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Effects of Empagliflozin on Symptoms, Physical Limitations and Quality of Life in Patients Hospitalized for Acute Heart Failure – Results From the EMPULSE Trial

Running title: Kosiborod et al.; *Empagliflozin and KCCQ in Acute Heart Failure*

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Abstract

Background: Patients hospitalized for acute heart failure (AHF) experience poor health status, including high burden of symptoms and physical limitations, and poor quality of life. Sodium-glucose cotransporter 2 (SGLT2) inhibitors improve health status in chronic HF, but their impact on these outcomes in AHF are not well characterized. We investigated the effects of the SGLT2 inhibitor empagliflozin on symptoms, physical limitations and quality of life, using the Kansas City Cardiomyopathy Questionnaire (KCCQ) in the EMPULSE trial.

Methods: Patients hospitalized for AHF were randomized to empagliflozin 10 mg daily or placebo for 90 days. The KCCQ was assessed at randomization and 15, 30 and 90 days. The effects of empagliflozin on the primary endpoint of clinical benefit (hierarchical composite of all-cause death, heart failure events, and a 5-point or greater difference in KCCQ Total Symptom Score (TSS) change from baseline to 90 days) were examined *post hoc* across the tertiles of baseline KCCQ-TSS. In pre-specified analyses, changes (randomization to Day 90) in KCCQ domains, including TSS, Physical Limitations (PLS), quality of life (QoL), clinical summary (CSS) and overall summary (OSS) scores were evaluated using a repeated measures model.

Results: In total, 530 patients were randomized (265 each arm). Baseline KCCQ-TSS was low overall (mean, SD; 40.8, 24.0 points). Empagliflozin-treated patients experienced greater clinical benefit across the range of KCCQ-TSS, with no treatment effect heterogeneity (win ratio [95% CIs] from lowest to highest tertile: 1.49 [1.01, 2.20], 1.37 [0.94, 1.99], and 1.48 [1.00, 2.20], respectively; *P* for interaction=0.94). Beneficial effects of empagliflozin on health status were observed as early as 15 days and persisted through 90 days, at which point empagliflozin-treated patients experienced a greater improvement in KCCQ TSS, PLS, QoL, CSS and OSS (placebo-adjusted mean differences (95% CI): 4.45 (0.32, 8.59), *P*=0.03; 4.80 (0.00, 9.61), *P*=0.05; 4.66 (0.32, 9.01), *P*=0.04; 4.85 (0.77, 8.92), *P*=0.02; and 4.40 points (0.33, 8.48), *P*=0.03, respectively).

Conclusions: Initiation of empagliflozin in patients hospitalized for AHF produced clinical benefit regardless of the degree of symptomatic impairment at baseline; and improved symptoms, physical limitations and quality of life, with benefits seen as early as 15 days and maintained through 90 days.

Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT0415775.

Key Words: acute heart failure; empagliflozin; KCCQ; symptoms; physical limitations; quality of life; SGLT2 inhibitor

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Non-standard Abbreviations and Acronyms

AHF	Acute heart failure
COVID-19	Coronavirus Disease 2019
CSS	Clinical Summary Score
EMPULSE	EMPagliflozin in patients hospitalized with acUte heart faiLure who have been StabilizEd
HF	Heart failure
KCCQ	Kansas City Cardiomyopathy Questionnaire
OSS	Overall Summary Score
PLS	Physical limitations
QoL	Quality of life
TSS	Total Symptom Score

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Clinical Perspective

What is new?

- Patients hospitalized for acute heart failure (AHF) experience a high burden of symptoms and physical limitations, and poor quality of life (QoL). In the *post hoc* and pre-specified analyses of EMPULSE trial, we investigated the effects of the sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin on total clinical benefit across the range of symptomatic impairment at baseline; and its impact on symptoms, physical limitations and QoL, using the Kansas City Cardiomyopathy Questionnaire.
- We found that initiation of empagliflozin in patients hospitalized for AHF produced clinical benefit regardless of the degree of symptomatic impairment at baseline; and improved symptoms, physical limitations and quality of life, with benefits seen as early as 15 days and maintained through 90 days.

What are the clinical implications?

- These observations are of clinical relevance as very few therapies have been shown to improve symptoms and functional status in the early post-discharge period in patients hospitalized with AHF.
- The findings were consistent across multiple subgroups, extending the health status benefits of SGLT2 inhibitors to patients hospitalized with acute heart failure regardless of ejection fraction, de novo versus chronic decompensated HF status, and degree of symptomatic impairment at baseline.

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Introduction

Patients hospitalized for acute heart failure (AHF) are at high risk for cardiovascular death and readmission, and also experience an especially high burden of heart failure (HF) related symptoms and physical limitations.[1-3] Accordingly, improving health status (symptoms, functional status and quality of life) is a key goal of HF management in this vulnerable group. To date, there has been a lack of therapies with a compelling benefit on these outcomes in individuals with AHF, highlighting a critical unmet need.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as a therapeutic option for patients with HF. Several clinical trials have demonstrated that these agents significantly improve symptoms and physical limitations in ambulatory patients with HF, regardless of ejection fraction.[4-8] However, whether these effects are also observed in individuals with AHF – the group with greatest symptomatic and functional limitations – remains largely unknown. In the EMPULSE (EMPagliflozin in patients hospitalized with acUte heart faiLure who have been StabilizEd) trial, we previously demonstrated that empagliflozin 10 mg daily, as compared with placebo, resulted in a significant clinical benefit (composite of death, HF events or change in symptom burden) among individuals hospitalized with AHF, regardless of ejection fraction, HF status (de novo versus decompensated chronic HF), or diabetes status.[9, 10] In this report, we sought to address the following two key objectives: 1) to evaluate, in *post hoc* analyses, whether the effects of empagliflozin on the primary endpoint of total clinical benefit in the EMPULSE trial varied according to the degree of symptomatic impairment at baseline; and 2) to examine, in pre-specified analyses, the impact of empagliflozin on the broader range of health status outcomes, as measured by the various domains of the Kansas City Cardiomyopathy

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Questionnaire (KCCQ) – a validated, self-administered instrument that quantifies HF related symptoms, function and quality of life,[11] as well as the time course of these effects.

Methods

EMPULSE (ClinicalTrials.gov NCT0415775) was a randomized, double-blind, placebo-controlled trial in patients with AHF (both de novo and decompensated chronic HF, with reduced or preserved ejection fraction, and with or without type 2 diabetes), which evaluated the efficacy and safety of empagliflozin 10 mg once daily, compared with placebo, when added to standard care. The design, baseline characteristics, and primary results of the trial have been published.[9] The Ethics Committee of each of the 118 participating institutions (in 15 countries) approved the protocol, and all patients gave written informed consent. Boehringer Ingelheim was responsible for data collection and storage. The academic members of the executive committee provided an independent interpretation of the results. The authors made the decision to submit the manuscript for publication, and assume full responsibility for the accuracy and completeness of the data.

Study Patients

Men and women aged ≥18 years (or above the age of legal consent according to local legislation) were eligible if they were hospitalized with a primary diagnosis of AHF with dyspnea on exertion or at rest, and had at least two of the following: congestion on chest radiograph, rales on chest auscultation, clinically relevant edema, or an elevated jugular venous pressure. Participants were randomized after at least 24 hours and no later than 5 days after admission, as early as possible after stabilization and while still in hospital. Stabilization criteria were a systolic blood pressure of at least 100 mmHg; no inotropic support for at least 24 hours; no symptoms of hypotension; no increase in the intravenous diuretic dose and no intravenous vasodilators in the

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six hours prior to randomisation. Patients were required to have N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration of at least 1600 pg/mL or a B-type natriuretic peptide (BNP) concentration of at least 400 pg/mL (NT-proBNP or BNP of at least 2400 pg/mL or 600 pg/mL, respectively, if atrial fibrillation was present); and have received at least 40 mg (20 mg for Japanese patients) of intravenous furosemide or equivalent. Key exclusion criteria included: cardiogenic shock; pulmonary embolism, cerebrovascular accident or acute myocardial infarction as the primary trigger for the current hospitalisation or in the preceding 90 days; current or expected cardiac transplantation, left ventricular assist device, or inotropic support; an estimated glomerular filtration rate (eGFR) less than 20 mL/min/1·73m^2 or requiring dialysis; and prior ketoacidosis. A full list of exclusion criteria is provided in the design manuscript.[10]

Study Procedures

After the provision of informed consent, patients were screened, and if eligible, randomized to empagliflozin 10 mg daily or matching placebo. Efficacy and safety parameters were assessed during follow-up visits at 3, 5, 15, 30 and 90 days after randomisation. During the onsite visits at 15, 30 and 90 days patients' health status was assessed using the KCCQ. Because of the ongoing Coronavirus Disease 2019 (COVID-19) pandemic, phone or home visits were allowed if patients were unable to attend the study visit in-person.

Primary Outcome

The primary outcome was clinical benefit at 90 days, defined as a hierarchical composite endpoint of time to all-cause death, the number of HF events (defined as HF hospitalizations, urgent HF visits and unplanned outpatient HF visits), time to first HF event, and a 5-point or greater difference in change from baseline in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) after 90 days of treatment.

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Kansas City Cardiomyopathy Questionnaire

The KCCQ was completed electronically by patients, without assistance by site study staff (as validated), and evaluated at randomization, 15, 30 and 90 days. The KCCQ is a 23-item, self-administered disease-specific instrument that quantifies symptoms (frequency, severity and recent change), physical function, quality of life, and social function over the prior 2 weeks. KCCQ-TSS – which was a pre-specified secondary outcome, quantifies the symptom frequency and severity. Additional domains included in this analysis were KCCQ physical limitations (PLS) and quality of life (QoL) scores; as well as clinical summary score (CSS) which incorporates the physical function and symptoms domains, and KCCQ overall summary score (OSS) which is derived from all domains (total symptom score, physical function, quality of life and social function). For each domain, the validity, reproducibility, responsiveness and interpretability have been independently established.[11] Scores are transformed to a range of 0–100, in which higher scores reflect better health status.

Statistical Analysis

In a *post hoc* analysis, patients were divided into three subgroups, based on the tertiles of baseline KCCQ-TSS (which was the KCCQ domain pre-specified as a component of the primary, as well as a secondary endpoint): (i) <27.1, (ii) ≥27.1 and <52.1, (iii) ≥52.1 points. Baseline characteristics were summarized as means and standard deviations, medians, and interquartile ranges, or percentages. Ordinal regression likelihood ratio tests were used to compare trends across tertile categories of KCCQ-TSS at baseline.

To evaluate the effects of empagliflozin vs placebo on the primary hierarchical composite endpoint of clinical benefit across the KCCQ-TSS tertiles, we conducted a *post hoc* analysis comparing patients randomised to empagliflozin with those randomised to placebo, within

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tertiles of baseline KCCQ-TSS. Each comparison of two patients followed the hierarchy of comparing time to death, number of HF events, time to HF event or a 5 point or greater difference in change from baseline in the KCCQ-TSS at day 90, until conclusion of a win or loss or otherwise concluding by a tie, as previously described.[9] We calculated the win ratio as the number of wins in the empagliflozin group divided by the number of losses. The treatment effect by baseline KCCQ-TSS tertile interaction was tested using Cochran's Q statistic (inverse variance-weighting approach). A multiple imputation approach, according to whether patients were on-treatment or off-treatment, was used to impute missing data for the KCCQ-TSS, as previously described.[9]

We analyzed the differences between treatment groups in mean KCCQ-TSS, PLS, QoL, CSS and OSS at day 15, 30 and 90 using a mixed effects model for repeated measures adjusted for heart failure status and baseline score by visit interaction; KCCQ-TSS at 90 days was a pre-specified secondary endpoint, and the rest were pre-specified exploratory endpoints. In addition, we performed a *post hoc* analysis evaluating whether the effects of empagliflozin versus placebo on change in KCCQ-TSS from baseline to 90 days differed across multiple subgroups based on patients' demographic and clinical characteristics at baseline.

We conducted responder analyses examining proportions of patients with a deterioration (≥5 point worsening), and clinically important improvements in KCCQ-TSS at 90 days, using established, clinically meaningful thresholds for KCCQ (≥5 point [at least small], ≥10 point [moderate], and ≥20 point [large] change) for all responder analyses. Among these outcomes, proportion of patients with a ≥10 point improvement in KCCQ-TSS was a pre-specified secondary, whereas ≥5 point and ≥20 point improvements were pre-specified exploratory endpoints, and ≥5 point worsening endpoint was analyzed *post hoc*. The proportion of

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responders was compared between those treated with empagliflozin versus placebo using multiple imputation to account for missing KCCQ values. Odds ratios (OR) to estimate differences between treatment groups, and their corresponding 95% CI and 2-sided p-values were estimated from logistic regression models (which included treatment group, stratification variable (de novo versus decompensated chronic HF) and baseline KCCQ-TSS values). All analyses were performed with SAS software, version 9.3 or higher (SAS Institute). P-values of 0.05 were considered statistically significant, and were not adjusted for multiple comparisons.

Data Sharing Statement

The data that support the findings of this study are available upon reasonable request. To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Researchers should use the https://vivli.org/ link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

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Results

Overall, 530 patients were randomized (265 each arm); 526 patients (99.2% of the overall trial population) had KCCQ data available at baseline. Of these, 473 patients (89.2% of the overall trial population) had KCCQ evaluated at 15 days; 471 (88.9% of the overall trial population) had KCCQ evaluated at 30 days; and 451 (85.1% of the overall trial population) had KCCQ

evaluated at 90 days. The proportions of patients with missing KCCQ values were similar in the empagliflozin and placebo groups at 15, 30 and 90 days (12.1% versus 9.4%; 10.6% versus 11.7%, and 13.2% versus 16.6%, respectively). The number and proportion of patients in the KCCQ-TSS tertiles are shown in Table 1.

Compared with participants with higher KCCQ-TSS scores at baseline, those with lower scores were younger; more often women, black or African American, enrolled in North America, with history of hypertension and Type 2 diabetes; had higher New York Heart Association class, body mass index, NTproBNP; and were more likely to have chronic decompensated versus de novo AHF (Table 1).

Clinical Outcomes

The effects of empagliflozin on the primary hierarchical endpoint of clinical benefit stratified by KCCQ-TSS tertiles are summarized in Figure 1. Patients treated with empagliflozin experienced greater clinical benefit across the range of KCCQ-TSS, with no evidence of treatment effect heterogeneity (win ratio [95% CIs] from lowest to highest tertile: 1.49 [1.01, 2.20], 1.37 [0.94, 1.99], and 1.48 [1.00, 2.20], respectively; *P* for interaction=0.94; Figure 1).

Health Status Outcomes

Baseline KCCQ-TSS was low overall (mean, SD; 40.8, 24.0 points), and improved substantially by 90 days [mean (95% CI) change in empagliflozin group, +36.2 (33.3, 39.1); placebo group, +31.7 (28.8, 34.7)]. The mean changes in KCCQ-TSS, PLS, QoL, CSS and OSS over time are presented in Figure 2 (panels A, B, C, D and E, respectively). Empagliflozin-treated patients had a greater improvement in KCCQ-TSS, PLS, QoL, CSS and OSS at Day 90 (placebo-adjusted mean differences (95% CI): 4.45 (0.32, 8.59), *P*=0.03; 4.80 (0.00, 9.61), *P*=0.05; 4.66 (0.32, 9.01), *P*=0.04; 4.85 (0.77, 8.92), *P*=0.02; and 4.40 (0.33, 8.48), *P*=0.03, respectively), with

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significant benefits already present as early as 15 days (e.g., for KCCQ-TSS, placebo-adjusted mean difference 5.35 (1.51, 9.19) points; $P < 0.01$) and maintained through 90 days. The results in terms of KCCQ-TSS at 90 days for empagliflozin vs placebo-treated patients were generally consistent across the pre-specified demographic and clinical subgroups, including ejection fraction of ≤40 versus >40%, de novo versus chronic decompensated AHF, and degree of symptomatic impairment (measured by tertiles of KCCQ-TSS) at baseline (Figure 3).

The results of the responder analysis at 90 days are shown in Figure S1, and include the proportion of patients treated with empagliflozin versus placebo that had a clinically significant deterioration (≥5 point decline in KCCQ-TSS (8.0% vs 11.7%; OR 0.67, 95% CI: 0.35, 1.30; p=0.24); and at least small (87.5% vs 82.4%), moderate (83.1% vs 76.3%), or large (70.4% vs 65.5%) improvements in KCCQ-TSS (corresponding OR, 95% CI: 1.49, (0.84, 2.64), P=0.17; 1.52 (0.93, 2.50), P=0.10; 1.22 (0.79, 1.89), P=0.38); these results did not reach statistical significance.

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Discussion

In this secondary analysis of the EMPULSE trial, we observed that treatment with empagliflozin improved the endpoint of total clinical benefit among patients hospitalized with AHF to a similar extent across the entire range of KCCQ, indicating that the beneficial effects of empagliflozin on HF outcomes in this patient group are independent of the health status impairment at baseline. Moreover, empagliflozin significantly improved all key KCCQ domains, including TSS, PLS, QoL, CSS and OSS (which collectively encompass symptoms, physical function, quality of life, and social function), with benefits generally consistent regardless of demographic and clinical characteristics, seen as early as 15 days, and maintained through 90 days.

These results expand on the previously reported effects of empagliflozin specifically, and SGLT2 inhibitors overall, on health status, as measured by KCCQ in patients with HF. Several previous trials demonstrated that empagliflozin and dapagliflozin improve symptoms and physical limitations in outpatients with HF and reduced ejection fraction.[4-6] More recent trials also show that these agents similarly improve health status in ambulatory patients with HF and preserved ejection fraction.[7, 8] However, until now the data regarding the effects of this class on symptoms, physical function and quality of life in patients hospitalized for AHF has been very limited. The only trial that previously evaluated a similar patient population is SOLOIST, which enrolled patients with type 2 diabetes hospitalized with or recently discharged after an episode of decompensated HF, and showed favorable effects of sotagliflozin, a mixed SGLT1/2 inhibitor, on the 12-item KCCQ score at 4 months (mean 4.1 point improvement compared with placebo).[12] Our findings from EMPULSE add to these data in several ways. First, we specifically focused on patients earlier in the course of hospitalization, during a more acute phase. Second, we included patients with de novo AHF, a previously unstudied but important group. Third, our trial enrolled individuals both with and without Type 2 diabetes. Fourth, we demonstrated the benefits of SGLT2 inhibition in the immediate post-discharge period, starting as early as 15 days. Finally, we extended the analyses to the entire spectrum of HF-related health status by evaluating all key KCCQ domains.

Our results are of clinical importance, because very few therapies have been previously shown to improve symptoms and functional status in the early post-discharge period in individuals hospitalized with AHF. To our knowledge, the only other pharmacotherapy shown to have such benefits (aside from SGLT inhibition) is intravenous ferric caroboxymaltose, which improved KCCQ-12 overall summary score by 3.7 points at 12 weeks in the AFFIRM-AHF

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trial.[13] However, that study specifically focused on individuals with iron defficiency and ejection fraction below 50%, and these benefits did not emerge until after the first 2 weeks. Demonstrating health status benefits in this patient population is especially challenging, since the individuals hospitalized for AHF have marked symptomatic and functional impairments at the time of randomization, and as the result of aggressive management during hospitalization and immediate post-discharge period tend to experience marked improvements in health status, regardless of whether they are assigned to active treatment or placebo. This was the case in EMPULSE, as well as in many other prior trials in AHF.[2, 12, 13] Our findings of significant improvements in every domain of KCCQ, seen just after two weeks post-discharge, and persisting to 3 months are, therefore, especially notable.

These observations may also be of potential relevance when considered in the context of the 30-day mortality and readmission metric which, at least in the US, is currently used to assess the quality of care for patients hospitalized for AHF (and for which poor performance may lead to financial penalties).[14] To our knowledge, the very early improvement in KCCQ (a well-known predictor of cardiovascular death and HF readmissions[15]) that we observed with empagliflozin at 15 days is the first such observation; and if corroborated by future studies would suggest that initiation of SGLT2 inhibitors during hospitalization for AHF may be a tool of improving the quality of hospital-to-home transitions.

The results of this study should be considered in the context of several potential limitations. First, although KCCQ-TSS was a component of the primary composite endpoint, and a pre-defined secondary endpoint, and prospective assessments of KCCQ domains were pre-specified, several of the analyses, including the evaluation of the primary endpoint by tertiles of baseline KCCQ-TSS were performed *post-hoc*. Second, as in most trials, some patients had

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missing health status assessments during follow up; however, the proportion of participants with missing KCCQ values was similar among those treated with empagliflozin and placebo. Third, the relatively modest sample size of this study did not provide sufficient power for the responder analyses. However, the large spontaneous improvement in KCCQ observed in both empagliflozin and placebo groups during the immediate post-discharge period (and likely associated with intensification of HF treatment) makes the traditional KCCQ thresholds for responder analyses more methodologically challenging, and less meaningful. Fourth, the follow up period of 90 days was relatively short. Finally, as in all trials, the inclusion and exclusion criteria may limit generalizability.

In conclusion, initiation of empagliflozin in patients hospitalized for AHF produced clinical benefit regardless of the degree of symptomatic impairment at baseline; and improved symptoms, physical limitations and quality of life, with benefits seen as early as 15 days and maintained through 90 days.

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sponsor performed statistical analyses of the trial according to a prespecified statistical analysis plan with oversight by the Executive Committee. An independent data and safety monitoring committee reviewed the safety data. Figure support was provided by Michael Trim at 7.4 Limited, Bollington, Cheshire, UK, and supported financially by BI. General administrative support in relation to development of the final submission package, supported financially by BI, was provided by Charlie Bellinger, Elevate Scientific Solutions, Horsham, West Sussex, UK.

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Supplemental Materials

Figure S1

References

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Table 1. Baseline Characteristics of the EMPULSE Study Population by tertiles of KCCQ.

	KCCQ-TSS at Baseline				*p*-value for trend
	Tertile 1 (n=166)	Tertile 2 (n=184)	Tertile 3 (n=176)	Total (n=526)	
Demographic characteristics					
Age, years, mean (SD)	66.5 (13.4)	69.5 (12.9)	69.4 (13.3)	68.5 (13.3)	0.045
Sex, n (%)					0.014
Male	98 (59.0)	125 (67.9)	126 (71.6)	349 (66.3)	
Female	68 (41.0)	59 (32.1)	50 (28.4)	177 (33.7)	
Race, n (%)					<0.001
White	130 (78.3)	150 (81.5)	129 (73.3)	409 (77.8)	
Black/African-American	22 (13.3)	19 (10.3)	13 (7.4)	54 (10.3)	
Asian	11 (6.6)	12 (6.5)	34 (19.3)	57 (10.8)	
Other	2 (1.2)	3 (1.6)	0	5 (1.0)	
Missing	1 (0.6)	0	0	1 (0.2)	
Geographic region, n (%)					<0.001
Asia	10 (6.0)	12 (6.5)	34 (19.3)	56 (10.6)	
Europe	96 (57.8)	129 (70.1)	112 (63.6)	337 (64.1)	
North America	60 (36.1)	43 (23.4)	30 (17.0)	133 (25.3)	
Medical history, n (%)					
Cause of HF					0.733
Ischemic	47 (28.3)	54 (29.3)	47 (26.7)	148 (28.1)	
Non-ischemic	119 (71.7)	130 (70.7)	129 (73.3)	378 (71.9)	
Previous MI	36 (21.7)	44 (23.9)	47 (26.7)	127 (24.1)	0.277
Previous CABG or PCI	45 (27.1)	53 (28.8)	55 (31.3)	153 (29.1)	0.398
Hypertension	143 (86.1)	151 (82.1)	130 (73.9)	424 (80.6)	0.004
T2DM	93 (56.0)	78 (42.4)	66 (37.5)	237 (45.1)	<0.001
Atrial fibrillation	84 (50.6)	92 (50.0)	84 (47.7)	260 (49.4)	0.592
HF characteristics					
HF status, n (%)					0.025
De novo	43 (25.9)	65 (35.3)	66 (37.5)	174 (33.1)	
Decompensated chronic	123 (74.1)	119 (64.7)	110 (62.5)	352 (66.9)	
NYHA class, n (%)					<0.001
II	26 (15.7)	76 (41.3)	84 (47.7)	186 (35.4)	
III	105 (63.3)	96 (52.2)	76 (43.2)	277 (52.7)	
IV	33 (19.9)	10 (5.4)	6 (3.4)	49 (9.3)	
KCCQ-TSS (points), mean (SD)	14.4 (7.8)	37.9 (7.3)	68.8 (12.6)	40.8 (24.0)	<0.001
KCCQ-TSS (points), median (IQR)	14.6 (8.3–20.8)	37.5 (31.3–44.8)	66.7 (58.3–77.1)	37.5 (21.9–58.3)	
Vital signs, mean (SD)					
Systolic BP, mmHg	124.6 (18.0)	123.0 (18.0)	124.6 (18.2)	124.0 (18.1)	0.997
Diastolic BP, mmHg	72.4 (13.4)	72.9 (11.1)	74.2 (12.3)	73.2 (12.3)	0.166
Heart rate, bpm	77.8 (14.8)	76.5 (14.3)	74.9 (12.9)	76.4 (14.0)	0.056
Body mass index, kg/m^2	32.6 (9.1)	30.0 (7.7)	27.4 (5.9)	29.9 (7.9)	<0.001
Laboratory values					
eGFR, mL/min per 1.73 m^2, mean (SD)	52.8 (20.9)	55.1 (20.6)	54.2 (19.5)	54.1 (20.3)	0.566

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NTproBNP, pg/mL, median (IQR)	3687.3 (2143.9–6446.8)	3188.7 (1725.2–5936.8)	2520.2 (1463.1–6012.9)	3245.8 (1735.4–6104.3)	0.004
Heart Failure treatments, n (%)					
ACEI/ARB/ARNI	107 (64.5)	136 (73.9	125 (71.0)	368 (70.0)	0.194
Beta-blocker	136 (81.9)	137 (74.5)	145 (82.4)	418 (79.5)	0.877
MRA	83 (50.0)	89 (48.4)	102 (58.0)	274 (52.1)	0.133
Diuretics other than MRA	144 (86.7)	154 (83.7)	143 (81.3)	441 (83.8)	0.169
Implanted devices, n (%)					
Pacemaker	2 (1.2)	6 (3.3)	2 (1.1)	10 (1.9)	0.935
ICD	19 (11.4)	21 (11.4)	21 (11.9)	61 (11.6)	0.886

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BP, blood pressure; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NTproBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; T2DM, type 2 diabetes mellitus; and TSS, total symptom score.

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Figures Legends

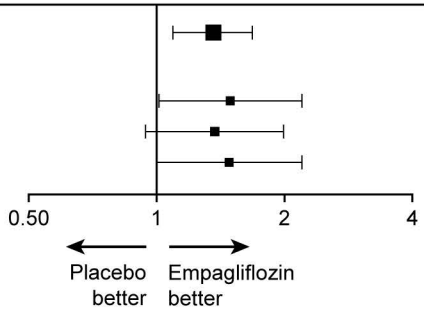
Figure 1. Effects of Empagliflozin versus Placebo on the Primary Hierarchical Composite Endpoint of Clinical Benefit Across Tertiles of KCCQ-TSS. CI, confidence interval; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire-total symptom score.

Figure 2. Effects of Empagliflozin versus Placebo on Change in KCCQ Domains Over Time. A, TSS. B, OSS. C, CSS. D, PLS. E, QoL. The data are presented as adjusted least-square means ± SE. CI, confidence interval; CSS, clinical summary score; KCCQ, Kansas City Cardiomyopathy Questionnaire; OSS, overall summary score; PLS, physical limitations score; QoL, quality of life; SE, standard error; TSS, total symptom score.

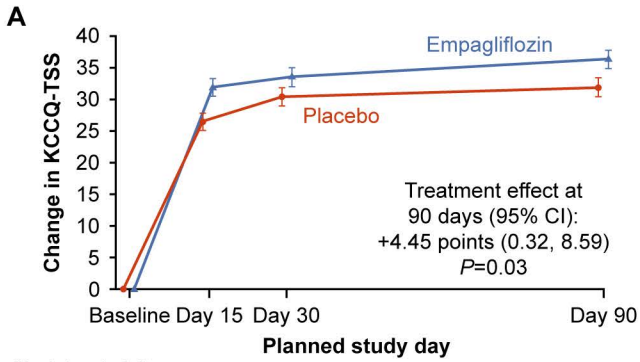
Figure 3. Effects of Empagliflozin Versus Placebo on KCCQ-TSS at Day 90 Across Pre-Specified Subgroups. AF, atrial fibrillation; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire-total symptom score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

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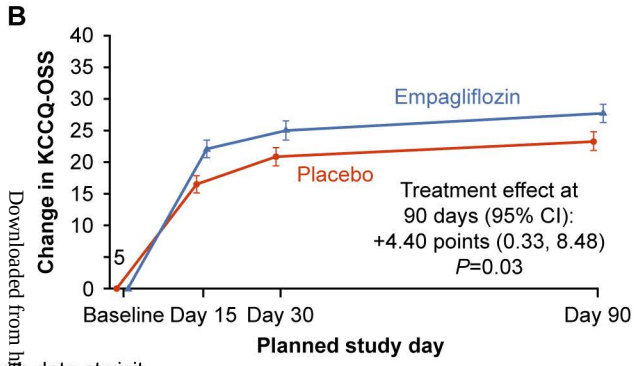
Subgroup Category	N analyzed Empagliflozin 10 mg	Placebo	Win ratio (95% CI)	Interaction *P*-value
All patients	265	265	1.36 (1.09,1.68)	
Baseline KCCQ-TSS				0.94
<27.1	84	82	1.49 (1.01, 2.20)	
≥27.1 and <52.1	93	91	1.37 (0.94, 1.99)	
≥52.1	85	91	1.48 (1.00, 2.20)	



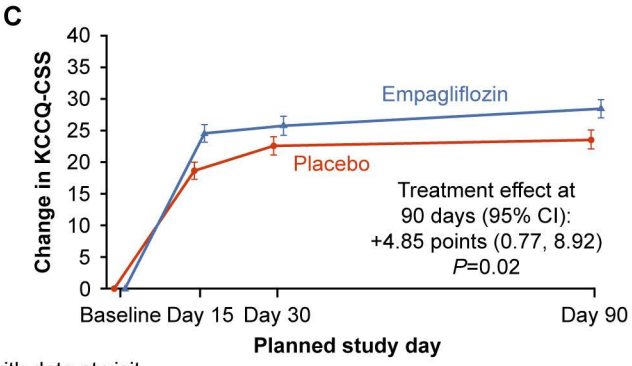
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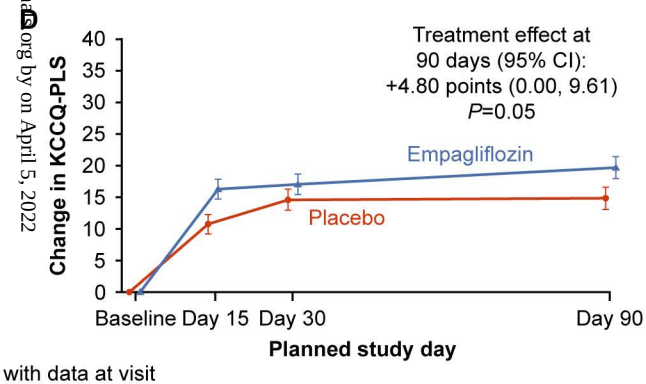
N with data at visit				
Placebo	250	240	234	221
Empagliflozin	245	233	237	230



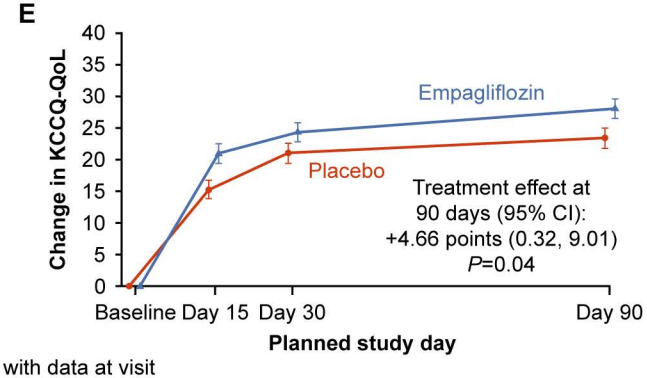
N with data at visit				
Placebo	250	240	234	221
Empagliflozin	245	233	237	230



N with data at visit				
Placebo	250	240	234	221
Empagliflozin	245	233	237	230

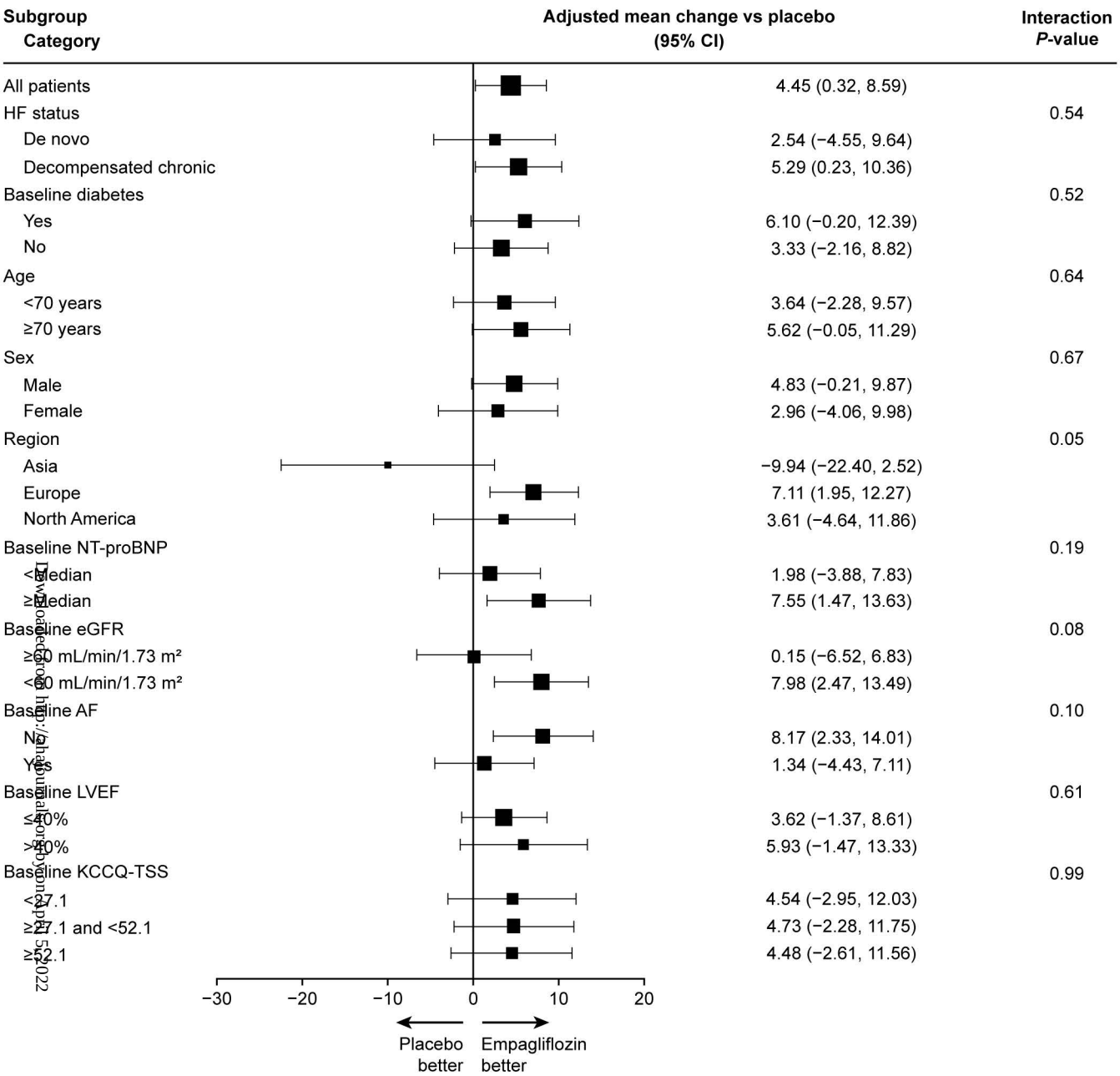


N with data at visit				
Placebo	245	232	225	217
Empagliflozin	240	225	228	225



N with data at visit				
Placebo	250	240	234	221
Empagliflozin	245	233	237	230

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