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ORIGINAL RESEARCH

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

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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).

**OBJECTIVES** This study sought to evaluate the association of left ventricular ejection fraction (LVEF), congestion, or both, with outcomes and the impact of empagliflozin in reducing HF risk post-AMI.

**METHODS** In the EMPACT-MI (Trial to Evaluate the Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients with Acute Myocardial Infarction) 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 were followed up for a median of 17.9 months.

**RESULTS** Among 6,522 patients, the mean baseline LVEF was 41 ± 9%; 2,648 patients (40.6%) presented with LVEF <45% alone, 1,483 (22.7%) presented with congestion alone, and 2,181 (33.4%) presented with both. Among patients in the placebo arm of the trial, multivariable adjusted risk for each 10-point reduction in LVEF included all-cause death or HF hospitalization (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; $P < 0.0001$). The 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 hospitalizations, 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, the severity of left ventricular 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. (Trial to Evaluate the Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients with Acute Myocardial Infarction [EMPACT-MI]; NCT04509674) (J Am Coll Cardiol 2024;83:2233-2246)


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**ABBREVIATIONS AND ACRONYMS**

**eGFR** = estimated glomerular filtration rate

**HF** = heart failure

**LV** = left ventricular

**LVEF** = left ventricular ejection fraction

**LVSD** = left ventricular systolic dysfunction

**MI** = myocardial infarction

**NT-proBNP** = N-terminal pro-B-type natriuretic peptide

**PCI** = percutaneous coronary intervention

**RR** = rate ratio

**SGLT2i** = sodium-glucose cotransporter 2 inhibitor

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) 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 (LVSD) 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 who are at high risk of heart failure may benefit from treatment with an SGLT2i.

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In the EMPACT-MI (Trial to Evaluate the Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients with Acute Myocardial Infarction) trial, patients with acute MI and either a newly decreased LVEF to <45% or signs or symptoms of congestion requiring treatment were randomized to receive either the SGLT2i 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

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all-cause mortality, but it did reduce the risk of first and total HF hospitalizations, as well as other adverse HF events.[4,5] In this prespecified 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 in stable condition and at high risk for HF on the basis of either newly developed LVSD (documented LVEF <45%) or congestion were randomized within 14 days of an acute MI. Patients were also required to have at least 1 of the following enrichment factors: age ≥65 years, newly developed LVEF <35%, a history of MI, atrial fibrillation, type 2 diabetes, an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 $m^2$, elevated natriuretic peptides or uric acid levels, elevated pulmonary artery or right ventricular systolic pressure, 3-vessel coronary artery disease, peripheral artery disease, or no revascularization for the index MI. Further details of the study group, including baseline characteristics and a full list of eligibility criteria, have been previously reported.[7]

In total, 6,522 participants were randomized to empagliflozin (10 mg daily) or matching placebo on top of standard of care and were followed up for a median of 17.9 months. Patients with preexisting heart failure or type 1 diabetes or who were planned for treatment with an SGLT2i or SGLT1/2i 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 before randomization during the index hospitalization. LVEF was reported as a number or a range according to local practice (<15%, 15%-<25%, 25%-<35%, 35%-<45%, 45%-<55% or ≥55%), and the modality of assessment was recorded. Congestion was defined as the presence of symptoms (eg, dyspnea, decreased exercise tolerance, fatigue) or signs (eg, pulmonary rales, crackles, or crepitations; elevated jugular venous pressure; congestion on chest radiography) that required treatment (eg, augmentation or initiation of oral diuretic therapy; intravenous diuretic therapy; intravenous vasoactive therapy; mechanical intervention) at any time during the hospitalization. Patients who 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 before randomization, was used for this analysis.

**STUDY OUTCOMES AND STATISTICAL ANALYSIS.** We evaluated both time to first HF hospitalization 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 on the basis of the intention-to-treat principle and included all randomized participants. The distribution of baseline site assessed LVEF was evaluated with mean ± SD and median (Q1-Q3). When only an LVEF range was reported, we used the midpoint value for analyses. LVEF was categorized into 3 groups: 1) <35%; 2) 35% to <45%; and 3) ≥45% (referent). Baseline characteristics were summarized by LVEF (3 groups) and by the presence or absence of congestion (2 groups) using mean ± SD and median (Q1-Q3) 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 the chi-square test for categorical variables for congestion groups.

After analyzing LVEF and congestion separately, we combined both exposures into a 5-group category of patients, as follows: 1) baseline LVEF <35% with congestion; 2) baseline LVEF <35% without congestion; 3) baseline LVEF 35% to <45% with congestion; 4) baseline LVEF 35% to <45% without congestion; and 5) 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 associations 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 an HR or rate ratio (RR) along with their 95% CIs 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 [Chronic Kidney Disease Epidemiology Collaboration] formula <45 vs 45-<60 vs 60-<90 vs ≥90 mL/min/1.73 $m^2$), geographic region, type 2 diabetes, persistent or permanent atrial fibrillation, previous MI, peripheral artery disease, smoking status, congestion, and baseline LVEF (categorical or continuous).

We evaluated treatment effects of empagliflozin vs 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 HRs or RRs with their 95% CIs, and for each treatment group we provided incidence or event rates per 100 patient-years of follow-up. These multivariable models were adjusted for the same covariates as described earlier (including 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 vs placebo by continuous LVEF was also evaluated and displayed graphically using a cubic spline model that included a set of cubic polynomials that 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 on the basis of the narrow standardized MedDRA query "cardiac failure." On the basis of 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, 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 prespecified list of cardiac failure events were to be reported as serious, despite not meeting the serious adverse event criteria of being fatal, life-threatening, causing disability or causing permanent damage, leading to or prolonging hospitalization. Therefore, investigator-reported HF adverse events included outpatient nonfatal HF events, hospitalization for HF, prolongation of hospitalization resulting from HF, and fatal HF events. In these analyses, the treatment effect of empagliflozin vs 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 for the 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 randomized 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).

## RESULTS

**BASELINE CHARACTERISTICS.** Baseline LVEF was reported as a discrete number in 5,087 (78.0%) patients and as a category in 1,383 (21.2%) patients. Baseline LVEF ranged from 10% to 79% (mean ± SD, [41.1% ± 9.1%]; median 40% [Q1-Q3: 35%-45%]) whereas 3,715 (57.0%) patients presented with signs or symptoms of congestion. The most common qualifying congestive symptom was dyspnea (n = 2,977; 45.6%), and the most common qualifying sign was pulmonary rales (n = 1,989; 30.5%) (Supplemental Table 1). Overall, 791 (12.2%) patients presented with LVEF <35% with congestion, 602 (9.2%) with LVEF <35% without congestion, 1,390 (21.3%) with LVEF 35%-<45% and congestion, 2,046 (31.4%) with LVEF 35%-<45% without congestion, and 1,483 (22.7%) with baseline LVEF ≥45% with congestion. 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 N-terminal pro-B-type natriuretic peptide (NT-proBNP) values, and less likely to have previous percutaneous coronary intervention (PCI) or coronary artery bypass grafting 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**, **Figures 1A to 1C**). 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 ($P$ for trend <0.0001), with the highest-risk group comprising those patients with baseline LVEF <35% with congestion and the lowest-risk group comprising those patients with baseline LVEF 35% to 45% without congestion, even lower than patients with a baseline LVEF ≥45% (Figures 2A to 2C).

**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 3A). Empagliflozin reduced the time to first HF hospitalization by 23% and the total HF hospitalizations by 33%, and this effect was consistent across the range of baseline LVEF (all $P$ for trend ≥0.79) (Figures 3B to 3C). The reduction in first and total HF hospitalizations with empagliflozin was consistent across baseline LVEF when analyzed continuously (all $P$ for interactions ≥0.90) (Figures 4A to 4C), in patients with and without congestion (all $P$ for interactions ≥0.57) (Figures 3B to 3C), and across the combinations of baseline LVEF and congestion (all $P$ for trend ≥0.42) (Figures 3B to 3C).

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 and 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 $P$ for trend >0.40), the presence or absence of congestion (all $P$ for interaction >0.50), and across combinations of baseline LVEF and congestion (all $P$ for trend >0.25) (Supplemental Figures 2A to 2D).

**SAFETY.** There were no increased rates of serious adverse events (23.7% vs 24.7%) or adverse events necessitating permanent discontinuation of the study drug (3.8% vs 3.8%) in the empagliflozin compared with placebo groups, respectively (Supplemental Table 4). Although rates of hypotension and volume depletion were similar between empagliflozin and placebo, numerically fewer patients experienced acute kidney injury in the empagliflozin group vs placebo group (0.8% vs 1.3%). The pattern was consistent across categories of baseline LVEF and congestion (Supplemental Table 4).

**TABLE 1 Risk of Cardiovascular Outcomes per 10-Point Reduction in Baseline LVEF (%) in the Placebo Arm**

| | N | HR/RR (95% CI) for 10-Point Reduction in Baseline LVEF[a] | *P* Value[b] |
|---|---|---|---|
| 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 |

[a]HR for time to first event per 10% reduction in baseline LVEF from a Cox proportional hazards regression model adjusted for age, sex, diabetes, region, estimated glomerular filtration rate, persistent or permanent atrial fibrillation, previous myocardial infarction, peripheral artery disease, smoking, and congestion. RR for total events per 10% reduction in baseline LVEF from a negative binomial regression model that adjusted for the same covariates with the log of time (days) used as offset. 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%). [b]P values are derived from the Wald statistic.

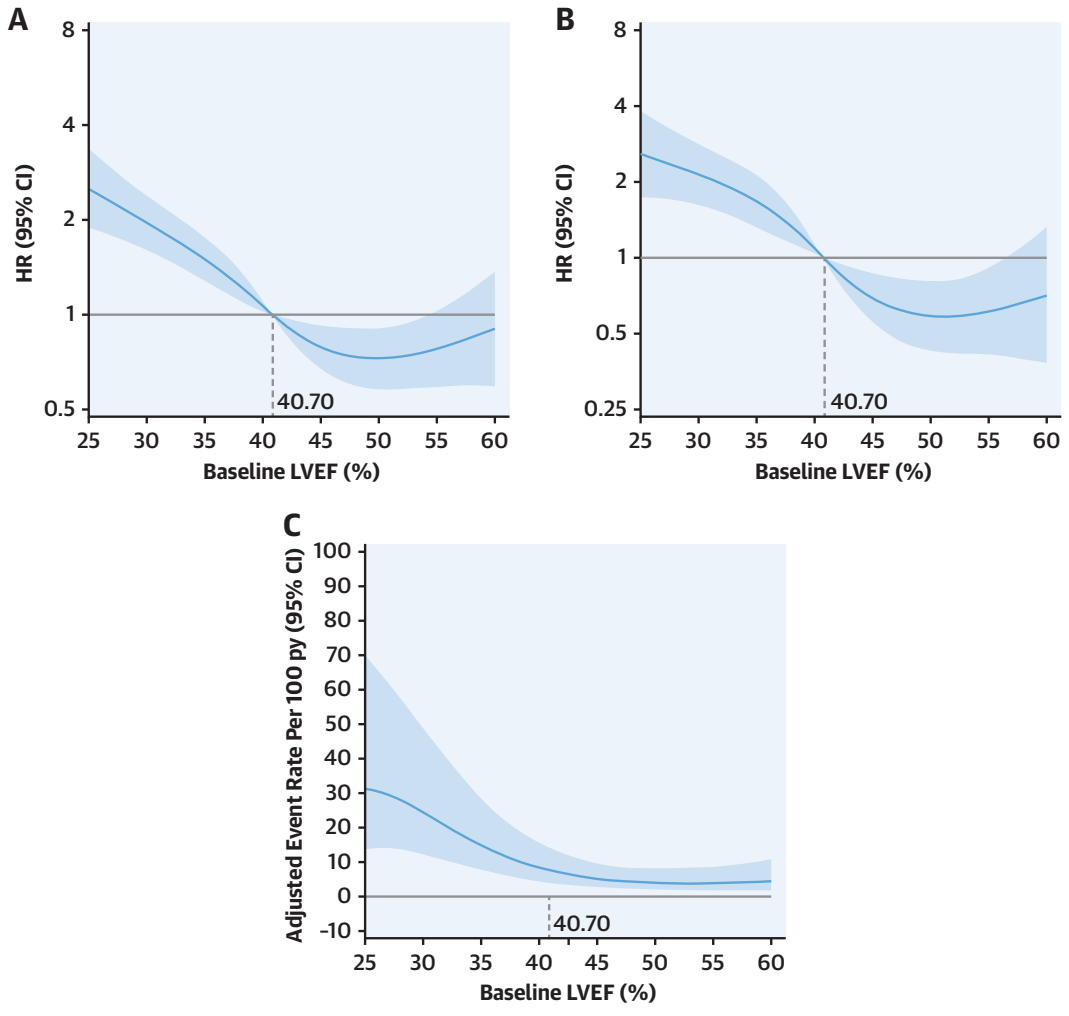
LVEF = left ventricular ejection fraction; RR = rate ratio.

## DISCUSSION

Empagliflozin reduced both first and recurrent HF hospitalizations, regardless of the severity of left ventricular (LV) dysfunction or the presence or absence of congestion, but it 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 SGLT2i in other disease states (ie, 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 LV dysfunction and the 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 the presence or absence of congestion.

The finding of a beneficial treatment effect on HF outcomes by SGLT2i across a range of eligible LVEFs has previously been seen in trials of both HF with reduced and preserved ejection fraction.[10-12] The mechanism of benefit of SGLT2i in chronic HF is understood to include many cardiac (including reverse remodeling), kidney, vascular, and systemic effects.[13,14] The mechanisms by which SGLT2i could

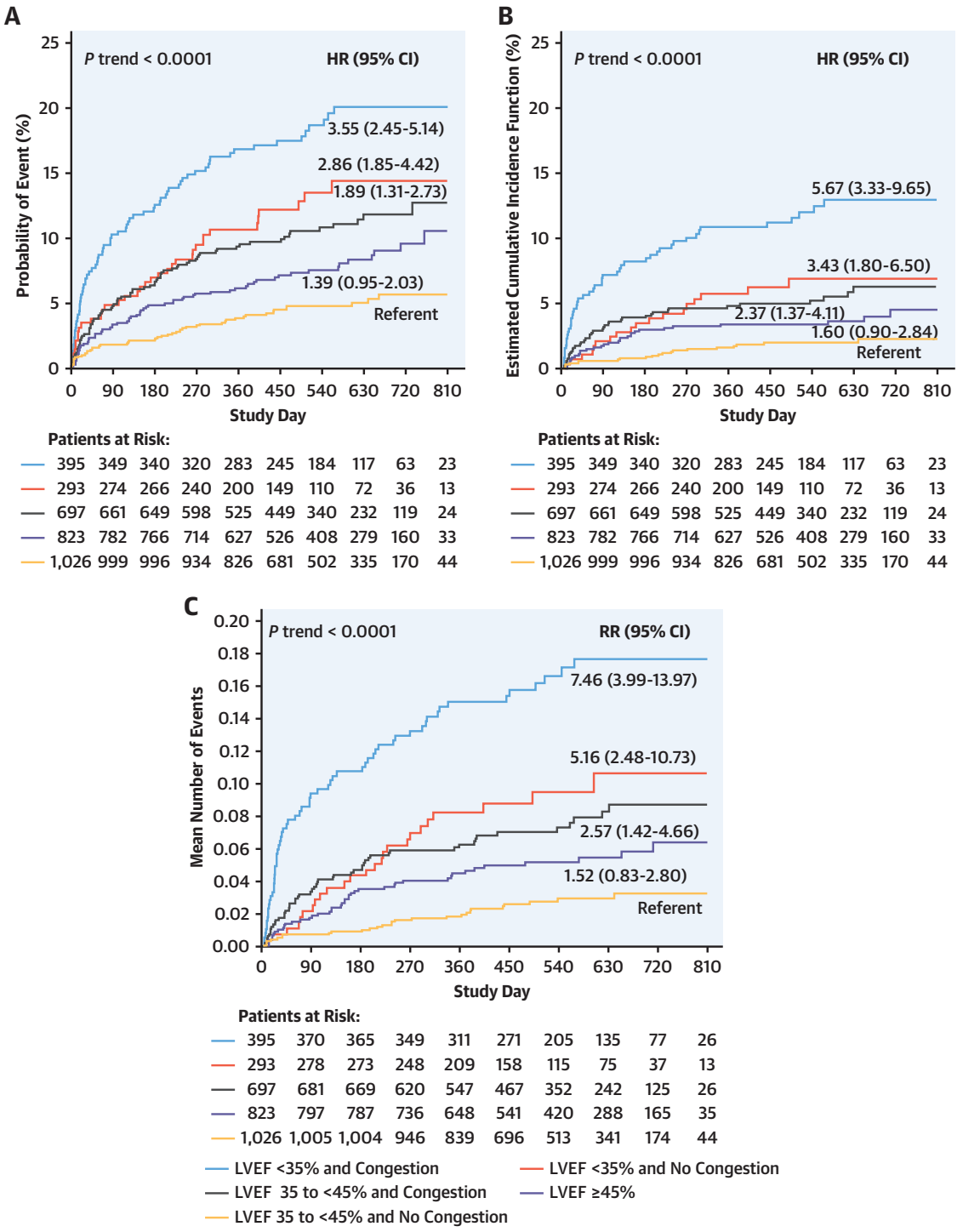
**FIGURE 1** Risk of Cardiovascular Outcomes According to Continuous Baseline LVEF




(A) Time to first hospitalization for heart failure or all-cause mortality. (B) Time to first heart failure hospitalization. (C) Total heart failure hospitalizations. Graphic results of cubic spline analyses showing the association of baseline left ventricular ejection fraction (LVEF) on outcomes among placebo-assigned patients. The median value of left ventricular ejection fraction was 40%. py = person years.

lead to a reduction in HF hospitalizations after acute MI have been reported in the EMMY (EMpagliflozin in patients with acute MYocardial infarction) trial.[15] In 476 patients enrolled on the basis of 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, findings suggesting that empagliflozin reduced adverse remodeling and may have reduced congestion, as assessed by changes 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 revascularization ("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 SGLT2i benefit on HF outcomes in patients post-MI, as was

**FIGURE 2** Risk of Cardiovascular Outcomes Across Baseline LVEF and Congestion

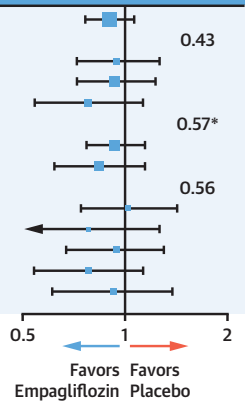



(A) Time to first hospitalization for heart failure or all-cause mortality. (B) Time to first heart failure hospitalization. (C) Total heart failure hospitalizations. Risk groups were categorized as ordered: baseline left ventricular ejection fraction (LVEF) <35% with congestion (n = 395; blue); baseline left ventricular ejection fraction <35% without congestion (n = 293; red); baseline left ventricular ejection fraction 35% to <45% with congestion (n = 697; black); baseline left ventricular ejection fraction ≥45% with or without congestion (n = 823; purple), and baseline left ventricular ejection fraction 35% to <45% without congestion (n = 1,026; yellow). Models adjusted for age, sex, diabetes, region, estimated glomerular filtration rate, persistent or permanent atrial fibrillation, previous myocardial infraction, peripheral artery disease, and smoking. RR = rate ratio.

**FIGURE 3** Effect of Empagliflozin Across Baseline LVEF Categories and Congestion

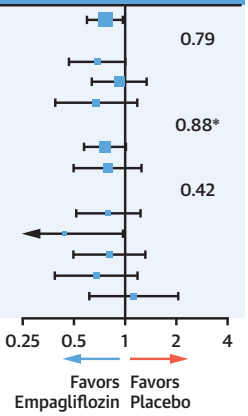
**A**

| | Empagliflozin | | Placebo | | | |
|---|---|---|---|---|---|---|
| | n With Event/ N Analyzed (%) | Incidence/ 100 py | n With Event/ N Analyzed (%) | Incidence/ 100 py | HR (95% CI) | *P* Value for Trend Test |
| **Overall** | 267/3,260 (8.2) | 5.9 | 298/3,262 (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% | 112/1,713 (6.5) | 4.6 | 124/1,723 (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 | 188/1,852 (10.2) | 7.2 | 209/1,863 (11.2) | 8.1 | 0.93 (0.77-1.14) | |
| Without congestion | 79/1,408 (5.6) | 4.0 | 89/1,399 (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 | 45/1,020 (4.4) | 3.1 | 48/1,026 (4.7) | 3.3 | 0.92 (0.61-1.38) | |



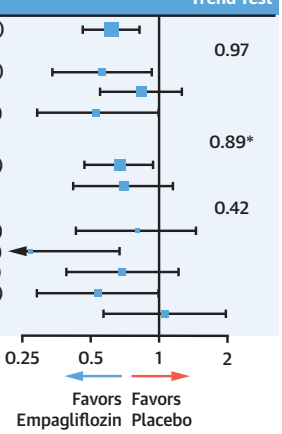

**B**

| | Empagliflozin | | Placebo | | | |
|---|---|---|---|---|---|---|
| | n With Event/ N Analyzed (%) | Incidence/ 100 py | n With Event/ N Analyzed (%) | Incidence/ 100 py | HR (95% CI) | *P* Value for Trend Test |
| **Overall** | 118/3,260 (3.6) | 2.6 | 153/3,262 (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% | 52/1,713 (3.0) | 2.2 | 58/1,723 (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 | 84/1,852 (4.5) | 3.2 | 113/1,863 (6.1) | 4.4 | 0.77 (0.58-1.02) | |
| Without congestion | 34/1,408 (2.4) | 1.7 | 40/1,399 (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 | 23/1,020 (2.3) | 1.6 | 20/1,026 (1.9) | 1.4 | 1.13 (0.62-2.06) | |



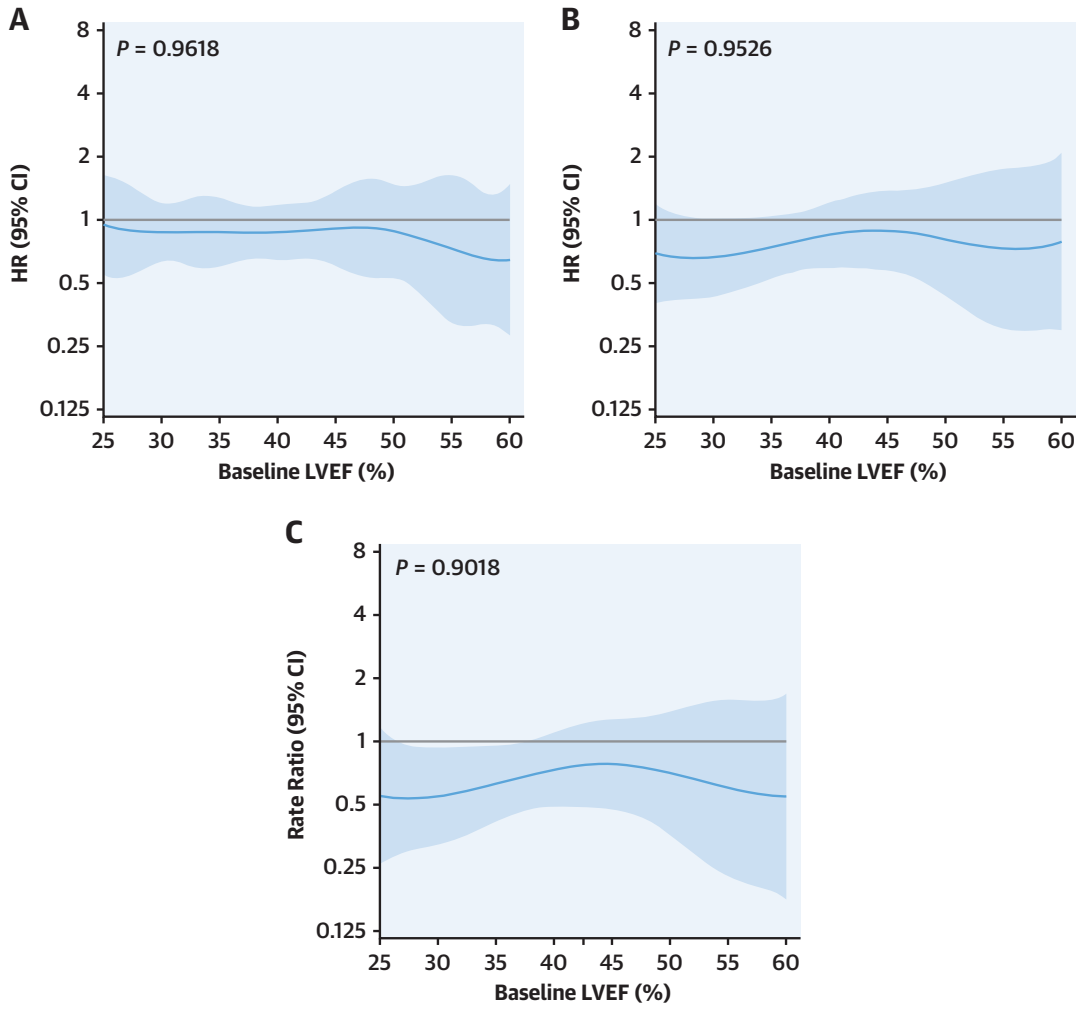

**C**

| | Empagliflozin | | Placebo | | | |
|---|---|---|---|---|---|---|
| | n With Event/ N Analyzed | Events/ 100 py | n Events/ N Analyzed | Events/ 100 py | RR (95% CI) | *P* Value for Trend Test |
| **Overall** | 148/3,260 | 2.4 | 207/3,262 | 3.4 | 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% | 65/1,713 | 2.3 | 78/1,723 | 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 | 106/1,852 | 2.9 | 153/1,863 | 4.4 | 0.67 (0.47-0 94) | |
| Without congestion | 42/1,408 | 1.7 | 54/1,399 | 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 | 29/1,020 | 1.7 | 27/1,026 | 1.6 | 1.06 (0.57-1.98) | |




(A) Time to first hospitalization for heart failure 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, previous myocardial infraction, peripheral artery disease, smoking, treatment, and a treatment by subgroup interaction. LVEF = left ventricular ejection fraction; py = patient-years; RR = rate ratio.

**FIGURE 4** Effect of Empagliflozin on Cardiovascular Outcomes According to Continuous LVEF




(A) Time to first heart failure hospitalization or all-cause death. (B) Time to first heart failure hospitalization. (C) Total heart failure hospitalization. Graphic results of cubic spline analyses showing the effect of empagliflozin on outcomes across baseline left ventricular ejection fraction (LVEF).

suggested previously when SGLT2i outcomes in patients with HF were studied in relation to the use of diuretic agents.[16] A cardiac magnetic resonance-based trial, EMPRESS-MI (Empagliflozin to PREvent worsening of left ventricular volumes and systolic function after Myocardial Infarction; NCT05020704), which is investigating the cardiac and renal effects of empagliflozin in an EMPACT-MI-like group, will report more mechanistic details.

In EMPACT-MI, we further confirm previous reports of the association between both baseline LVEF and congestion and adverse outcomes in patients with acute MI.[17-19] Patients with the lowest LVEF had the highest rates of HF hospitalizations and death in the combined analyses of EPHESUS (Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SUrvival Study), CAPRICORN (CArvedilol Post-infaRct survIval COntRolled evaluatioN), OPTIMAAL

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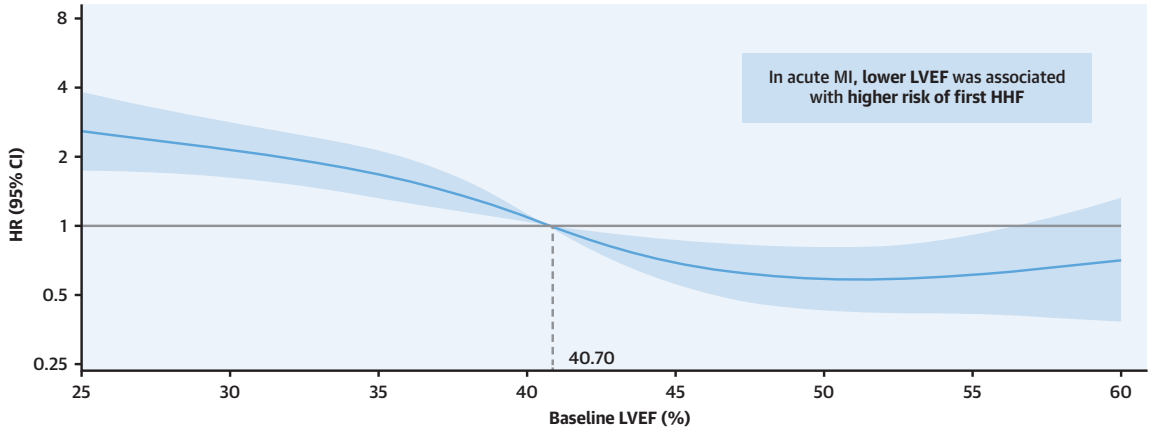
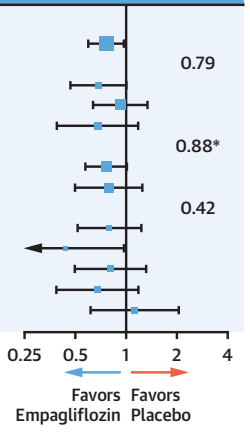
## CENTRAL ILLUSTRATION Effect of Empagliflozin on Hospitalization for Heart Failure Across Baseline Left Ventricular Ejection Fraction Categories and Congestion

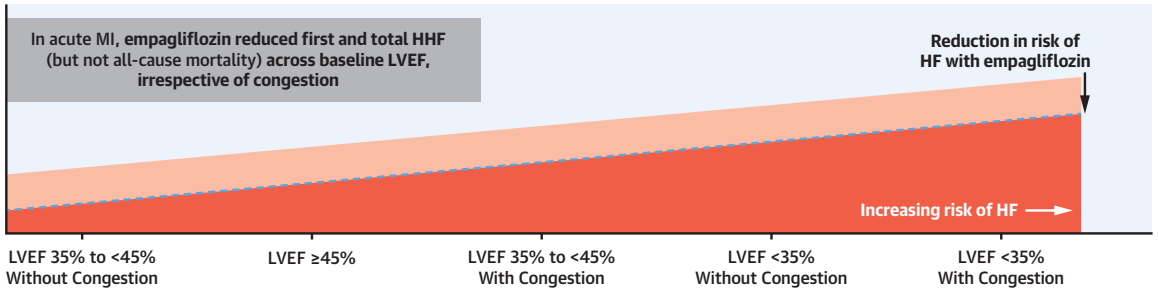
### EMPACT-MI: Effect of LVEF on First HHF (Component of Primary Endpoint) (Placebo Group)




### EMPACT-MI: Effect of Empagliflozin on Time to First HHF (Component of Primary Endpoint)

| | Empagliflozin n/N (%) | Placebo n/N (%) | HR (95% CI) | *P* Value for Trend Test |
|---|---|---|---|---|
| **First HHF** | | | | |
| Overall | 118/3,260 (3.6) | 153/3,262 (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% | 52/1,713 (3.0) | 58/1,723 (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 | 84/1,852 (4.5) | 113/1,863 (6.1) | 0.77 (0.58-1.02) | |
| Without congestion | 34/1,408 (2.4) | 40/1,399 (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 | 23/1,020 (2.3) | 20/1,026 (1.9) | 1.13 (0.62-2.06) | |

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**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, previous myocardial infraction, peripheral artery disease, smoking, treatment, and a treatment by subgroup interaction. EMPACT-MI = Trial to Evaluate the Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients with Acute Myocardial Infarction; HF = heart failure; HHF = hospitalization for heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

(OPtimal Therapy In Myocardial infarction with the Angiotensin II Antagonist Losartan), and VALIANT (VALsartan In Acute myocardial iNfarcTion).[17,18] Before 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 did patients without congestion. Most patients with an 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% and 45% without congestion. This observation suggests that post-MI congestion may be a stronger risk factor for adverse outcomes than moderate LVSD. Some earlier acute MI trials (eg, the AIRE [Acute Infarction Ramipril Efficacy] trial) mandated that all enrolled patients had pulmonary congestion, whereas others mandated that all patients had a low LVEF (eg, CAPRICORN and SAVE [Survival and Ventricular Enlargement]).[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 previous trial to report rates of adverse outcomes according to the presence or absence of congestion was the PARADISE-MI (Prospective ARNI [angiotensin receptor-neprilysin inhibitor] vs ACE [angiotensin-converting enzyme] Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction) trial,[25] which reported that patients with congestion and an LVEF ≤40% had double the rate of HF hospitalization and cardiovascular death than did patients with an 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, thus underscoring the unmet need for therapies, especially those targeted at groups with the highest risk.

The DAPA-MI (DAPAgliflozin in patients with Myocardial Infarction) trial attempted to establish whether 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 group for HF risk, and patients could be enrolled with any degree of regional or global LV dysfunction. In the relatively unselected group in DAPA-MI, the rate of HF events (only 59 adjudicated HF hospitalizations in 4,098 patients over a median follow-up of 11.6 months) was too low to provide sufficient power to assess the impact of the intervention on clinical outcomes, thereby 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 patients who met the enrollment criteria (ie, across the range of eligible LVEFs and with and without congestion) will benefit with a reduction in HF hospitalizations by empagliflozin. For those patients without low LVEF and without congestion, a treatment effect of SGLT2i has yet to be shown.

The PARADISE-MI trial, which compared sacubitril with valsartan vs ramipril in a post-MI group similar to that of EMPACT-MI, highlights the need for trials to quantify the benefits of therapies in different patient groups.[27] The combination of sacubitril and valsartan was shown in PARADIGM-HF to reduce cardiovascular death and HF hospitalization markedly in patients with HF and reduced LVEF,[28] but in PARADISE-MI, the combination of sacubitril and 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 with valsartan on the secondary outcome of HF events (HR: 0.84; 95% CI: 0.70-1.02) that was significant among investigator-reported events. A recent analysis of the treatment effect of sacubitril with valsartan in PARADISE-MI found a consistent lack of treatment effect regardless of a 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 patients with acute MI who were at increased risk of HF.

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

**STUDY STRENGTHS AND 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 LV function was not recorded, and instead it 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 prespecified definitions and structured data collection. No adjustment to the statistical inference of multiple comparisons was conducted given the exploratory nature of subgroup analyses.

## CONCLUSIONS

Across the spectrum of baseline LVEF and in the presence or absence of congestion, empagliflozin reduced both first and recurrent HF hospitalizations 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, thus underscoring the need for further trials to identify effective novel therapies.

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Dr Bayes-Genis has lectured and/or participated in advisory boards for Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Medtronic, Novartis, Novo Nordisk, Roche, and Vifor. Dr Goodman has received research grant support (steering committee or data and safety monitoring committee) and/or speaker or consulting honoraria (advisory boards) from Amgen, Anthos Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, CYTE Ltd, Daiichi-Sankyo/American Regent, Eli Lilly, Esperion, Ferring Pharmaceuticals, HLS Therapeutics, Idorsia, JAMP Pharma, Merck, Novartis, Novo Nordisk A/C, Pendopharm/Pharmascience, Pfizer, Regeneron, Sanofi, Servier, Tolmar Pharmaceuticals, and Valeo Pharma; and has received salary support or honoraria from the Canadian Heart Failure Society, Canadian Heart Research Centre, and MD Primer, Canadian VIGOUR Centre, Cleveland Clinic Coordinating Center for Clinical Research, Duke Clinical Research Institute, Jewish General Hospital, New York University Clinical Coordinating Centre, PERFUSE Research Institute, Peter Munk Cardiac Centre Clinical Trials and Translation Unit, and the TIMI Study Group (Brigham Health). 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Dr Januzzi has served as a trustee of the American College of Cardiology; has served as a board member of Imbria Pharmaceuticals; has served as director at Jana Care; has received research support from Abbott, Applied Therapeutics, Bayer, Bristol Myers Squibb, HeartFlow, Innolife, Medtronic, and Roche; has received consulting income from Abbott, AstraZeneca, Bayer, Beckman, Boehringer Ingelheim, Cytokinetics, Janssen, Merck, Novartis, Prevencio, Quidel/Ortho, and Roche; and has participated in clinical endpoint committees/data safety monitoring boards for Abbott, AbbVie, Axon, Bayer, CVRx, Medtronic, Pfizer, Roche, and Takeda. 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Dr Zieroth has received research grant support, served on advisory boards for, or participated in speaker engagements with AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Cytokinetics, Eli Lilly, GSK, Janssen, Medtronic, Merck, Novartis, Novo Nordisk, Otsuka, Pfizer, Roche, Salubrisbio, Servier, and Vifor Pharma; has served on a clinical trial committee or as a national lead for studies sponsored by AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, and Pfizer; and has nonindustry relationships with the Canadian Medical and Surgical KT Group, CCS, CHFS, Charite, EOCI, Liv, Medscape, Ology, PACE-CME, Radcliffe, Reach MD, and the Translational Medicine Academy. Dr Brueckmann is an employee of Boehringer Ingelheim. Dr Sumin is an employee of Boehringer Ingelheim. Dr Bhatt has served on the advisory boards of Angiowave, Bayer, Boehringer Ingelheim, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, and Stasys; has served on the Board of Directors of the American Heart Association New York City, Angiowave (with stock options), Bristol Myers Squibb (with stock), DRS.LINQ (with stock options), and High Enroll (with stock); has served as a consultant for Broadview

Ventures, GlaxoSmithKline, Hims, SFJ, and Youngene; has served on data monitoring committees for Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic, Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi-Sankyo; for the ABILITY-DM trial, funded by Concept Medical; for ALLAY-HF, funded by Alleviant Medical), Novartis, Population Health Research Institute; and Rutgers University (for the NIH-funded MINT Trial); has received honoraria from the American College of Cardiology (Senior Associate Editor, *Clinical Trials and News*, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), CSL Behring (American Heart Association lecture), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national coleader, funded by Bayer), WebMD (CME steering committees), Wiley (steering committee); has served as Deputy Editor for *Clinical Cardiology;* has been named on a patent for sotagliflozin assigned to Brigham and Women's Hospital, which assigned it to Lexicon; neither Dr Bhatt nor Brigham and Women's Hospital receives any income from this patent); has received research funding from Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Alnylam, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CinCor, Cleerly, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Eli Lilly, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Otsuka, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, Youngene, and 89Bio; has received royalties from Elsevier (Editor, *Braunwald's Heart Disease*); has served as site co-investigator for Abbott, Biotronik, Boston Scientific, CSI, Endotronix, St Jude Medical (now Abbott), Philips, SpectraWAVE, Svelte, and Vascular Solutions; has served as a trustee of the American College of Cardiology; and has conducted unfunded research for FlowCo. Dr Hernandez has served as a consultant to Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cytokinetics, Eidos, GlaxoSmithKline, Intellia, Intercept, Myokardia, Novartis, Novo Nordisk, Prolaio, and TikkunLev; and has received research funding from American Regent, Amgen, Bayer, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Novo Nordisk, and Verily. Dr Butler has served as a consultant for Abbott, American Regent, Amgen, Applied Therapeutic, AskBio, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, Cardiocell, Cardior, CSL Bearing, CVRx, Cytokinetics, Daxor, Edwards, Element Science, Faraday, Foundry, G3P, Innolife, Impulse Dynamics, Imbria, Inventiva, Ionis, Lexicon, Eli Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Owkin, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Prolaio, Regeneron, Renibus, Roche, Salamandra, Sanofi, SC Pharma, Secretome, Sequana, SQ Innovation, Tenex, Tricog, Ultromics, Vifor, and Zoll. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## PERSPECTIVES

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** In stabilized patients within 14 days of acute MI, empagliflozin reduces heart failure hospitalizations but not all-cause mortality across the spectrum of LVEF and presence or absence of congestion.

**TRANSLATIONAL OUTLOOK:** Further research is needed to clarify the mechanisms by which SGLT2i reduce heart failure hospitalizations after acute MI.

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**KEY WORDS** acute myocardial infarction, congestion, empagliflozin, heart failure, left ventricular dysfunction

**APPENDIX** For supplemental tables and figures, please see the online version of this paper.