.44)	0.715
Tertile 2 (61.2–82.3)	1.64 (0.40 to 2.89)		1.97 (0.59 to 3.35)		1.97 (0.50 to 3.43)	
Tertile 3 (≥82.3)	0.41 (-0.83 to 1.65)		0.97 (-0.40 to 2.34)		1.20 (-0.25 to 2.66)	

CI = confidence interval; CSS = Clinical Summary Score; KCCQ = Kansas City Cardiomyopathy; OSS = Overall Summary Score; TSS = Total Symptom Score

*P-value from trend test assuming ordering of the KCCQ tertiles.

Figure Legends

Figure 1: Effect of empagliflozin on outcomes by baseline KCCQ tertiles.

CI = confidence interval; CSS =Clinical Summary Score; KCCQ = Kansas City Cardiomyopathy Questionnaire; OSS = Overall summary score; TSS, total symptom score.

*P-value from trend test assuming ordering of the KCCQ tertiles

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

Changes in (A) Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, (B) Kansas City Cardiomyopathy Questionnaire Total Symptom Score, and (C) Kansas City Cardiomyopathy Questionnaire Overall Summary Score, from baseline to 12, 32, and 52 weeks for empagliflozin vs. placebo.

Adj. mean diff = adjusted mean difference; CI = confidence interval; CSS =Clinical Summary Score; KCCQ = Kansas City Cardiomyopathy Questionnaire; OSS = Overall summary score; TSS, total symptom score.

Figure 3: Adjusted mean difference in Kansas City Cardiomyopathy Questionnaire-clinical summary score, total symptom score, overall summary score, and sub-domains for empagliflozin vs. placebo at 12, 32, and 52 weeks.

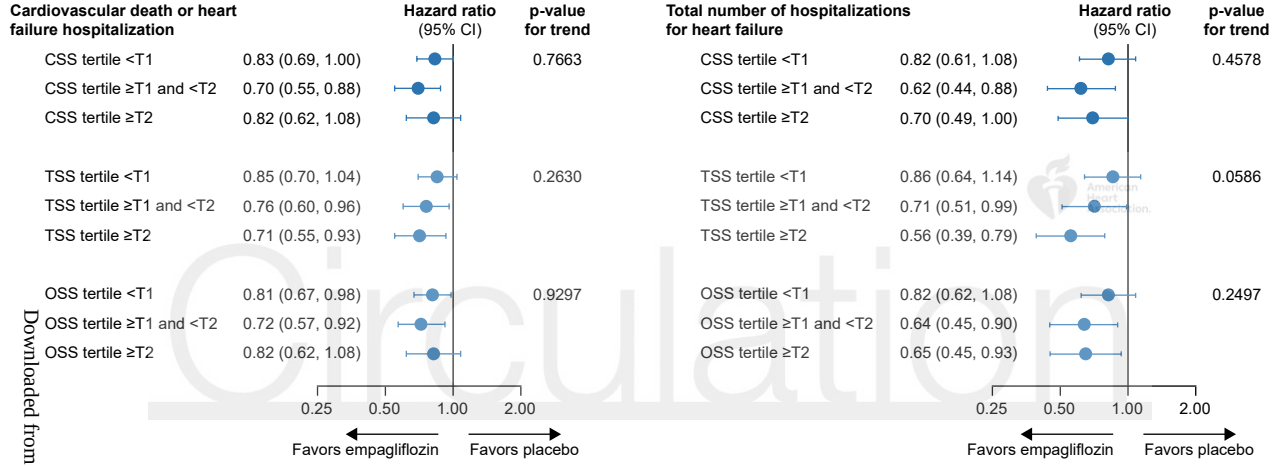
CI=confidence interval; KCCQ=Kansas City Cardiomyopathy Questionnaire.

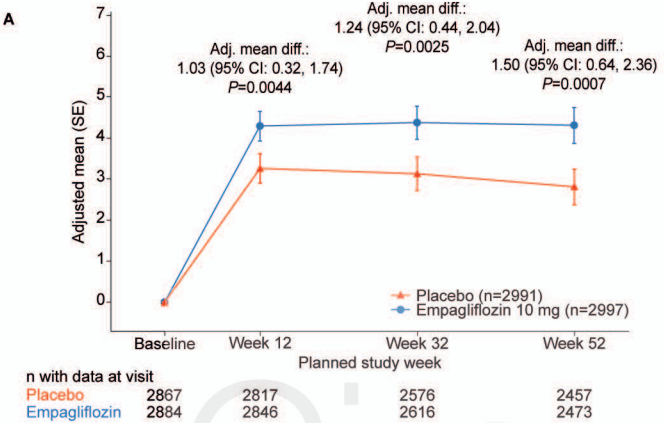
Figure 4: Responder analysis for improvement and deterioration across the KCCQ domains.

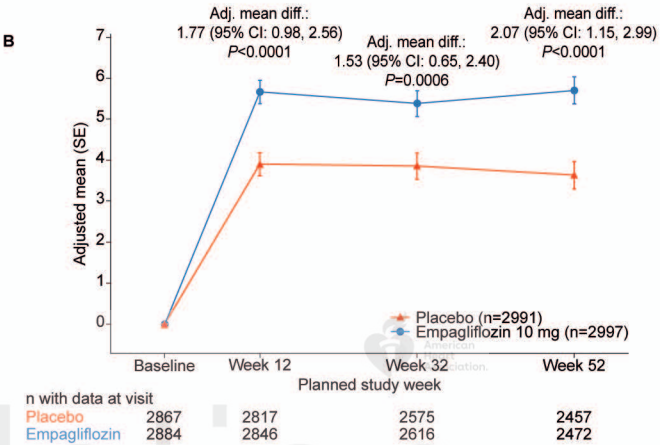
CI = confidence interval; CSS =Clinical Summary Score; KCCQ = Kansas City Cardiomyopathy Questionnaire; OSS = Overall summary score; TSS, total symptom score

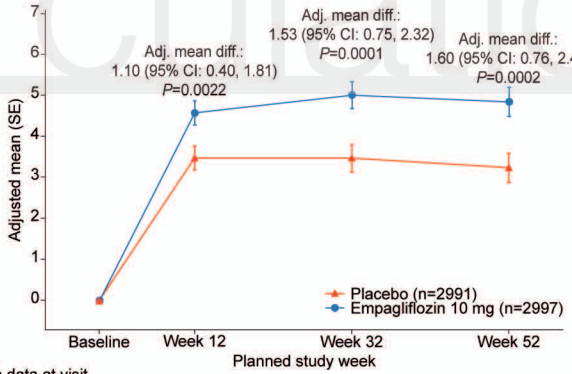
Figure 5: Responder analysis with proportion of responders at 12, 32 and 52 weeks with empagliflozin versus placebo.

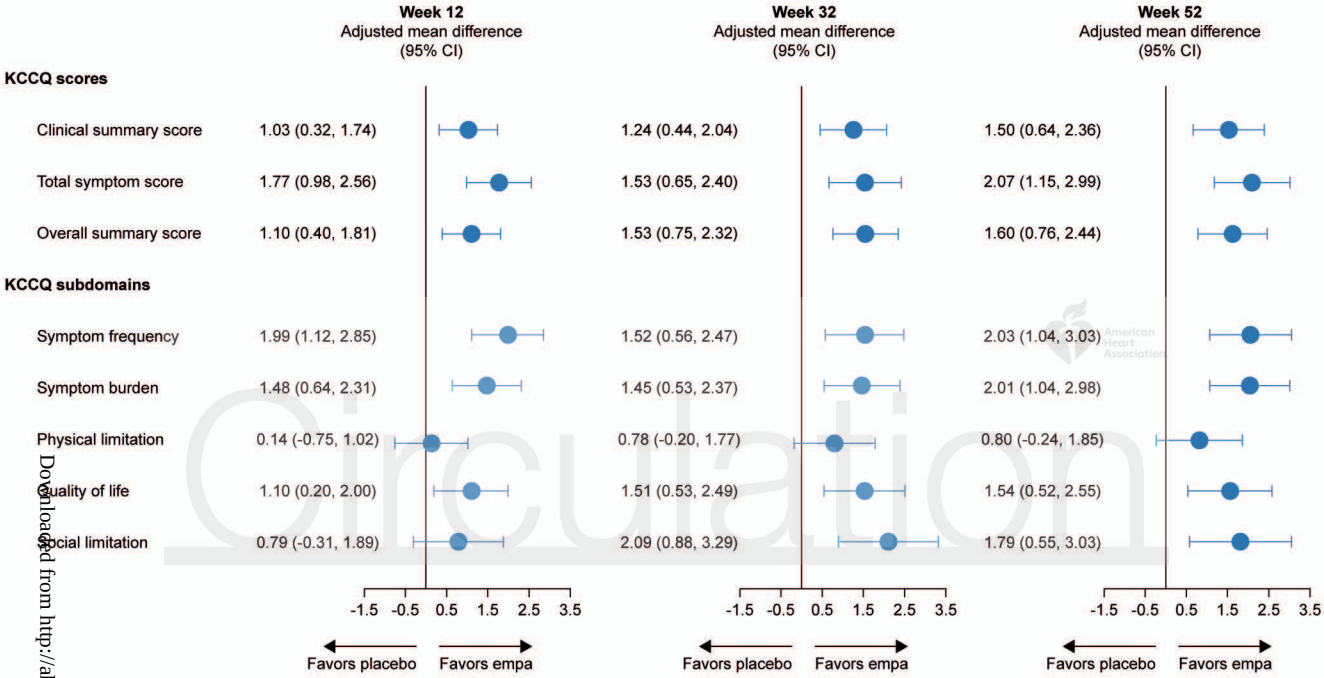
NNT= number needed to treat; CSS =Clinical Summary Score; KCCQ = Kansas City Cardiomyopathy Questionnaire; OSS = Overall summary score; TSS, total symptom score

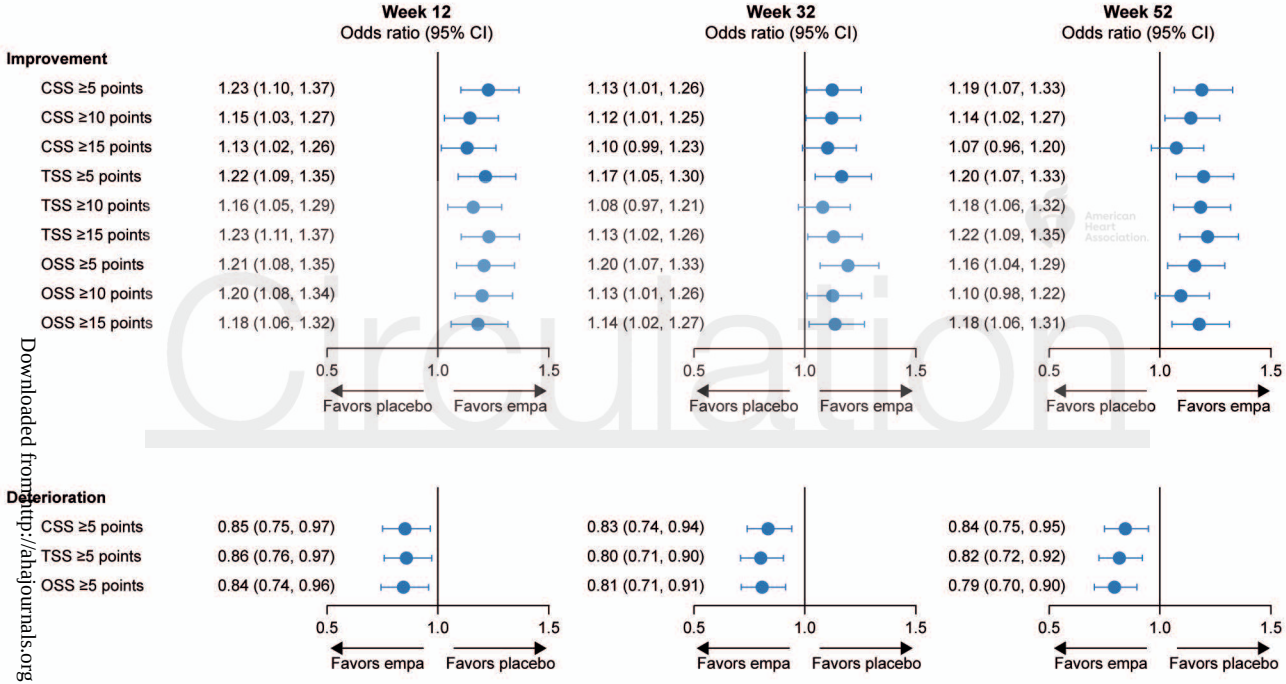




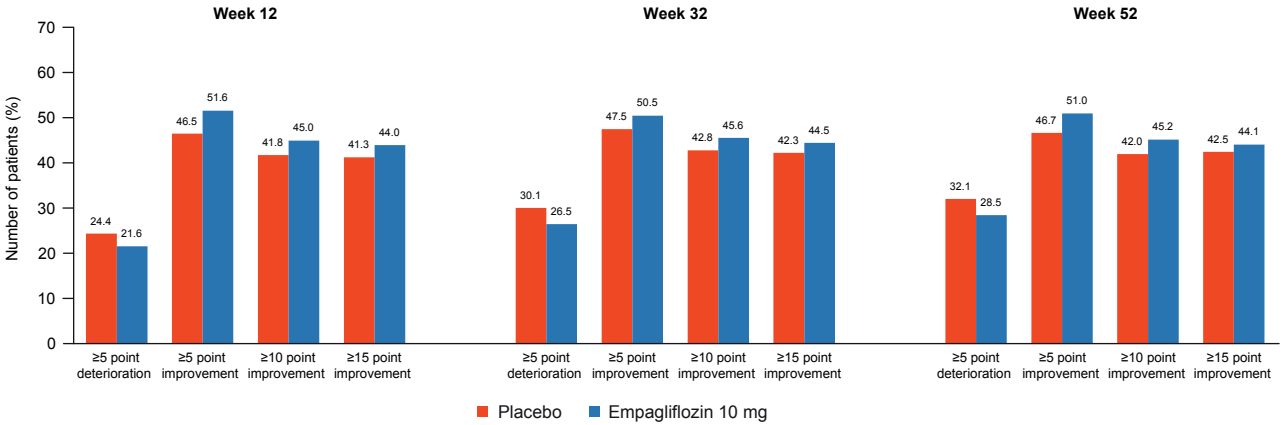




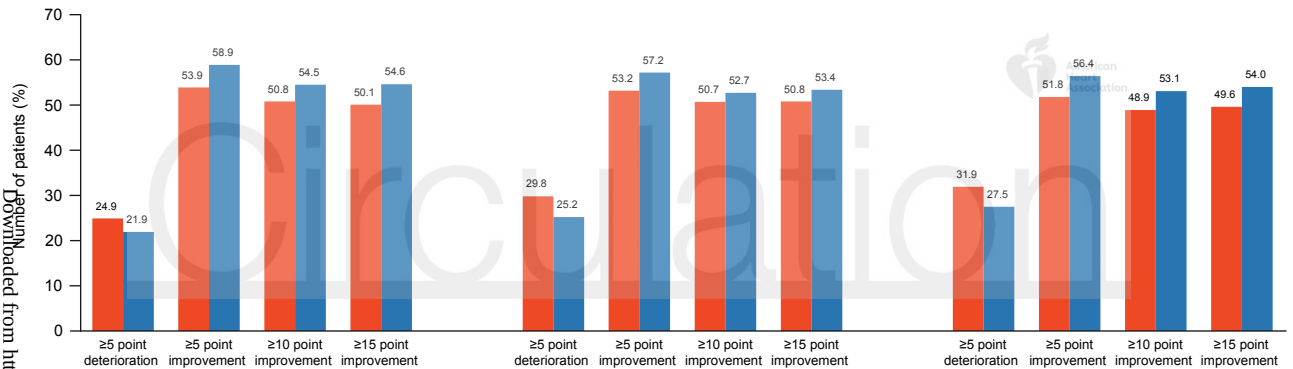




CSS



TSS



OSS