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Left Ventricular Function, Congestion, and Effect of Empagliflozin on Heart Failure Risk After Myocardial Infarction

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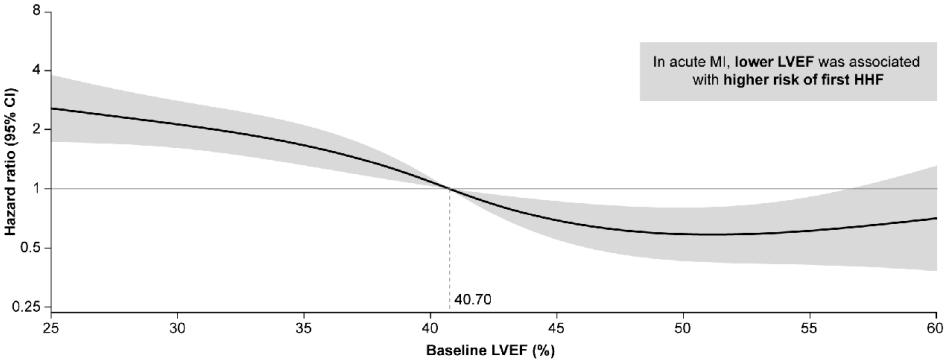
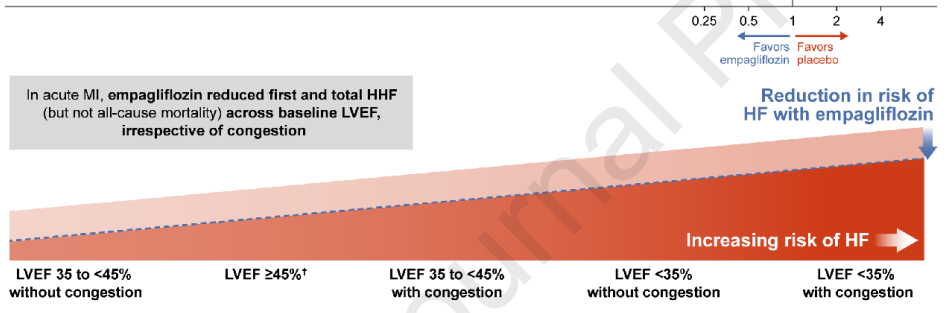
EMPACT-MI: Effect of LVEF on first HHF (component of primary end point) (placebo group)



EMPACT-MI: Effect of empagliflozin on time to first HHF (component of primary end point)

	Empagliflozin n/N (%)	Placebo n/N (%)	HR (95% CI)	*p*-value for trend test
First HHF				
Overall	118/3260 (3.6)	153/3262 (4.7)	0.77 (0.60, 0.98)	
By baseline LVEF				0.79
LVEF <35%	45/705 (6.4)	65/688 (9.4)	0.69 (0.47, 1.01)	
LVEF 35 to <45%	52/1713 (3.0)	58/1723 (3.4)	0.93 (0.64, 1.35)	
LVEF ≥45%	21/818 (2.6)	30/823 (3.6)	0.68 (0.39, 1.19)	
By signs or symptoms of congestion that required treatment				0.88*
With congestion	84/1852 (4.5)	113/1863 (6.1)	0.77 (0.58, 1.02)	
Without congestion	34/1408 (2.4)	40/1399 (2.9)	0.80 (0.50, 1.26)	
By baseline LVEF and signs or symptoms of congestion that required treatment				0.42
LVEF <35% with congestion	36/396 (9.1)	47/395 (11.9)	0.80 (0.52, 1.24)	
LVEF <35% without congestion	9/309 (2.9)	18/293 (6.1)	0.44 (0.20, 0.98)	
LVEF 35 to <45% with congestion	29/693 (4.2)	38/697 (5.5)	0.81 (0.50, 1.32)	
LVEF ≥45%†	21/818 (2.6)	30/823 (3.6)	0.68 (0.39, 1.19)	
LVEF 35 to <45% without congestion	23/1020 (2.3)	20/1026 (1.9)	1.13 (0.62, 2.06)	



Central Illustration ORIG: Effect of empagliflozin across baseline LVEF categories and congestion

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Guest Editor in Chief: Athena Poppas, MD

Guest Associate Editor: Ajar Kochar, MD, MHS

Left Ventricular Function, Congestion, and Effect of Empagliflozin on Heart Failure Risk After Myocardial Infarction

Short Title: Empagliflozin Post-MI by LV Function and Congestion

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Abstract

Background: Empagliflozin reduces the risk of heart failure (HF) hospitalizations but not all-cause mortality when started within 14 days of acute myocardial infarction (AMI).

Objective: To evaluate the association between left ventricular ejection fraction (LVEF), congestion, or both on outcomes and the impact of empagliflozin in reducing HF risk post-MI.

Methods: In the EMPACT-MI trial, patients were randomized within 14 days of an AMI complicated by either newly reduced LVEF<45%, congestion, or both to empagliflozin 10 mg daily or placebo and followed for a median of 17.9 months.

Results: Among 6522 patients, the mean baseline LVEF was 41%±9%; 2648 patients (40.6%) presented with LVEF<45% alone, 1483 (22.7%) presented with congestion alone, and 2181 (33.4%) presented with both. Among patients in the placebo arm, multivariable adjusted risk for each 10-point reduction in LVEF included all-cause death or HF hospitalization (hazard ratio [HR] 1.49; 95%CI, 1.31-1.69; P<0.0001), first HF hospitalization (HR, 1.64; 95%CI, 1.37-1.96; P<0.0001), and total HF hospitalizations (rate ratio [RR], 1.89; 95%CI, 1.51-2.36; P<0.0001). Presence of congestion was also associated with a significantly higher risk for each of these outcomes (HR 1.52, 1.94, and RR 2.03, respectively). Empagliflozin reduced the risk for first (HR 0.77, 95%CI 0.60-0.98) and total (RR 0.67, 95%CI 0.50-0.89) HF hospitalization, irrespective of LVEF or congestion or both. The safety profile of empagliflozin was consistent across baseline LVEF and irrespective of congestion status.

Conclusions: In patients with AMI, severity of LV dysfunction and the presence of congestion was associated with worse outcomes. Empagliflozin reduced first and total HF hospitalizations across the range of LVEF with and without congestion.

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Condensed Abstract

In acute myocardial infarction, greater severity of left ventricular dysfunction and presence of congestion portend a worse prognosis. Empagliflozin reduced both first (HR 0.77, 95%CI 0.60-0.98) and total (RR 0.67, 95%CI 0.50-0.89) HF hospitalizations, regardless of the severity of left ventricular dysfunction or the presence or absence of congestion but did not reduce all-cause mortality in EMPACT-MI. The magnitude of the heart failure effect by empagliflozin is comparable to previously reported benefits of SGLT2 inhibitors in other disease states (i.e., in patients with diabetes and high cardiovascular risk, heart failure with reduced and preserved ejection fraction, and chronic kidney disease).

Keywords: acute myocardial infarction; left ventricular dysfunction; congestion; heart failure; empagliflozin

Abbreviations

1. CAPRICORN: CArvedilol Post-infaRct survIval COntRolled evaluatioN
2. DAPA-MI: DAPAgliflozin in patients with Myocardial Infarction
3. EMMY: EMpagliflozin in patients with acute MYocardial infarction
4. EMPACT-MI: Trial to Evaluate the Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients with Acute Myocardial Infarction
5. EMPRESS-MI: Empagliflozin to PREvent worsening of left ventricular volumes and systolic function after Myocardial Infarction
6. EPHESUS: Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SUrvival Study

7. OPTIMAAL: OPtimal Therapy In Myocardial infarction with the Angiotensin II Antagonist Losartan
8. PARADISE-MI: Prospective ARNI versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction
9. SAVE: Survival and Ventricular Enlargement
10. VALIANT: VALsartan In Acute myocardial iNfarcTion

Clinical Trial Registration: NCT04509674.

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Introduction

Sodium glucose cotransporter-2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure (HF) in patients with HF with reduced or preserved left ventricular ejection fraction (LVEF), type 2 diabetes and high cardiovascular risk, and chronic kidney disease.(1) Patients with acute myocardial infarction (MI), especially those presenting with left ventricular systolic dysfunction or signs or symptoms of congestion, are at risk for in-hospital and long-term adverse cardiovascular outcomes, including incident hospitalization for HF and mortality.(2) Several key interventions, including early reperfusion and therapies that target neurohormonal activation such as beta-blockers and renin-angiotensin-aldosterone system inhibitors, have improved outcomes in acute MI; however these patients remain at elevated risk.(3) Consequently, we hypothesized that patients with acute MI at high risk of heart failure may benefit from treatment with an SGLT2 inhibitor.

In the trial to Evaluate the Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients with Acute Myocardial Infarction (EMPACT-MI), patients with acute MI and either newly decreased LVEF to <45% or signs or symptoms of congestion requiring treatment, were randomized to receive either the SGLT2 inhibitor empagliflozin or placebo on top of standard of care.(4) Empagliflozin did not reduce the primary outcome of time to first HF hospitalization or all-cause mortality. Of the components of the primary endpoint, empagliflozin did not reduce all-cause mortality but reduced the risk of first and total HF hospitalizations as well as other adverse HF events.(4,5) In this pre-specified secondary analysis of EMPACT-MI, we investigated the effect of empagliflozin across the spectrum of eligible LVEF with or without the presence of congestion.

Methods

Study Design and Participants

The design, baseline characteristics, and primary results of the EMPACT-MI trial have been reported previously.(6) Briefly, patients who were stable and at high-risk for HF based on either newly developed left ventricular systolic dysfunction (LVSD; documented LVEF <45%) or congestion were randomized within 14 days of an acute MI. Patients were also required to have at least one of the following enrichment factors: age ≥65 years, newly developed LVEF <35%, history of MI, atrial fibrillation, type 2 diabetes, estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2, elevated natriuretic peptides or uric acid levels, elevated pulmonary artery or right ventricular systolic pressure, three vessel coronary artery disease, peripheral artery disease, or no revascularization for the index myocardial infarction. Further details of the study population including baseline characteristics and a full list of eligibility criteria have been previously reported.(7)

In total, 6522 participants were randomized to empagliflozin 10 mg daily or matching placebo on top of standard of care and were followed for a median of 17.9 months. Patients with pre-existing heart failure, type 1 diabetes, or who were planned for treatment with an SGLT2 or SGLT1/2 inhibitor were excluded. All participants provided written informed consent and the study protocol was approved by the relevant ethics committee or institutional review board at each participating center and the coordinating center.

Left Ventricular Ejection Fraction and Congestion

Site investigators were asked to report LVEF prior to randomisation during the index hospitalisation. LVEF was reported as a number or a range as per local practice (<15%, 15-<25%, 25-<35%, 35-<45%, 45-<55% or ≥55%) and the modality of assessment was recorded. Congestion was defined as presence of symptoms (e.g., dyspnea; decreased exercise tolerance;

fatigue) or signs (e.g., pulmonary rales, crackles or crepitations; elevated jugular venous pressure; congestion on chest X-ray), that required treatment (e.g., augmentation or initiation of oral diuretic therapy; intravenous (IV) diuretic therapy; IV vasoactive agent; mechanical intervention, etc.) at any time during the hospitalization. Patients that lacked either a measurement of LVEF (number and range) or documentation of the presence or absence of congestion (N=52) were excluded from this analysis. The baseline LVEF, defined as the last measurement prior to randomization, was used for this analysis.

Study Outcomes and Statistical Analysis

We evaluated both time to first and total (first and recurrent) HF hospitalizations. All HF hospitalization events were determined by blinded site investigators who, trained on the trial protocol, reviewed and designated endpoints according to prespecified definitions without central adjudication. All analyses were performed based on the intention-to-treat principle and included all randomized participants. The distribution of baseline site assessed LVEF was evaluated with mean (standard deviation [SD]) and median (interquartile range [IQR]). When only an LVEF range was reported, we used the midpoint value for analyses. LVEF was categorized into 3 groups: (i) <35%; (ii) 35-<45%; and (iii) ≥45% (referent). Baseline characteristics were summarized by LVEF (3 groups) and presence or absence of congestion (2 groups) using means (SD) and medians (IQR) for continuous variables, and proportions for categorical variables. Differences in baseline characteristics between LVEF were evaluated using an ordinal logistic regression likelihood ratio test and using analysis of variance for continuous variables and chi-squared test for categorical variables for congestion groups.

After analyzing LVEF and congestion separately, we combined both exposures into a five-group category of patients as follows: (i) baseline LVEF <35% with congestion; (ii) baseline

LVEF <35% without congestion; (iii) baseline LVEF 35-<45% with congestion; (iv) baseline LVEF 35-<45% without congestion; and (v) baseline LVEF ≥45%, with and without congestion. We evaluated event rates among placebo-assigned patients for the primary endpoint for these 5 groups to define the order and set the referent group as the lowest risk category.

Among placebo-assigned patients, the independent association of LVEF, congestion, and their combination with the risk for the primary endpoint of time to first hospitalization for HF or all-cause death, first hospitalization for HF, and for total (first and recurrent) HF hospitalizations were evaluated. We used a multivariable Cox proportional hazards regression model for time to first event analyses and a negative binomial regression model with log (observation time) as an offset variable for total (first and recurrent) events analyses. Effect estimates were expressed as a hazard ratio (HR) or rate ratio (RR) along with their 95% confidence intervals (CI) for comparison of each category of LVEF and congestion with the referent category and for a continuous 10-point reduction in LVEF. In further analyses continuous LVEF was expressed using a cubic spline model.(8) All these multivariable models included factors for age, sex, eGFR (assessed categorically using the CKD-EPI formula <45 vs 45-<60 vs 60-<90 vs ≥90 ml/min/1.73m^2), geographical region, type 2 diabetes, persistent/permanent atrial fibrillation, prior MI, peripheral artery disease, smoking status, congestion, and baseline LVEF (categorical or continuous).

We evaluated treatment effects of empagliflozin versus placebo across the spectrum of LVEF, congestion, and their combination, for the primary outcome and time to first HF hospitalization using Cox proportional hazards regression models and for total HF hospitalizations using negative binomial regression models. Effect estimates were expressed as HR or RR with their 95% CI and for each treatment group we provided incidence or event rates

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per 100 patient-years of follow-up. These multivariable models were adjusted for the same covariates as described above (incl. sex which was not part of the primary model), with the addition of treatment and an interaction term between treatment and the subgroup variable to explore potential effect modification as a function of LVEF or congestion. The effect of empagliflozin versus placebo by continuous LVEF was also evaluated and displayed graphically using a cubic spline model that included a set of cubic polynomials which were constrained to meet at each of a set of equally distanced knots to explore for interaction.

In exploratory analyses, we examined investigator-reported HF adverse events based on the narrow standardized MedDRA query "cardiac failure". Based on the established safety profile of empagliflozin, EMPACT-MI used a focused safety reporting approach where the investigators were required to report only serious adverse events (SAEs), adverse events leading to discontinuation of trial medication for at least 7 consecutive days, and adverse events of special interest. According to the trial procedures, any adverse events of a pre-specified list of cardiac failure events were to be reported as serious, despite not meeting the SAE criteria of being fatal, life threatening, causing disability or permanent damage, leading to or prolonging hospitalisation. Therefore, investigator-reported HF adverse events included outpatient non-fatal HF events, hospitalization for HF, prolongation of hospitalization due to HF, and fatal HF events. In these analyses the treatment effect of empagliflozin versus placebo was evaluated by baseline LVEF, congestion, and their combination for the time to first event and total number of HF adverse events, as well as time to first event and total number of HF adverse events or all-cause mortality. Further details of ascertainment of these endpoints were published previously.(5)

Safety outcomes of interest, including hypotension, volume depletion, and acute kidney injury were assessed according to randomised treatment in all treated patients, and by baseline

LVEF and congestion. All statistical analyses were performed using SAS software version 9.4 (SAS institute Inc., Cary, NC, USA).

Results

Baseline Characteristics

Baseline LVEF was reported as a discrete number in 5087 (78.0%) and as a category in 1383 (21.2%) of patients. Baseline LVEF ranged from 10% to 79% (mean 41.1% [SD 9.1]; median 40% [IQR, 35-45%]) while 3715 (57.0%) patients presented with signs or symptoms of congestion. The most common qualifying congestive symptom was dyspnea (n=2977; 45.6%) and qualifying sign was pulmonary rales (n=1989; 30.5%) (Supplemental Table 1). Overall, 791 (12.2%) of patients presented with LVEF<35% with congestion, 602 (9.2%) with LVEF<35% without congestion, 1390 (21.3%) with LVEF 35-<45% and congestion, 2046 (31.4%) with LVEF 35-<45% without congestion, and 1483 (22.7%) with baseline LVEF ≥45%. Additionally, 158 patients [2.4%] presented with a baseline LVEF ≥45% but without congestion, a deviation from the trial protocol (Supplemental Figure 1).

Baseline characteristics by LVEF and by congestion for pooled empagliflozin and placebo groups are shown in Supplemental Table 2 and Supplemental Table 3, respectively. Patients with lower LVEF were more often younger, male, more likely to have presented with ST-segment elevation MI and higher NT-proBNP and were less likely to have previous PCI or CABG and a history of hypertension. Patients with congestion were more often older and female, more likely to have presented with non-ST-segment elevation MI, lower eGFR and higher NT-proBNP, and more likely to have a history of hypertension and atrial fibrillation.

Outcomes in the Placebo Arm

The risk of adverse outcomes increased with decreasing LVEF within the placebo group (Table 1 and Figure 1). After adjusting for covariates, each 10-point reduction in LVEF was associated with an increased risk of time to first all-cause death or HF hospitalization (HR, 1.49; 95% CI, 1.31-1.69; P<0.0001), a 64% increased risk of time to first HF hospitalization (HR, 1.64; 95% CI, 1.37-1.96; P<0.0001), and an 89% increased risk of total HF hospitalizations (RR, 1.89; 95% CI, 1.51-2.36; P<0.0001). The presence of congestion was associated with a higher risk of time to first HF hospitalization or all-cause death (HR 1.52, 95% CI, 1.16-1.99; P=0.0023), time to first HF hospitalization (HR 1.94, 95% CI, 1.32-2.86; P=0.0007), and total HF hospitalizations (RR 2.03, 95% CI, 1.31-3.16; P=0.0017). When both congestion and LVEF were considered together, there was a stepwise higher risk for all-cause mortality or HF hospitalization (P-trend <0.0001), with the highest risk group being those with baseline LVEF <35% with congestion and the lowest risk group being those with baseline LVEF 35-45% without congestion, even lower than patients with a baseline LVEF≥45% (Figure 2).

Effect of Empagliflozin on Outcomes

Empagliflozin did not reduce the risk of all-cause mortality or HF hospitalization across the range of baseline LVEF or congestion (Figure 3). Empagliflozin reduced the time to first HF hospitalization by 23% and total HF hospitalizations by 33% and this effect was consistent across the range of baseline LVEF (all P-trend ≥0.43; Figure 3). The reduction in first and total HF hospitalizations with empagliflozin was consistent across baseline LVEF when analyzed continuously (all P-interactions ≥0.90; Figure 4), in patients with and without congestion (all P-interactions ≥0.57; Figure 3), and across the combinations of baseline LVEF and congestion (all P-trend ≥0.42; Figure 3).

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The reduction of HF risk was similarly observed in the exploratory analysis of HF adverse events. The risk reduction with empagliflozin for time to first HF adverse event, total number of HF adverse events, as well as time to first HF adverse event or all-cause mortality and total number of HF adverse events or all-cause mortality was consistent irrespective of LVEF categories (all p-trend >0.40), presence or absence of congestion (all p-interaction >0.50) and across combinations of baseline LVEF and congestion (all p-trend >0.25, Supplemental Figure 2).

Safety

There were no increased rates of serious adverse events (23.7% versus 24.7%) or adverse events necessitating permanent discontinuation of study drug (3.8% versus 3.8%) in the empagliflozin compared with placebo groups, respectively (Supplemental Table 3). While rates of hypotension and volume depletion were similar between empagliflozin and placebo, numerically fewer patients experienced acute kidney injury in the empagliflozin group versus placebo group (0.8% vs 1.3%). The pattern was consistent across categories of baseline LVEF and congestion (Supplemental Table 3).

Discussion

Empagliflozin reduced both first and recurrent HF hospitalizations, regardless of the severity of LV dysfunction or the presence or absence of congestion but did not reduce all-cause mortality (Central Illustration). The magnitude of risk reduction in HF hospitalizations in EMPACT-MI (23% for first events and 33% of total events) was similar to previously reported benefits of SGLT2 inhibitors in other disease states (i.e., in patients with diabetes and high cardiovascular risk, HF with reduced and preserved ejection fraction, and chronic kidney disease).(9) In patients with acute MI, greater severity of left ventricular dysfunction and presence of congestion

portended a worse prognosis in the placebo group. The finding of a reduction in HF risk with empagliflozin was supported by a reduction in HF adverse events, including first and total number of HF adverse events (including outpatient HF adverse events), and first and total number of HF adverse events or all-cause mortality, regardless of baseline LVEF or presence or absence of congestion.

The finding of a beneficial treatment effect on HF outcomes by SGLT2 inhibitors across a range of eligible LVEF has previously been seen in trials of both HF with reduced and preserved ejection fraction.(10-12) The mechanism of benefit of SGLT2 inhibitors in chronic HF is understood to include many cardiac (including reverse remodelling), kidney, vascular, and systemic effects.(13,14) The mechanisms by which SGLT2 inhibitors could lead to a reduction in HF hospitalizations after acute MI have been reported in the EMMY trial.(15) In 476 patients enrolled based on elevated cardiac enzymes following an acute MI and within 72 hours of a primary PCI, empagliflozin reduced natriuretic peptide levels and LV volumes, and increased LVEF, suggesting that empagliflozin reduced adverse remodeling and may have reduced congestion, as assessed by change in NT-proBNP and E/e'. Reverse remodeling may be one of the mechanisms of benefit of empagliflozin on HF outcomes in EMPACT-MI. It is also possible that some patients had transient low LVEF that resolved following revascularisation ("stunned myocardium") and that this may have diluted the observed treatment effect. The consistent treatment effect in the presence or absence of congestion suggests that the treatment of congestion is not the primary mechanism of action of SGLT2 inhibitors' benefit on HF outcomes in patients post-MI, as has been suggested previously when SGLT2 inhibitor outcomes in patients with HF were studied in relation to use of diuretics.(16) A cardiac magnetic resonance-

based trial, EMPRESS-MI (NCT05020704), which is investigating the cardiac and renal effects of empagliflozin in an EMPACT-MI-like population, will report more mechanistic details.

In EMPACT-MI, we further confirm previous reports of the association between both baseline LVEF or congestion and adverse outcomes in patients with acute MI.(17-19) Patients with the lowest LVEF had the highest rates of HF hospitalisations and death in the combined analyses of EPHESUS, CAPRICORN, OPTIMAAL and VALIANT. (17,18) Prior to the current report, the relationship between congestion and outcomes had not been extensively described. In this analysis, patients with congestion had higher risks of adverse outcomes than those without. Most patients with LVEF >45% had concomitant congestion, which could explain why the subgroup of patients with LVEF>45% had a higher risk for adverse outcomes compared with patients with an LVEF between 35-45% without congestion. This observation suggests post-MI congestion may be a stronger risk factor for adverse outcomes than moderate LVSD. Some prior acute MI trials (e.g. the AIRE trial) mandated that all enrolled patients had pulmonary congestion whereas others mandated that all patients had a low LVEF (e.g. CAPRICORN and SAVE).(20-22) The EPHESUS trial required the presence of both low LVEF and congestion, unless the patient had diabetes when congestion in addition to low LVEF was not necessary.(23) The VALIANT trial (valsartan vs. valsartan and captopril vs. captopril) enrolled patients according to the presence of congestion and/or LVEF≤40%.(24) The only prior trial to report rates of adverse outcomes according to the presence or absence of congestion was the PARADISE-MI trial,(25) which reported that patients with congestion and LVEF≤40% had double the rate of HF hospitalization and cardiovascular death than those with LVEF≤40% without congestion. Rates of adverse outcomes have been reduced over recent decades. However, despite modern therapies patients with low LVEF and/or congestion remain at high risk of HF hospitalization and death,

underscoring the unmet need for therapies especially those targeted at populations with highest risk.

The DAPA-MI trial attempted to establish if dapagliflozin reduced the composite of cardiovascular death or hospitalization for HF after MI.(26) In DAPA-MI there were limited inclusion criteria aimed at enriching the population for HF risk and patients could be enrolled with any degree of regional or global LV dysfunction. In the relatively unselected population in DAPA-MI, the rate of HF events (only 59 adjudicated HF hospitalizations in 4098 patients over a median follow up of 11.6 months) was too low to provide sufficient power to assessing the impact of the intervention on clinical outcomes, necessitating a change in endpoint to a hierarchical composite including different cardiometabolic measures. Thus, in DAPA-MI, no conclusion could be made about the treatment effect of dapagliflozin on HF hospitalizations or death.(26) From the results of EMPACT-MI, it may be concluded that the population who met the enrolment criteria (i.e. across the range of eligible LVEF and with and without congestion) will benefit with a reduction in HF hospitalizations by empagliflozin. For those without low LVEF and without congestion, a treatment effect of SGLT2 inhibitors has yet to be shown.

The PARADISE-MI trial that compared sacubitril/valsartan versus ramipril in a similar post-MI population as EMPACT-MI, highlights the need for trials in order to quantify the benefits of therapies in different patient populations.(27) Sacubitril/valsartan was shown in PARADIGM-HF to markedly reduce cardiovascular death and HF hospitalization in patients with HF and reduced LVEF,(28) but in PARADISE-MI sacubitril/valsartan did not reduce a similar primary outcome of cardiovascular death or HF event (outpatient HF or HF hospitalization). In PARADISE-MI there was a suggestion of a possible treatment effect of sacubitril/valsartan on the secondary outcome of HF events (HR 0.84, 95% CI, 0.70-1.02) which

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was significant among investigator-reported events. A recent analysis of the treatment effect of sacubitril/valsartan in PARADISE-MI found a consistent lack of treatment effect regardless of higher or lower LVEF or the presence or absence of clinical congestion.(25) In EMPACT-MI a reduction in HF hospitalizations was similarly demonstrated in those with acute MI at increased risk of HF.

After acute MI, patients receive several new classes of drugs in close temporal proximity after revascularization, including contrast exposure. This raises the general concern about adding newer therapies. The current analysis suggests that the well-established safety of empagliflozin extends to this population and across baseline LVEF and in the presence and absence of congestion.

Limitations

The main strength of the present study is that the effect of empagliflozin in acute MI was determined in a large, international, randomized, placebo-controlled trial conducted among patients with varying degrees of LV systolic function and with or without clinical signs or symptoms of congestion. Limitations include that measurement of LVEF was estimated by local site investigators during routine care without confirmation by a central echocardiography core-laboratory evaluation. The exact timing of the measurement of baseline left ventricular function was not recorded and instead was recorded in the window for qualification for the trial. Endpoints were not adjudicated by an expert panel rather they were assessed by blinded site investigators using pre-specified definitions and structured data collection. No adjustment to the statistical inference of multiple comparisons was conducted given the exploratory nature of subgroup analyses,

In summary, across the spectrum of baseline LVEF and in the presence or absence of congestion, empagliflozin reduced both first and recurrent HF hospitalisation but did not reduce all-cause mortality. Patients at high risk of HF after MI (and especially those with the lowest LVEF and congestion) are at high risk for adverse cardiovascular outcomes, underscoring the need for further trials to identify effective novel therapies.

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Clinical Perspectives

Competency in Medical Knowledge: In acute myocardial infarction, patients with a greater severity of left ventricular dysfunction and presence of congestion portend a worse prognosis.

Competency in Patient Care: When started in stabilized patients within 14 days of acute myocardial infarction (MI), empagliflozin significantly reduces first and total HF hospitalizations but not all-cause mortality across the spectrum of left ventricular ejection fraction with and without congestion.

Translational Outlook 1: The mechanism by which SGLT2 inhibitors can lead to a reduction in heart failure hospitalizations after acute myocardial infarction are likely complex and remain incompletely understood.

Translational Outlook 2: The chronologic progression and prognostic significance of recovery or persistence of left ventricular dysfunction following acute myocardial infarction may predict response to neurohormonal inhibitor therapies. Further trials in this field are needed given that despite modern therapies, acute myocardial infarction patients with low left ventricular ejection fraction and/or congestion remain at high risk of heart failure hospitalization and death.

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FIGURE LEGENDS

Figure 1. Risk of cardiovascular outcomes according to continuous baseline LVEF. A. Time to first HHF or all-cause mortality; B. Time to first heart failure hospitalization; C. Total heart failure hospitalizations. Graphical results of cubic spline analyses showing the association of baseline LVEF on outcomes among placebo assigned patients. The median value of LVEF was 40%. Abbreviations: HHF: hospitalization for heart failure; LVEF: left ventricular ejection fraction.

Figure 2. Risk of cardiovascular outcomes across baseline LVEF and congestion. A. Time to first HHF or all-cause mortality; B. Time to first heart failure hospitalization; C. Total heart failure hospitalizations. Risk groups were categorized as ordered baseline LVEF<35% with congestion [n=395; black]; baseline LVEF<35% without congestion [n=293; blue]; baseline LVEF 35-<45% with congestion [n=697; purple]; baseline LVEF≥45% with or without congestion [n=823; red] and baseline LVEF 35-<45% without congestion [n=1026; orange referent]). Models adjusted for age, sex, diabetes, region, estimated glomerular filtration rate, persistent or permanent atrial fibrillation, prior myocardial infraction, peripheral artery disease, and smoking. Abbreviations: HHF: hospitalization for heart failure; LVEF: left ventricular ejection fraction.

Figure 3. Effect of empagliflozin across baseline LVEF categories and congestion. A. Time to first HHF or all-cause mortality; B. Time to first heart failure hospitalization; C. Total heart failure hospitalizations. p-value of an interaction test for heterogeneity with or without congestion. Models adjusted for age, sex, diabetes, region, estimated glomerular filtration rate, persistent or permanent atrial fibrillation, prior myocardial infraction, peripheral artery disease, smoking, treatment and a treatment by subgroup interaction. Abbreviations: HHF: hospitalization for heart failure; LVEF: left ventricular ejection fraction.

Figure 4. Effect of empagliflozin on cardiovascular outcomes according to continuous LVEF. A. Time to first HHF or all-cause death; B. Time to first heart failure hospitalization; C. Total heart failure hospitalization. Graphical results of cubic spline analyses showing the effect of empagliflozin on outcomes across baseline LVEF.

Central Illustration. Effect of empagliflozin on hospitalization for heart failure across baseline LVEF categories and congestion. *p-value of an interaction test for heterogeneity with or without congestion. Models adjusted for age, sex, diabetes, region, estimated glomerular filtration rate, persistent or permanent atrial fibrillation, prior myocardial infraction, peripheral artery disease, smoking, treatment and a treatment by subgroup interaction. Abbreviations: HHF: hospitalization for heart failure; LVEF: left ventricular ejection fraction.

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Table 1. Risk of cardiovascular outcomes per 10-point reduction in baseline LVEF (%) in the placebo arm.

	N with event	HR / RR (95% CI) for 10-point reduction in baseline LVEF (%)	p-value
Time to first heart failure hospitalization or all-cause death	297	1.49 (1.31-1.69)	<0.0001
Time to first heart failure hospitalization	153	1.64 (1.37-1.96)	<0.0001
Total heart failure hospitalizations	153	1.89 (1.51-2.36)	<0.0001

Abbreviations: HR, hazard ratio; LVEF: left ventricular ejection fraction; RR, rate ratio. Hazard ratio for time to first event per 10% reduction in baseline left ventricular ejection fraction from a Cox proportional hazards regression model adjusted for age, sex, diabetes, region, estimated glomerular filtration rate, persistent or permanent atrial fibrillation, prior myocardial infarction, peripheral artery disease, smoking, and congestion. Rate ratio for total events per 10% reduction in baseline left ventricular ejection fraction from a negative binomial regression model that adjusted for the same covariates with the log of time (days) used as offset. P-values are derived from the Wald statistic. When baseline LVEF was reported as a range, the baseline LVEF was imputed (baseline LVEF<15% imputed to 10%; 15-<25% imputed to 20%; 25-<35% imputed to 30%; 35-<45% imputed to 40%; 45-<55% imputed to 50%; ≥55% imputed to 60%).

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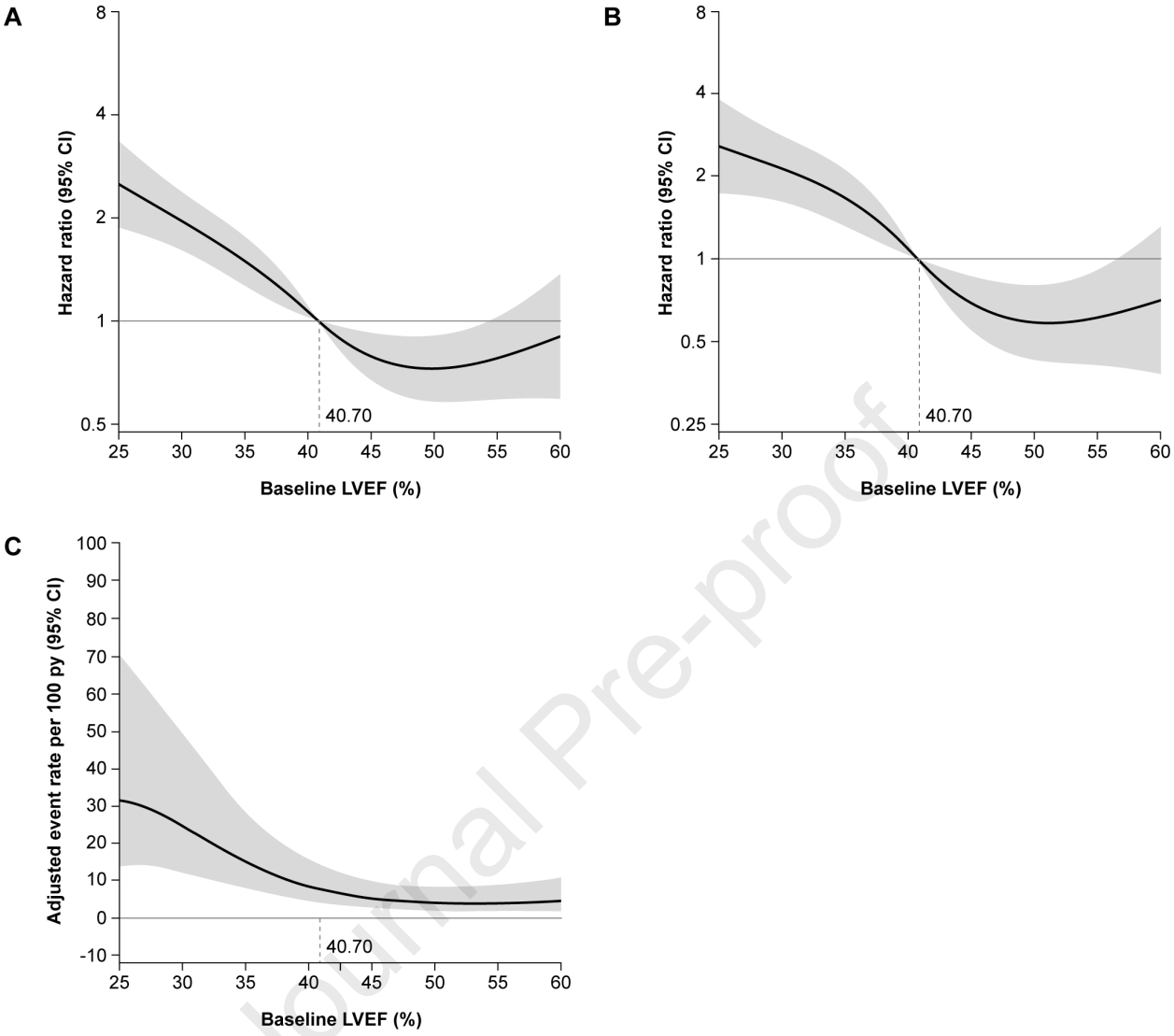

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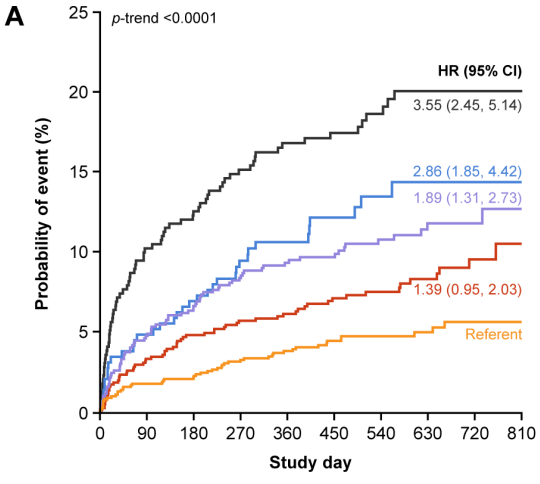
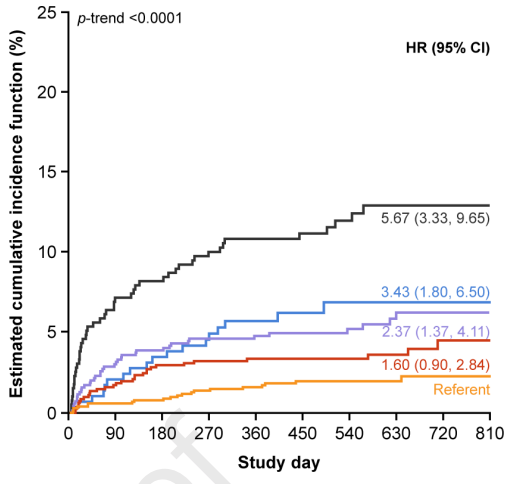
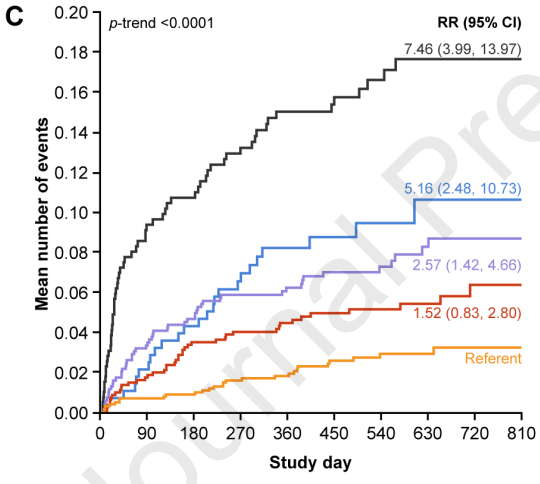




Patients at risk

LVEF <35% and congestion	395	349	340	320	283	245	184	117	63	23
LVEF <35% and no congestion	293	274	266	240	200	149	110	72	36	13
LVEF 35 to <45% and congestion	697	661	649	598	525	449	340	232	119	24
LVEF ≥45%	823	782	766	714	627	526	408	279	160	33
LVEF 35 to <45% and no congestion	1026	999	996	934	826	681	502	335	170	44



Patients at risk

LVEF <35% and congestion	395	370	365	349	311	271	205	135	77	26
LVEF <35% and no congestion	293	278	273	248	209	158	115	75	37	13
LVEF 35 to <45% and congestion	697	681	669	620	547	467	352	242	125	26
LVEF ≥45%	823	797	787	736	648	541	420	288	165	35
LVEF 35 to <45% and no congestion	1026	1005	1004	946	839	696	513	341	174	44

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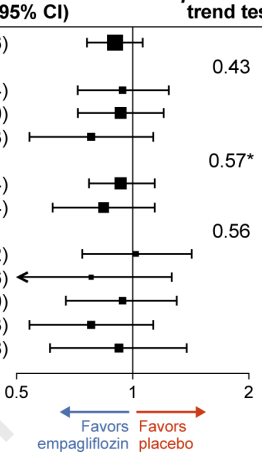
A	Empagliflozin n with event/ N analyzed (%)	Empagliflozin Incidence/ 100 py	Placebo n with event/ N analyzed (%)	Placebo Incidence/ 100 py	HR (95% CI)	*p*-value for trend test
Overall	267/3260 (8.2)	5.9	298/3262 (9.1)	6.6	0.90 (0.76, 1.06)	
By baseline LVEF						0.43
LVEF <35%	101/705 (14.3)	10.9	109/688 (15.8)	12.3	0.94 (0.72, 1.24)	
LVEF 35 to <45%	112/1713 (6.5)	4.6	124/1723 (7.2)	5.1	0.93 (0.72, 1.20)	
LVEF ≥45%	51/818 (6.2)	4.3	64/823 (7.8)	5.5	0.78 (0.54, 1.13)	
By signs or symptoms of congestion that required treatment						0.57*
With congestion	188/1852 (10.2)	7.2	209/1863 (11.2)	8.1	0.93 (0.77, 1.14)	
Without congestion	79/1408 (5.6)	4.0	89/1399 (6.4)	4.6	0.84 (0.62, 1.14)	
By baseline LVEF and signs or symptoms of congestion that required treatment						0.56
LVEF <35% with congestion	70/396 (17.7)	13.7	73/395 (18.5)	14.1	1.02 (0.74, 1.42)	
LVEF <35% without congestion	31/309 (10.0)	7.5	36/293 (12.3)	9.8	0.78 (0.48, 1.26)	
LVEF 35 to <45% with congestion	67/693 (9.7)	6.8	76/697 (10.9)	7.9	0.94 (0.67, 1.30)	
LVEF ≥45%	51/818 (6.2)	4.3	64/823 (7.8)	5.5	0.78 (0.54, 1.13)	
LVEF 35 to <45% without congestion	45/1020 (4.4)	3.1	48/1026 (4.7)	3.3	0.92 (0.61, 1.38)	



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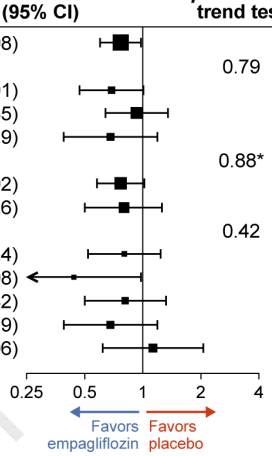
B	Empagliflozin n with event/ N analyzed (%)	Empagliflozin Incidence/ 100 py	Placebo n with event/ N analyzed (%)	Placebo Incidence/ 100 py	HR (95% CI)	*p*-value for trend test
Overall	118/3260 (3.6)	2.6	153/3262 (4.7)	3.4	0.77 (0.60, 0.98)	
By baseline LVEF						0.79
LVEF <35%	45/705 (6.4)	4.9	65/688 (9.4)	7.3	0.69 (0.47, 1.01)	
LVEF 35 to <45%	52/1713 (3.0)	2.2	58/1723 (3.4)	2.4	0.93 (0.64, 1.35)	
LVEF ≥45%	21/818 (2.6)	1.8	30/823 (3.6)	2.6	0.68 (0.39, 1.19)	
By signs or symptoms of congestion that required treatment						0.88*
With congestion	84/1852 (4.5)	3.2	113/1863 (6.1)	4.4	0.77 (0.58, 1.02)	
Without congestion	34/1408 (2.4)	1.7	40/1399 (2.9)	2.0	0.80 (0.50, 1.26)	
By baseline LVEF and signs or symptoms of congestion that required treatment						0.42
LVEF <35% with congestion	36/396 (9.1)	7.0	47/395 (11.9)	9.1	0.80 (0.52, 1.24)	
LVEF <35% without congestion	9/309 (2.9)	2.2	18/293 (6.1)	4.9	0.44 (0.20, 0.98)	
LVEF 35 to <45% with congestion	29/693 (4.2)	3.0	38/697 (5.5)	3.9	0.81 (0.50, 1.32)	
LVEF ≥45%	21/818 (2.6)	1.8	30/823 (3.6)	2.6	0.68 (0.39, 1.19)	
LVEF 35 to <45% without congestion	23/1020 (2.3)	1.6	20/1026 (1.9)	1.4	1.13 (0.62, 2.06)	



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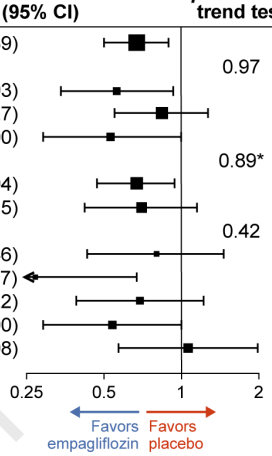
C	Empagliflozin n with event/ N analyzed	Empagliflozin Events/ 100 py	Placebo n events/ N analyzed	Placebo Events/ 100 py	RR (95% CI)	*p*-value for trend test
Overall	148/3260	2.4	207/3262	3.6	0.67 (0.50, 0.89)	
By baseline LVEF						0.97
LVEF <35%	60/705	5.6	87/688	10.0	0.56 (0.34, 0.93)	
LVEF 35 to <45%	65/1713	2.3	78/1723	2.8	0.84 (0.55, 1.27)	
LVEF ≥45%	23/818	1.1	42/823	2.0	0.53 (0.29, 1.00)	
By signs or symptoms of congestion that required treatment						0.89*
With congestion	106/1852	2.9	153/1863	4.4	0.67 (0.47, 0.94)	
Without congestion	42/1408	1.7	54/1399	2.4	0.70 (0.42, 1.15)	
By baseline LVEF and signs or symptoms of congestion that required treatment						0.42
LVEF <35% with congestion	49/396	9.4	62/395	11.9	0.80 (0.43, 1.46)	
LVEF <35% without congestion	11/309	2.3	25/293	8.4	0.27 (0.11, 0.67)	
LVEF 35 to <45% with congestion	36/693	2.9	51/697	4.2	0.69 (0.39, 1.22)	
LVEF ≥45%	23/818	1.4	42/823	2.6	0.54 (0.29, 1.00)	
LVEF 35 to <45% without congestion	29/1020	1.7	27/1026	1.6	1.06 (0.57, 1.98)	



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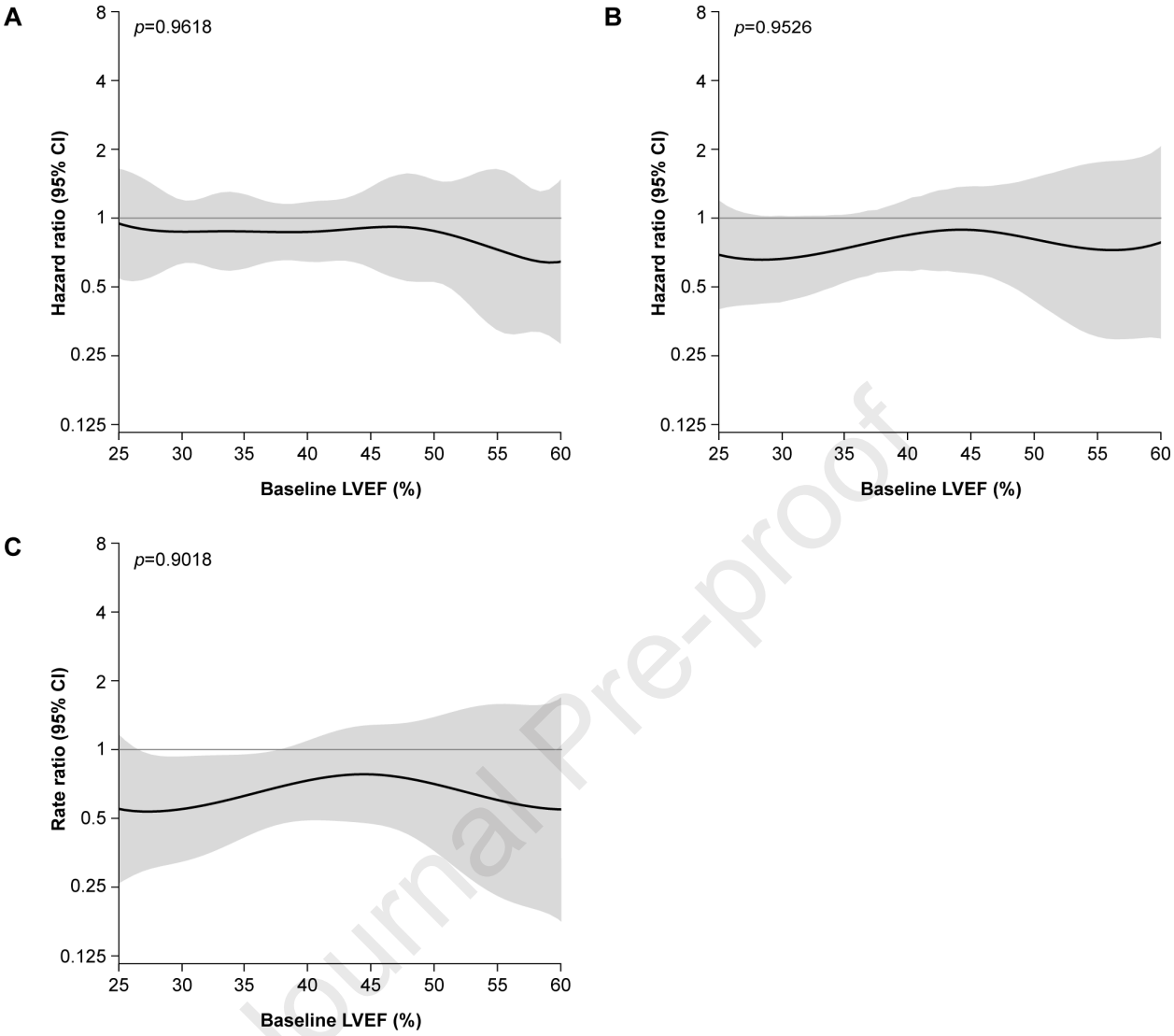

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Supplemental Material

Supplemental Figure 1. Distribution of index MI presentation by baseline LVEF with or without congestion among pooled empagliflozin and placebo groups.

Supplemental Table 1. Distribution of qualifying symptoms, signs and treatments of congestion.

Supplemental Table 2. Baseline characteristics according to baseline LVEF among pooled empagliflozin and placebo patients.

Supplemental Table 3. Baseline characteristics with and without congestion among pooled empagliflozin and placebo patients.

Supplemental Table 4. Selected safety outcomes by randomised treatment group and according to baseline LVEF category based on treated patients.

Supplemental Figure 2. Effect of empagliflozin vs. placebo on HF adverse events across baseline LVEF categories and presence of congestion:

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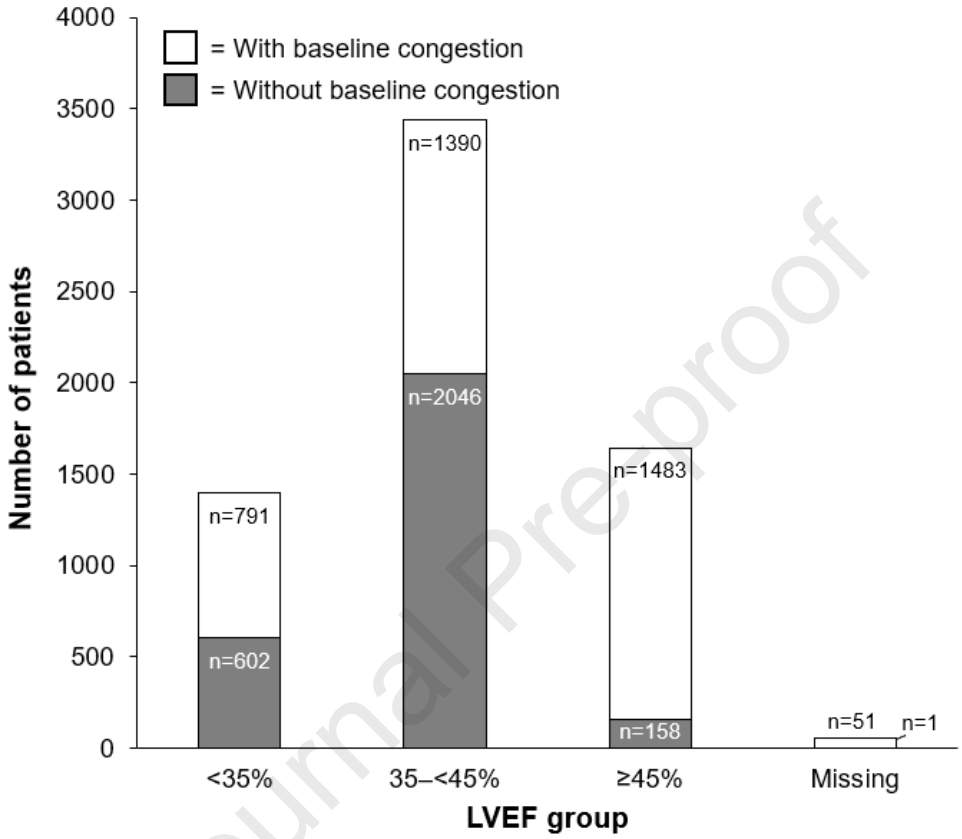
Supplemental Figure 1. Distribution of index MI presentation by baseline LVEF with or without congestion among pooled empagliflozin and placebo groups.



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Supplemental Table 1. Baseline distribution of qualifying symptoms, signs and treatments of congestion.

	Empagliflozin, N (%)	Placebo, N (%)	Total, N (%)
Symptoms or Signs of Congestion requiring Treatment	**1852 (56.8)**	**1863 (57.1)**	**3715 (57.0)**
Symptoms of Congestion	**1740 (53.4)**	**1744 (53.5)**	**3484 (53.4)**
Dyspnea	1495 (45.9)	1482 (45.4)	2977 (45.6)
Decreased exercise tolerance	906 (27.8)	895 (27.4)	1801 (27.6)
Fatigue	874 (26.8)	876 (26.9)	1750 (26.8)
Edema	318 (9.8)	326 (10.0)	644 (9.9)
Other	186 (5.7)	179 (5.5)	365 (5.6)
Signs of Congestion	**1520 (46.6)**	**1511 (46.3)**	**3031 (46.5)**
Pulmonary rales, crackles or crepitations	991 (30.4)	998 (30.6)	1989 (30.5)
Peripheral edema	260 (8.0)	245 (7.5)	505 (7.7)
Increased jugular venous pressure	126 (3.9)	128 (3.9)	254 (3.9)
Imaging or lab evidence consistent with HF	973 (29.8)	955 (29.3)	1928 (29.6)
Other (e.g., other signs of volume overload)	119 (3.7)	127 (3.9)	246 (3.8)
Treatment for Congestion	**1852 (56.8)**	**1863 (57.1)**	**3715 (57.0)**
Initiation or augmentation of oral diuretics	1331 (40.8)	1308 (40.1)	2639 (40.5)
IV diuretic or vasoactive agent	1299 (39.8)	1325 (40.6)	2624 (40.2)
Mechanical or surgical intervention	64 (2.0)	59 (1.8)	123 (1.9)
Mechanical fluid removal	12 (0.4)	6 (0.2)	18 (0.3)

The qualifying characteristics of congestion and treatments were not mutually exclusive, and patients could have presented with multiple features.

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Supplemental Table 2. Baseline characteristics according to baseline LVEF among pooled empagliflozin and placebo patients.

	EF <35%, (N=1393)	EF 35-<45%, (N=3436)	EF ≥45% (N=1641)	P-value
Characteristic				
Age [years]	62.2 ±11.3	63.5 ±10.8	65.0 ±10.8	<0.0001
Sex, No (%)				
Male	1113 (79.9)	2590 (75.4)	1159 (70.6)	<0.0001
Female	280 (20.1)	846 (24.6)	482 (29.4)	
STEMI, No (%)	1115 (80.0)	2588 (75.3)	1115 (67.9)	<0.0001
NSTEMI, No (%)	277 (19.9)	847 (24.7)	526 (32.1)	
Race, No (%)				
White	1171 (84.1)	2915 (84.8)	1318 (80.3)	<0.0001
Black or African American	26 (1.9)	50 (1.5)	14 (0.9)	
Asian	142 (10.2)	394 (11.5)	295 (18.0)	
Other	6 (0.4)	8 (0.2)	2 (0.1)	
Medical history, No. (%)				
Hypertension	843 (60.5)	2334 (67.9)	1330 (81.0)	<0.0001
COPD	80 (5.7)	162 (4.7)	98 (6.0)	0.65
AF	146 (10.5)	358 (10.4)	210 (12.8)	0.03
Previous stroke or TIA	59 (4.2)	145 (4.2)	95 (5.8)	0.03
Previous MI	179 (12.8)	430 (12.5)	224 (13.7)	0.47
Previous PCI	163 (11.7)	431 (12.5)	246 (15.0)	0.006
Previous CABG	23 (1.7)	63 (1.8)	33 (2.0)	0.46
Smoker, No (%)				
Never	353 (25.3)	883 (25.7)	483 (29.4)	0.0007
Current	520 (37.3)	1167 (34.0)	510 (31.1)	
Former	520 (37.3)	1386 (40.3)	648 (39.5)	
NT-proBNP highest [pg/mL] (median (IQR))	N=525 2658.00 (1128.00, 5437.00)	N=1427 1770.00 (741.10, 3357.00)	N=587 1424.20 (517.00, 2647.00)	<0.0001#
eGFR (CKD-EPI) [mL/min/1.73 m2]	76.71±20.53	77.03 ±19.69	73.70 ±19.83	<0.0001
eGFR <60 (CKD-EPI) [mL/min/1.73 m2], No. (%)	314 (22.5)	700 (20.4)	434 (26.4)	0.004
Serum Creatinine [mg/dL]	1.0 ±0.3	1.0 ±0.3	1.0 ±0.3	0.90
Haemoglobin [g/dL]	N=1341 13.71 ±1.84	N= 3345 13.67 ±1.71	N= 1576 13.58 ±1.83	0.045
BMI [kg/m^2]	27.82 ±5.11	28.11 ±4.97	28.20 ±5.05	0.045
Systolic BP [mmHg]	116.9 ±14.4	120.6 ±14.7	122.9 ±15.1	<0.0001
Diastolic BP [mmHg]	72.6 ±10.3	73.6 ±9.7	73.7 ±10.1	0.005
Medical therapy at baseline, No (%)				
Beta blockers	1046 (75.1)	2681 (78.0)	1289 (78.5)	0.03
ACEi or ARB	845 (60.7)	2377 (69.2)	1184 (72.2)	<0.0001
MRA	725 (52.0)	1329 (38.7)	515 (31.4)	<0.0001
Loop diuretic	588 (42.2)	988 (28.8)	626 (38.1)	0.10

All continuous variables reported as mean ± standard deviation except for NT-proBNP which was reported as median (interquartile range); categorical variables reported as number (frequency). #p-value base on log-transformed result.

Supplemental Table 3. Baseline characteristics with and without congestion among pooled empagliflozin and placebo patients.

	Congestion (N=3715)	Without congestion (N=2807)	P-value
Characteristic			
Age [years]	64.6 ±10.7	62.3 ±11.0	<0.0001
Sex, No. (%)			
Male	2726 (73.4)	2171 (77.3)	0.0002
Female	989 (26.6)	636 (22.7)	
STEMI, No. (%)	2642 (71.1)	2203 (78.5)	<0.0001
NSTEMI, No. (%)	1071 (28.8)	604 (21.5)	
Race, No. (%)			
White	3127 (84.2)	2324 (82.8)	0.0455
Black or African American	41 (1.1)	51 (1.8)	
Asian	490 (13.2)	344 (12.3)	
Other	7 (0.2)	9 (0.3)	
Medical history, No. (%)			
Hypertension	2800 (75.4)	1738 (61.9)	<0.0001
COPD	225 (6.1)	119 (4.2)	0.0012
AF	493 (13.3)	226 (8.1)	<0.0001
Previous stroke or TIA	197 (5.3)	105 (3.7)	0.0030
Previous MI	511 (13.8)	336 (12.0)	0.0337
Previous PCI	506 (13.6)	348 (12.4)	0.1472
Previous CABG	71 (1.9)	49 (1.7)	0.6223
Smoker, No (%)			
Never	988 (26.6)	750 (26.7)	0.6447
Current	1249 (33.6)	970 (34.6)	
Former	1478 (39.8)	1087 (38.7)	
NT-proBNP highest [pg/mL] (median (IQR))	N=1494 2010.10 (927.00, 4209.00)	N=1054 1539.59 (565.00, 2880.00)	0.0001#
eGFR (CKD-EPI) [mL/min/1.73 m2]	73.32 ±20.28	79.84 ±18.85	<0.0001
eGFR (CKD-EPI) <60 [mL/min/1.73 m2], No. (%)	1029 (27.7)	429 (15.3)	<0.0001
Serum Creatinine [mg/dL]	1.0 ±0.3	1.0 ±0.3	<0.0001
Haemoglobin [g/dL]	N=3582 13.60 ±1.83	N=2730 13.74 ±1.68	0.0026
BMI [kg/m^2]	28.18 ±5.08	27.93 ±4.94	0.0464
Systolic BP [mmHg]	120.8 ±15.0	119.8 ±14.6	0.0093
Diastolic BP [mmHg]	19.8 ±14.6	73.5 ±9.9	0.5082
Medical therapy at baseline, No. (%)			
Beta blockers	2905 (78.2)	2144 (76.4)	0.0825
ACEi or ARB	2502 (67.3)	1936 (69.0)	0.1643
MRA	1755 (47.2)	818 (29.1)	<0.0001
Loop diuretic	1859 (50.0)	353 (12.6)	<0.0001

All continuous variables reported as mean ± standard deviation except for NT-proBNP which was reported as median (interquartile range); categorical variables reported as number (frequency). #p-value base on log-transformed result.

Supplemental Table 4. Selected safety outcomes by randomised treatment group and according to baseline LVEF category based on treated patients.

	Overall (n=6463)		EF <35%		EF 35-<45%		EF ≥45%	
	Pbo (n=3229)	Empa (n=3234)	Pbo (n=680)	Empa (n=702)	Pbo (n=1712)	Empa (n=1700)	Pbo (n=809)	Empa (n=809)
Any adverse event leading to permanent treatment discontinuation								
Events, n (%)	122 (3.8)	122 (3.8)	31 (4.6)	36 (5.1)	54 (3.2)	64 (3.8)	36 (4.4)	22 (2.7)
Event rate per 100 pt-yrs	2.96	2.93	3.89	4.29	2.41	2.92	3.46	2.00
Serious adverse events								
Events, n (%)	798 (24.7)	765 (23.7)	217 (31.9)	222 (31.6)	390 (22.8)	370 (21.8)	186 (23.0)	166 (20.5)
Event rate per 100 pt-yrs	22.69	21.43	33.78	33.05	20.03	19.28	20.73	17.41
Volume depletion								
Events, n (%)	40 (1.2)	35 (1.1)	10 (1.5)	13 (1.9)	23 (1.3)	15 (0.9)	7 (0.9)	7 (0.9)
Event rate per 100 pt-yrs	0.98	0.84	1.26	1.56	1.03	0.68	0.67	0.64
Hypotension								
Events, n (%)	36 (1.1)	34 (1.1)	9 (1.3)	12 (1.7)	22 (1.3)	15 (0.9)	5 (0.6)	7 (0.9)
Event rate per 100 pt-yrs	0.88	0.82	1.13	1.44	0.99	0.68	0.48	0.64
Acute kidney injury								
Events, n (%)	43 (1.3)	27 (0.8)	17 (2.5)	9 (1.3)	15 (0.9)	13 (0.8)	11 (1.4)	5 (0.6)
Event rate per 100 pt-yrs	1.05	0.65	2.16	1.07	0.67	0.59	1.06	0.46

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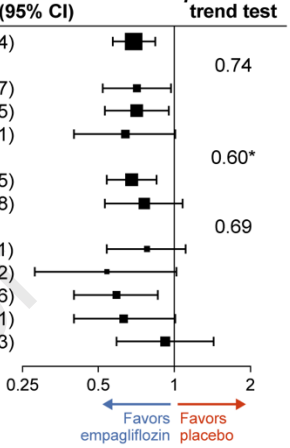
Supplemental Figure 2. Effect of empagliflozin vs. placebo on HF adverse events across baseline LVEF categories and presence of congestion.

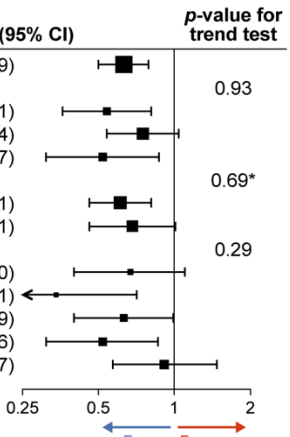
A. Time to first HF adverse event.

A	Empagliflozin n with event/ N analyzed (%)	Empagliflozin Incidence/ 100 py	Placebo n with event/ N analyzed (%)	Placebo Incidence/ 100 py	HR (95% CI)	*p*-value for trend test
Overall	178/3260 (5.5)	4.0	254/3262 (7.8)	5.7	0.69 (0.57, 0.84)	
By baseline LVEF						0.74
LVEF <35%	68/705 (9.6)	7.5	96/688 (14.0)	11.3	0.71 (0.52, 0.97)	
LVEF 35 to <45%	78/1713 (4.6)	3.3	111/1723 (6.4)	4.6	0.71 (0.53, 0.95)	
LVEF ≥45%	30/818 (3.7)	2.6	46/823 (5.6)	4.0	0.64 (0.40, 1.01)	
By signs or symptoms of congestion that required treatment						0.60*
With congestion	123/1852 (6.6)	4.8	185/1863 (9.9)	7.4	0.68 (0.54, 0.85)	
Without congestion	55/1408 (3.9)	2.8	69/1399 (4.9)	3.6	0.76 (0.53, 1.08)	
By baseline LVEF and signs or symptoms of congestion that required treatment						0.69
LVEF <35% with congestion	53/396 (13.4)	10.6	71/395 (18.0)	14.4	0.78 (0.54, 1.11)	
LVEF <35% without congestion	15/309 (4.9)	3.6	25/293 (8.5)	7.0	0.54 (0.28, 1.02)	
LVEF 35 to <45% with congestion	40/693 (5.8)	4.1	70/697 (10.0)	7.5	0.59 (0.40, 0.86)	
LVEF ≥45%	30/818 (3.7)	2.6	46/823 (5.6)	4.0	0.63 (0.40, 1.01)	
LVEF 35 to <45% without congestion	38/1020 (3.7)	2.7	41/1026 (4.0)	2.8	0.92 (0.59, 1.43)	



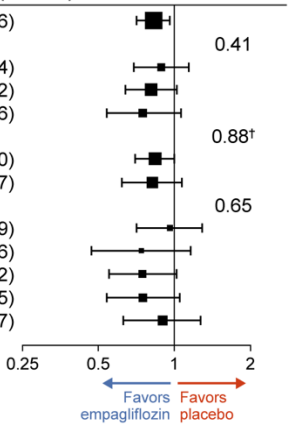
B. Total number of HF adverse events.

B	Empagliflozin n events/ N analyzed	Empagliflozin Events/ 100 py	Placebo n events/ N analyzed	Placebo Events/ 100 py	RR (95% CI)	*p*-value for trend test
Overall	227/3260	3.9	354/3262	6.2	0.63 (0.50, 0.79)	
By baseline LVEF						0.93
LVEF <35%	88/705	8.9	148/688	16.5	0.54 (0.36, 0.81)	
LVEF 35 to <45%	104/1713	3.9	142/1723	5.2	0.75 (0.54, 1.04)	
LVEF ≥45%	33/818	1.6	63/823	3.1	0.52 (0.31, 0.87)	
By signs or symptoms of congestion that required treatment						0.69*
With congestion	158/1852	4.7	263/1863	7.7	0.61 (0.46, 0.81)	
Without congestion	69/1408	2.9	91/1399	4.2	0.68 (0.46, 1.01)	
By baseline LVEF and signs or symptoms of congestion that required treatment						0.29
LVEF <35% with congestion	69/396	14.6	112/395	21.9	0.67 (0.40, 1.10)	
LVEF <35% without congestion	19/309	4.0	36/293	11.8	0.34 (0.16, 0.71)	
LVEF 35 to <45% with congestion	56/693	4.8	90/697	7.6	0.63 (0.40, 0.99)	
LVEF ≥45%	33/818	2.1	63/823	4.0	0.52 (0.31, 0.86)	
LVEF 35 to <45% without congestion	48/1020	2.9	52/1026	3.2	0.91 (0.57, 1.47)	



C. Time to first HF adverse event or all-cause mortality.

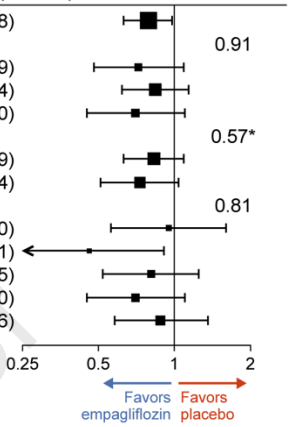
C	Empagliflozin n with event/ N analyzed (%)	Empagliflozin Incidence/ 100 py	Placebo n with event/ N analyzed (%)	Placebo Incidence/ 100 py	HR (95% CI)	*p*-value for trend test
Overall	313/3260 (9.6)	6.9	377/3262 (11.6)	8.5	0.83 (0.71, 0.96)	
By baseline LVEF						0.41
LVEF <35%	117/705 (16.6)	12.8	133/688 (19.3)	15.6	0.89 (0.69, 1.14)	
LVEF 35 to <45%	132/1713 (7.7)	5.5	165/1723 (9.6)	6.9	0.81 (0.64, 1.02)	
LVEF ≥45%	60/818 (7.3)	5.1	78/823 (9.5)	6.9	0.75 (0.54, 1.06)	
By signs or symptoms of congestion that required treatment						0.88†
With congestion	217/1852 (11.7)	8.5	265/1863 (14.2)	10.6	0.84 (0.70, 1.00)	
Without congestion	96/1408 (6.8)	4.9	112/1399 (8.0)	5.8	0.82 (0.62, 1.07)	
By baseline LVEF and signs or symptoms of congestion that required treatment						0.65
LVEF <35% with congestion	83/396 (21.0)	16.6	91/395 (23.0)	18.4	0.96 (0.71, 1.29)	
LVEF <35% without congestion	34/309 (11.0)	8.3	42/293 (14.3)	11.7	0.74 (0.47, 1.16)	
LVEF 35 to <45% with congestion	73/693 (10.5)	7.5	100/697 (14.3)	10.7	0.75 (0.55, 1.02)	
LVEF ≥45%	60/818 (7.3)	5.1	78/823 (9.5)	6.9	0.75 (0.54, 1.05)	
LVEF 35 to <45% without congestion	59/1020 (5.8)	4.2	65/1026 (6.3)	4.5	0.90 (0.63, 1.27)	



Empagliflozin after MI by LV Function and Congestion

D. Total number of HF adverse events or all-cause mortality.

D	Empagliflozin n events/ N analyzed	Empagliflozin Events/ 100 py	Placebo n events/ N analyzed	Placebo Events/ 100 py	RR (95% CI)	*p*-value for trend test
Overall	396/3260	8.9	532/3262	11.3	0.79 (0.63, 0.98)	
By baseline LVEF						0.91
LVEF <35%	151/705	25.1	211/688	34.9	0.72 (0.48, 1.09)	
LVEF 35 to <45%	174/1713	7.8	216/1723	9.2	0.84 (0.62, 1.14)	
LVEF ≥45%	66/818	3.7	103/823	5.3	0.70 (0.45, 1.10)	
By signs or symptoms of congestion that required treatment						0.57*
With congestion	277/1852	11.2	385/1863	13.4	0.83 (0.63, 1.09)	
Without congestion	119/1408	6.1	147/1399	8.3	0.73 (0.51, 1.04)	
By baseline LVEF and signs or symptoms of congestion that required treatment						0.81
LVEF <35% with congestion	110/396	37.8	151/395	39.9	0.95 (0.56, 1.60)	
LVEF <35% without congestion	41/309	14.4	60/293	31.5	0.46 (0.23, 0.91)	
LVEF 35 to <45% with congestion	99/693	10.9	135/697	13.5	0.81 (0.52, 1.25)	
LVEF ≥45%	66/818	4.8	103/823	6.9	0.70 (0.45, 1.10)	
LVEF 35 to <45% without congestion	75/1020	5.1	81/1026	5.7	0.88 (0.58, 1.36)	



*p-value of an interaction test for heterogeneity with or without congestion. Models adjusted for age, sex, diabetes, region, estimated glomerular filtration rate, persistent or permanent atrial fibrillation, prior myocardial infraction, peripheral artery disease, smoking, treatment and a treatment by subgroup interaction.

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