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Effect of Empagliflozin on Heart Failure Outcomes After Acute Myocardial Infarction: Insights from the EMPACT-MI Trial

Running title: *Hernandez et al.; Empagliflozin and Post-Myocardial Infarction Heart Failure*

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Abstract

Background: Empagliflozin reduces the risk of heart failure events in patients with type 2 diabetes at high cardiovascular risk, chronic kidney disease, and in those with prevalent heart failure irrespective of ejection fraction. While EMPACT-MI showed empagliflozin does not reduce the risk of the composite of hospitalization of heart failure and all-cause mortality, the impact of empagliflozin on first and recurrent heart failure events in patients after myocardial infarction is unknown.

Methods: EMPACT-MI was a double-blind, randomized, placebo-controlled, event-driven trial that randomized 6522 patients hospitalized for acute myocardial infarction at risk for heart failure based on newly developed left ventricular ejection fraction of <45% and/or signs or symptoms of congestion to receive empagliflozin 10 mg daily or placebo within 14 days of admission. In prespecified secondary analyses, treatment groups were analyzed for heart failure outcomes.

Results: Over a median of follow-up of 17.9 months, the risk for first heart failure hospitalization and total heart failure hospitalizations was significantly lower in the empagliflozin compared with the placebo group (118 (3.6%) vs. 153 (4.7%) patients with events, HR 0.77 [95% CI 0.60, 0.98], P=0.031 for first heart failure hospitalization and 148 vs. 207 events, RR 0.67 [95% CI 0.51, 0.89], P=0.006 for total heart failure hospitalizations). Subgroup analysis showed consistency of empagliflozin benefit across clinically relevant patient subgroups for first and total heart failure hospitalizations. Post-discharge need for new use of diuretics, renin-angiotensin modulators, and mineralocorticoid receptor antagonists were less in patients randomized to empagliflozin than placebo (all p<0.05).

Conclusion: In patients after acute myocardial infarction with left ventricular dysfunction or congestion, empagliflozin reduced the risk of heart failure.

Clinical Trial Registration: ClinicalTrials.gov; NCT04509674.

Key Words: Myocardial infarction, heart failure, empagliflozin, heart failure hospitalizations

Non-standard Abbreviations and Acronyms

SGLT2	Sodium-glucose cotransporter-2
DAPA-MI	Dapagliflozin Effects on Cardiometabolic Outcomes in Patients with an Acute Heart Attack
EMPACT-MI	Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients with Acute Myocardial Infarction
STEMI	ST elevation myocardial infarction
ARNI	Angiotensin receptor-neprilysin inhibitor
ACEI	angiotensin-converting-enzyme inhibitors
ARB	Angiotensin receptor blocker
MRA	Mineralocorticoid receptor antagonist
ICD	Implantable cardiac defibrillator
CRT	Cardiac resynchronization therapy
PARADISE-MI	Prospective ARNI versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction

Clinical Perspective

What is new?

- Empagliflozin reduced the risk of first and total heart failure hospitalizations by 23% and 33%, respectively, in patients with left ventricular dysfunction or congestion after acute myocardial infarction.
- The benefit of empagliflozin was consistent across various patient subgroups and across a broad range of heart failure outcomes, including adverse events of heart failure and post-discharge initiation of heart failure therapies

What are the clinical implications?

- Acute myocardial infarction is frequently complicated by new onset of heart failure or leads to the development of chronic heart failure post-discharge.
- Empagliflozin may have a role for the prevention of heart failure in high-risk patients after myocardial infarction, especially those with left ventricular dysfunction or congestion.

Acute myocardial infarction is frequently complicated by new onset of heart failure or leads to the development of chronic heart failure post-discharge.[1] Once heart failure manifests after myocardial infarction, it is associated with higher mortality and recurrent hospitalization risk, and other complications.[2] Guidelines emphasize the identification of the high risk patients and the implementation of therapeutic interventions to prevent the development and progression of heart failure.[3,4] Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been consistently shown to reduce the risk of heart failure events both in patients at high-risk of developing heart failure, e.g., those with type 2 diabetes at high cardiovascular risk or chronic kidney disease, as well as those with prevalent heart failure, irrespective of left ventricular ejection fraction.

Previously, empagliflozin was shown to reduce the risk markers associated with developing heart failure after an acute myocardial infarction, including lowering natriuretic peptide levels, improving left ventricular ejection fraction, and decreasing cardiac volumes.[5] In the Dapagliflozin Effects on Cardiometabolic Outcomes in Patients with an Acute Heart Attack (DAPA-MI) trial, results for heart failure outcomes with dapagliflozin were inconclusive as the trial primary endpoint was changed to a 7-level win ratio due to the lower than expected event rate.[6]

The Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients with Acute Myocardial Infarction (EMPACT-MI) trial was designed to assess clinical outcomes of patients after myocardial infarction. The primary results have recently been reported.[7] While empagliflozin did not reduce the primary composite endpoint of time to first hospitalization for heart failure or all-cause death (hazard ratio [HR] 0.90; 95% confidence interval [CI] 0.76 to 1.06, p=0.21), the effect of empagliflozin on heart failure outcomes specifically remains clinically important in patients after myocardial infarction.[8] In this report, we provide the

detailed data on prespecified analyses on heart failure hospitalizations and other analyses related to heart failure events after acute myocardial infarction at risk for developing heart failure, with either newly developed left ventricular ejection fraction of <45% and/or signs or symptoms of congestion requiring treatment.

Methods

Trial Design

EMPACT-MI was an international, randomized, parallel-group, double-blind, placebo-controlled, event-driven trial. The trial design and primary results have been previously described.[7] The trial protocol was developed and amended by the Executive and Steering Committees. The Executive Committee provided scientific oversight of the development of the statistical analysis plan, patient recruitment and follow-up, and data analysis including pre-specified secondary analyses on subsequent development of heart failure. An independent Data Monitoring Committee reviewed the safety data. The trial was approved by the ethics committee at each trial site and all patients provided written informed consent. Statistical analyses for this analysis were performed by employees of the sponsor under the oversight of the Executive Committee.

Patients Population

EMPACT-MI randomized patients aged 18 years or older hospitalized with an acute myocardial infarction within 14 days of admission. Both patients with ST elevation myocardial infarction (STEMI) and non-STEMI were eligible. Similarly, patients with and without type 2 diabetes were included. Prior to randomization, the patients had either evidence of newly developed left ventricular ejection fraction <45% and/or signs (pulmonary rales, crackles or crepitations;

elevated jugular venous pressure; congestion on chest X-ray) or symptoms (e.g. dyspnea; decreased exercise tolerance; fatigue) of congestion requiring treatment (e.g. augmentation or initiation of oral diuretic therapy; i.v. diuretic therapy; i.v. vasoactive agent; mechanical intervention etc.). Patients were required to have at least one enrichment factor including age ≥65 years, newly developed left ventricular ejection fraction <35%, history of myocardial infarction, 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 index myocardial infarction. Patients with prior diagnosis of heart failure as well as who were taking or planned the use of SGLT2 inhibitor were excluded. Further details of the study population including the baseline characteristics and a full list of eligibility criteria have been previously reported as well as listed in the supplement. [9]

Study Procedures

Patients were randomized to either placebo or empagliflozin 10 mg daily in a 1:1 ratio, in addition to standard of care. In this streamlined trial, after randomization participants had a remote visit at 2 weeks, followed by a face-to-face visit at 6 months after randomization. Patients continued to have remote visits every 6 months until end of study when a final telephone call visit was performed. During these visits prespecified endpoints, safety events, and adherence to study drug were collected. Data on any concomitant medications were collected for six months post randomization, except for the initiation of non-study open-label SGLT2 or SGLT1/2 inhibitor, which was collected throughout the trial. All randomized patients were followed for the duration of the trial, regardless of intake of study medications.

Study Outcomes

The primary endpoint for EMPACT-MI was the composite of time to first hospitalization for heart failure or all-cause death and has been previously reported.[8] The key secondary outcomes in were total number of hospitalizations for heart failure or all-cause death, the total number of non-elective cardiovascular hospitalizations or all cause death, total number of non-elective all cause hospitalizations or all cause death and total number of hospitalizations for myocardial infarction or all-cause death and have also been previously reported. [8]

Heart Failure Outcomes (including Hospitalizations with primary reason heart failure)

For this report, the focus is on heart failure outcomes as pre-specified from the protocol as described above and from a pre-specfied publication analytical plan for heart failure related events. These additional heart failure related endpoints studied in this investigation included pre-specified time to first heart failure hospitalization, and pre-specified total (first and recurrent) heart failure hospitalizations. In addition, we also investigated time to first heart failure hospitalization or death due to heart failure, and total heart failure hospitalizations or death due to heart failure in exploratory, post-hoc analyses.

Heart Failure Adverse Events

In exploratory analyses, we also examined investigator-reported adverse events that were categorized as "cardiac failure" per MedDRA standards and included not only the events analyzed as prespecified endpoint of heart failure hospitalization but broader range of adverse events of heart failure including outpatient non-fatal adverse events as well as those requiring or prolonging hospitalization or with a fatal outcome. For a full list of all preferred terms and details of the methodology of the evaluation of Adverse Events of Heart Failure refer to the supplementary appendix.

For these exploratory analyses we examined time to first adverse event and total number of adverse events of heart failure, time to first adverse event and total number of adverse events of heart failure requiring/prolonging hospitalization or with fatal outcome, time to first adverse event and total number of outpatient non-fatal adverse events of heart failure as well as time to first event and total number of adverse events of heart failure or all-cause mortality and heart failure or CV death.

Endpoint Ascertainment

Endpoints of heart failure hospitalization and heart failure death were assessed by investigators blinded to study drug assignment who received standardized training and were monitored for quality assurance. Investigators were trained to report events based on prespecified definitions consistent with prior guidance on cardiovascular event classification. Further, these endpoints were verified according to the pre-specified algorithm as previously described and shown in the Supplement for Outcome Events Definitions.

Statistical Analysis

The analyses were performed based on the intention-to-treat principle and included all randomized study patients. Comparison between the empagliflozin and placebo arms for time to first-event endpoints were performed using primary Cox proportional hazards model, including baseline covariates of age, geographical region, eGFR (assessed categorically using the CKD-EPI formula <45 vs 45-<60 vs 60-<90 vs ≥90 ml/min/1.73m^2), left ventricular ejection fraction (<35% vs ≥35%), type 2 diabetes, persistent or permanent atrial fibrillation, prior myocardial infarction, peripheral artery disease, and smoking status. Data for patients who did not have an event were censored on the last day they were known to be free of the outcome. The assumption of proportional hazards was verified. For comparison of total (first and recurrent) events,

differences between empagliflozin and placebo were assessed using a negative binomial model including the same covariates that were used for time-to-first-event analyses and including logarithm of time as an adjustment for observation time. Sensitivity analyses were performed to assess the robustness of the results for time to first heart failure hospitalization and for total heart failure hospitalizations, including analyses based on inclusion of broader spectrum of heart failure hospitalizations which were not included into primary analysis (as described in study outcomes and supplement) and analyses based on models including only stratification variables of type 2 diabetes and geographical region.

Total hospitalization for heart failure events were further assessed in a time-to-event analysis using the pre-specified Wei-Lin-Weissfeld model[11], which produces estimated relative treatment effects in terms of the hazard ratio (HR) for the individual first and recurrent events by the order in which they occur (HR for first event, HR for second event, HR for third event). This model also includes a test of the consistency of the treatment estimates across the individual order of sequential events.

To assess the possible effect of mortality as a competing risk, we performed sensitivity analyses using the pre-specified semi-parametric joint frailty model with a piece-wise constant Weibull baseline hazard for total number of hospitalizations for heart failure considering all-cause mortality as competing risk.[10]

Consistency of effect of empagliflozin on time to first heart failure hospitalization and total heart failure hospitalizations were assessed across a broad range of pre-specified patient subgroups including the following; age (<65 and ≥65 years), sex, region, ethnicity, race, type of index myocardial infarction (STEMI and NSTEMI), type 2 diabetes, baseline eGFR (≥60 ml/min/1.73m^2 and <60 ml/min/1.73m^2), systolic blood pressure (<110 mmHg, ≥110-130

mmHg, and ≥130mmg), past history of myocardial infarction, persistent or permanent atrial fibrillation, median time from index MI diagnosis to randomization, and treatment with angiotensin receptor-neprilysin inhibitor (ARNI) or angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin receptor blocker (ARB), beta blocker, mineralocorticoid receptor antagonist (MRA), and loop/high-ceiling diuretics. These analyses were performed based on the Cox regression and respectively Negative Binomial regression models including factors as described above and additional terms for subgroup and interaction of subgroup-by-treatment (with interaction tests for categorical variables and trend tests for ordered variables).

An analysis was performed to assess new initiation of heart failure medications post discharge until 6 months after randomization for time to first initiation of diuretics (other than MRAs), ARNI, ACEI, ARB or ARNI, MRA, and beta-blockers in patients not on these respective medication at discharge. Time to first implantation of either implantable cardiac defibrillator (ICD) and/or cardiac resynchronization therapy (CRT) device was also assessed. All p-values reported for these exploratory analyses are 2-sided, and p-values less than 0.05 were considered statistically significant.

To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data, typically, one year after the approval has been granted by major Regulatory Authorities or after termination of the development program. Researchers should use the https://vivli.org/ link to request access to study data and visit.

Results

Baseline Characteristics

From December 2020 through March 2023, 6522 patients were randomly assigned to receive empagliflozin (3260) or placebo (3262) at 451 sites in 22 countries. Baseline characteristics were balanced between study drug groups (See Supplement Table 2). The randomized population had an LVEF<45% in 78.4% of patients and 57.0% had signs or symptoms of congestion that required treatment during index hospitalization. The most common enrichment factors included age ≥65 years (50.0%), type 2 diabetes (31.9%), and 3 vessel coronary disease (31.0%). A total of 6328 (97.0%) patients were followed for primary endpoint until trial end and 6467 (99.2%) provided vital status at the end of the trial.[8,9] Median follow-up duration was 17.9 months and median drug exposure was comparable between the two arms.[8]

Heart Failure Outcomes (including Hospitalizations with primary reason heart failure)

The risks of first heart failure hospitalization and the total number of heart failure hospitalizations were significantly reduced with empagliflozin compared with placebo (118 vs. 153 events, HR 0.77 [95% CI 0.60, 0.98], p=0.031 for first heart failure hospitalization and 148 vs. 207 events, RR 0.67 [95% CI 0.51, 0.89], p=0.006 for total heart failure hospitalizations) (Figure 1B, Figure 2, Supplementary Figure 3).

Overall, 271 (4.16%) patients had at least one heart failure hospitalization and 59 (0.9%) subsequently had a recurrent event, with a total of 355 heart failure hospitalization events. Analyses of total events by the order of events based on the Wei-Lin-Weissfeld model (i.e. time to first event, time to second event and time to third event) showed a consistent effect of empagliflozin (test for consistency of the effect across the order of events p=0.29; Figure 3).The sensitivity analyses for total number of heart failure hospitalizations using a joint frailty model to

account for the competing risk of mortality gave consistent results compared with the results using the negative binomial model (Supplementary Figure 2).

In exploratory analyses, the risks of first heart failure hospitalization or death due to heart failure (129 vs. 166 events, HR 0.78 [95% CI 0.62, 0.98], p=0.031) and total heart failure hospitalizations or death due to heart failure (168 vs. 236 events, RR 0.69 [95% CI 0.51, 0.93], p=0.015) were significantly reduced in the empagliflozin compared with the placebo arm (Supplementary Figures 3 and 4).

The sensitivity analyses of time to first and total heart failure hospitalizations including broader definitions of heart failure hospitalization showed consistent risk reductions with empagliflozin with those from the main analyses (Figure 2).

For first and total heart failure hospitalization sensitivity analyses based on a model including only the stratification factors, provided consistent results with those from the main analyses (Supplementary Figure 2). About half of the first heart failure hospitalizations appeared within the first 89 days after randomization and fewer patients on empagliflozin were hospitalized for heart failure within the first 89 days (56 [1.7%] vs. 77 [2.4%]) and after 89 days (62 [2.0%] vs. 76 [2.5%] from randomization.

Heart Failure Adverse Events

To assess the totality of heart failure events reported in the trial we evaluated adverse events of heart failure which included not only events analyzed as prespecified endpoint of heart failure hospitalization but a broader spectrum of adverse events including those requiring or prolonging hospitalization or with fatal outcome as well as outpatient non-fatal events. When analyzing total number of adverse heart failure events requiring or prolonging hospitalization or with fatal outcome, there were 497 events in total, and for total adverse events of heart failure that include

also outpatient events, there were in total 581 events. When assessing adverse events of heart failure requiring/prolonging hospitalization or with fatal outcome, there was a significantly lower risk of experiencing a first event (HR 0.78 [95% CI 0.63, 0.96], p=0.02, Supplementary Figures 5 and 6) and a lower risk in the total number of events (RR 0.66 [95% CI 0.50, 0.87], p=0.0035, Supplementary Figures 5 and 6) in the empagliflozin versus placebo group. For outpatient non-fatal adverse events of heart failure, there was a significantly lower risk of time to first event (HR 0.48 [95% CI 0.31, 0.73], p=0.0005, Supplementary Figures 5 and 6) and total number of events (RR 0.51 [95% CI 0.33, 0.80], p=0.0035, Supplementary Figures 5 and 6). Additionally, for the adverse events of heart failure, there was a significantly lower risk of time to first event (HR 0.70 [95% CI 0.57, 0.84], p=0.0002, Supplementary Figures 4, 5 and 6) and total number of events (RR 0.63 [95% CI 0.50, 0.79], p<0.0001, Supplementary Figures 5 and 6) with empagliflozin vs placebo. Significantly lower risk with empagliflozin vs placebo was also shown in the analysis of the composite endpoint of time to first adverse event of heart failure or all-cause mortality (HR 0.83 [95% CI 0.71, 0.96], p=0.013 based on 690 events, Figure 1A, Supplementary Figure 6) and total number of adverse events of heart failure or all-cause mortality (RR 0.79 [95% CI 0.63, 0.98], p=0.031 based on 928 events) (Supplementary Figure 6) as well as time to first adverse event of heart failure or CV death (HR 0.82 [95% CI 0.70, 0.96], p=0.013, Suppl. Figure 6) and total number of adverse events of heart failure or CV death (RR 0.79 [95% CI 0.63, 0.99], p=0.043, Supplementary Figure 6).

Subgroup Analysis

The risk reduction with empagliflozin vs. placebo was generally consistent across patient baseline subgroups studied, including clinically relevant subgroups by age, sex, region, race, ethnicity, persistent or permanent atrial fibrillation, type of index myocardial infarction (STEMI

vs. NSTEMI), type 2 diabetes (yes vs. no), baseline eGFR (≥60 ml/min/1.73m^2 and <60 ml/min/1.73m^2), or treatment with ACEI/ARB/ARNI, beta blocker, MRA, and diuretics, for both time to first heart failure hospitalization (Figure 4) and total (first and recurrent) heart failure hospitalizations (Figure 5). The only statistically positive interaction was observed for time to first heart failure hospitalization for race (p=0.027), while the hazard ratios were below 1 for all categories, there were very few events in the non-White patients.

Post-Discharge Heart Failure Therapy

Among patients discharged while not being on diuretic therapy, significantly fewer patients in the empagliflozin arm were started on a diuretics other than MRA within 6 months post discharge compared to those randomized to placebo (N=138 [12.2%], vs. N=174 [15.3%], HR 0.80 [95% CI 0.64, 1.00], p=0.046) (Figure 6A). Similarly, significantly fewer patients were initiated on ARNI (HR 0.73 [95% CI 0.58, 0.93], p=0.009) (Figure 6B); ACEI, ARB or ARNI (HR 0.75 [95% CI 0.57, 0.99], p=0.044) (Figure 6C); and MRA (HR 0.74 [95% CI 0.58, 0.95], p=0.017) (Figure 6D) among patients not on these therapies at discharge. There was numerically lower initiation of beta-blockers (HR 0.75 [95% CI 0.55, 1.04], p=0.084) and implantation of ICD and/or CRT in empagliflozin vs. the placebo group (N=68 [2.1%], vs. N=85 [2.6%], HR 0.80 [95% CI 0.58, 1.10], p=0.16).

Discussion

While empagliflozin did not reduce the primary composite endpoint of hospitalization for heart failure or all-cause death in the EMPACT-MI trial as previously reported,[8] we show here in these pre-specified analyses that empagliflozin reduced the time to first hospitalization for heart failure and the total number of hospitalizations for heart failure. These benefits were consistent across

relevant patient subgroups, including those with STEMI or non-STEMI and those with or without type 2 diabetes. We also observed consistent benefits of empagliflozin in exploratory analyses in the risk reduction of heart failure adverse events including the full range of heart failure events such as prolonged hospitalization due to heart failure or outpatient heart failure events. These results are consistent with previous trials with SGLT2 inhibitors in other patient populations and highlight the role of empagliflozin in preventing heart failure post-myocardial infarction.[11]

Clinical guidelines emphasize the early detection of patients at risk for developing heart failure.[3,4] Acute myocardial infarction complicated by symptoms of heart failure or left ventricular dysfunction underscores a high risk and portends poor outcomes.[1] If patients do not recover left ventricular function after an ischemic event, they are particularly vulnerable for developing chronic heart failure and subsequent high risk for mortality and hospitalizations. With these results of EMPACT-MI, we show that empagliflozin has a role for the treatment of patients after acute myocardial infarction who are at risk for heart failure by reducing the burden of development of heart failure. Empagliflozin reduced the risk of time to first hospitalization for heart failure by 23% and the total number of hospitalizations for heart failure by 33%. These results are not only directionally but quantitatively comparable to the effect of SGLT2 inhibitors seen in other patient populations, with benefits seen early as has been described previously.[11]

Other studies have aimed to lower the long-term risk in patients with acute myocardial infarction complicated by heart failure symptoms or left ventricular dysfunction. In the Prospective ARNI versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction (PARADISE-MI), valsartan-sacubitril did not lower the rate of death from cardiovascular causes or incident of heart failure compared to ramipril.[12]

There was also no reduction in the secondary endpoint of the risk of composite of hospitalization for heart failure or outpatient heart failure visits (HR 0.84 [95% CI 0.70, 1.02]). While DAPA-MI showed that dapagliflozin improved cardiometabolic measures such as weight loss, new onset of diabetes, there was no significant improvement observed in the composite of cardiovascular death or hospitalization for heart failure compared with placebo (HR 0.95 [95% CI 0.64, 1.40]).[6] However, the number of events for this composite was only 102, making the trial underpowered to reliably assess these clinical outcomes.

As the totality of evidence for SGLT2 inhibitors has evolved, it has become clear that heart failure benefits extend to patient populations with and without diabetes, as well as with and without prior heart failure and across the spectrum of left ventricular ejection fraction. Similarly, we also found that empagliflozin reduces the risk of heart failure across important subgroups. This includes older patients, those with and without type 2 diabetes, STEMI or non-STEMI, and irrespective of background medical therapies, providing evidence for a generalizable benefit in high-risk patients.

EMPACT-MI was conducted during the COVID-19 pandemic and previous studies have shown that the number of hospitalizations for heart failure had substantially decreased during this period. Patients with tolerable symptoms may either not have sought care or may have been managed in the outpatient setting as observed through adverse event reporting. Moreover, two regions where the trial was conducted were affected by war during the trial. Also, being a streamlined trial by design that did not include a central event adjudication committee, only heart failure hospitalization events were considered for primary analyses. Recent trials have reported that outpatient heart failure events contribute meaningfully to the total heart failure burden, e.g., of the 4744 patients in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure

(DAPA-HF) trial, there were a total of 549 hospitalizations for heart failure and 604 outpatient worsening of heart failure events.[13] Indeed we captured adverse events related to heart failure because they were included in a pre-specified list of adverse events that were to be always reported as serious. When considering all these reported adverse events of heart failure (including with fatal outcome, requiring or prolonging hospitalization and outpatient events), the number of events analyzed was 581 in EMPACT-MI.

An indirect measure to assess new onset heart failure burden post myocardial infarction may be the initiation of typical heart failure therapies post discharge. Considering the streamlined nature of the study, medication data were collected for only within the first 6 months post randomization (except for open-label SGLT2 or SGLT1/2 inhibitor use data that was collected throughout the trial). Even with this limitation, there was a significantly lower rate of patients starting diuretics (other than MRA), ARNI, RAAS inhibitors, or MRA post-discharge, further highlighting the impact of empagliflozin on clinical decisions requiring escalation of other medical therapy.

By design, this trial focused on clinical outcomes meaningful to clinicians and did not collect mechanistic data that would fully explain any results. The trial focused on randomizing patients early after myocardial infarction, a dynamic time in which patients can have stunned myocardium that may recover especially after revascularization and independent of concomitant pharmacotherapy. The outcomes of heart failure hospitalizations were assessed by trained site investigators according to pre-specified definitions with collection of corresponding data in structured eCRF as described in the supplement and evaluated through monitoring for completeness. Therefore, endpoints were not centrally adjudicated. A limitation of these analyses of heart failure endpoints is that the primary endpoint of the trial was not met, so in a strict

statistical sense should be considered exploratory. However, the reduction in heart failure outcomes observed is internally consistent within the trial across several definitions and subgroups as well as externally consistent with multiple other SGLT2 inhibitor trials in various clinical settings.

In conclusion, while empagliflozin was not associated with a reduction in the risk of death after myocardial infarction, the risk related to heart failure hospitalization was statistically significantly lower in patients randomized to empagliflozin compared with placebo. The magnitude of benefit observed was similar to that in previous trials involving SGLT2 inhibitors. Consistent benefit was seen across major patient subgroups as well as over the entire observation period starting early after the index myocardial infarction and across a broad range of heart failure outcomes. These data suggest the potential role for empagliflozin in high-risk post-myocardial infarction patients in preventing heart failure hospitalizations.

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Supplemental Materials

Major protocol-specified efficacy endpoints

Outcome events definitions and verification in the trial

Collection of adverse events

Analysis of heart failure adverse events

Supplementary Tables 1 - 4

Supplementary Figures 1 – 6

References

1. Harrington J, Jones WS, Udell JA, Hannan K, Bhatt DL, Anker SD, Petrie MC, Vedin O, Butler J, Hernandez AF. Acute Decompensated Heart Failure in the Setting of Acute Coronary Syndrome. *JACC Heart Fail*. 2022;10:404-414. doi: 10.1016/j.jchf.2022.02.008
2. Desta L, Jernberg T, Lofman I, Hofman-Bang C, Hagerman I, Spaak J, Persson H. Incidence, temporal trends, and prognostic impact of heart failure complicating acute myocardial infarction. The SWEDEHEART Registry (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies): a study of 199,851 patients admitted with index acute myocardial infarctions, 1996 to 2008. *JACC Heart Fail*. 2015;3:234-242. doi: 10.1016/j.jchf.2014.10.007
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599-3726. doi: 10.1093/eurheartj/ehab368
4. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e895-e1032. doi: 10.1161/CIR.0000000000001063
5. von Lewinski D, Kolesnik E, Tripolt NJ, Pferschy PN, Benedikt M, Wallner M, Alber H, Berger R, Lichtenauer M, Saely CH, et al. Empagliflozin in acute myocardial infarction: the EMMY trial. *Eur Heart J*. 2022;43:4421-4432. doi: 10.1093/eurheartj/ehac494
6. James S ED, Storey RF, et al. Dapagliflozin in Myocardial Infarction without Diabetes or Heart Failure. *NEJM Evidence*. 2023. doi: 10.1056/EVIDoa2300286
7. Harrington J, Udell JA, Jones WS, Anker SD, Bhatt DL, Petrie MC, Vedin O, Sumin M, Zwiener I, Hernandez AF, Butler J. Empagliflozin in patients post myocardial infarction rationale and design of the EMPACT-MI trial. *Am Heart J*. 2022;253:86-98. doi: 10.1016/j.ahj.2022.05.010
8. Butler J, Jones WS, et al. Empagliflozin After Acute Myocardial Infarction. *N Engl J Med*. 2024. doi: 10.1056/NEJMoa2314051. [In Press].
9. Harrington J, Udell JA, Jones WS, Anker SD, Bhatt DL, Petrie MC, Andersen KR, Sumin M, Zwiener I, Hernandez AF, Butler J. Baseline characteristics of patients enrolled in the EMPACT-MI trial. *Eur J Heart Fail*. 2023. doi: 10.1002/ejhf.2990
10. Rogers JK, Yaroshinsky A, Pocock SJ, Stokar D, Pogoda J. Analysis of recurrent events with an associated informative dropout time: Application of the joint frailty model. *Stat Med*. 2016;35:2195-2205. doi: 10.1002/sim.6853
11. Usman MS, Siddiqi TJ, Anker SD, Bakris GL, Bhatt DL, Filippatos G, Fonarow GC, Greene SJ, Januzzi JL, Jr., Khan MS, et al. Effect of SGLT2 Inhibitors on Cardiovascular Outcomes Across Various Patient Populations. *J Am Coll Cardiol*. 2023;81:2377-2387. doi: 10.1016/j.jacc.2023.04.034
12. Pfeffer MA, Claggett B, Lewis EF, Granger CB, Kober L, Maggioni AP, Mann DL, McMurray JJV, Rouleau JL, Solomon SD, et al. Angiotensin Receptor-Neprilysin

Inhibition in Acute Myocardial Infarction. *N Engl J Med*. 2021;385:1845-1855. doi: 10.1056/NEJMoa2104508

13. Docherty KF, Jhund PS, Anand I, Bengtsson O, Bohm M, de Boer RA, DeMets DL, Desai AS, Drozdz J, Howlett J, et al. Effect of Dapagliflozin on Outpatient Worsening of Patients With Heart Failure and Reduced Ejection Fraction: A Prespecified Analysis of DAPA-HF. *Circulation*. 2020;142:1623-1632. doi: 10.1161/CIRCULATIONAHA.120.047480

Figure Legends

Figure 1. (A) Time to First Adverse Event of Heart Failure or All-cause Mortality (B) Total Number of Heart Failure Hospitalizations

Figure 2. Major Heart Failure Outcomes

‡Hazard Ratio (95% confidence interval), p-value based on Cox proportional hazards model for time to first event endpoints, Event Rate Ratio (95% CI), based on Negative Binomial Regression for total number of events endpoints.

*Number of patients with event(s) for time to first event endpoints and number of events for total number of events endpoints.

†Number of patients with event(s) per 100 patient-years for time to first event endpoints and adjusted number of events per 100 patient-years (based on Negative Binomial Regression) for total number of event endpoints.

Figure 3. Time-to-event Analyses of Hospitalization for Heart Failure by Order of Event According to the Wei-Lin-Weissfeld Model

Figure 4. Time to First Heart Failure Hospitalization, According to Pre-specified Subgroups

*Median time from index MI diagnosis to randomisation: 5.0 days

NC, Not calculated

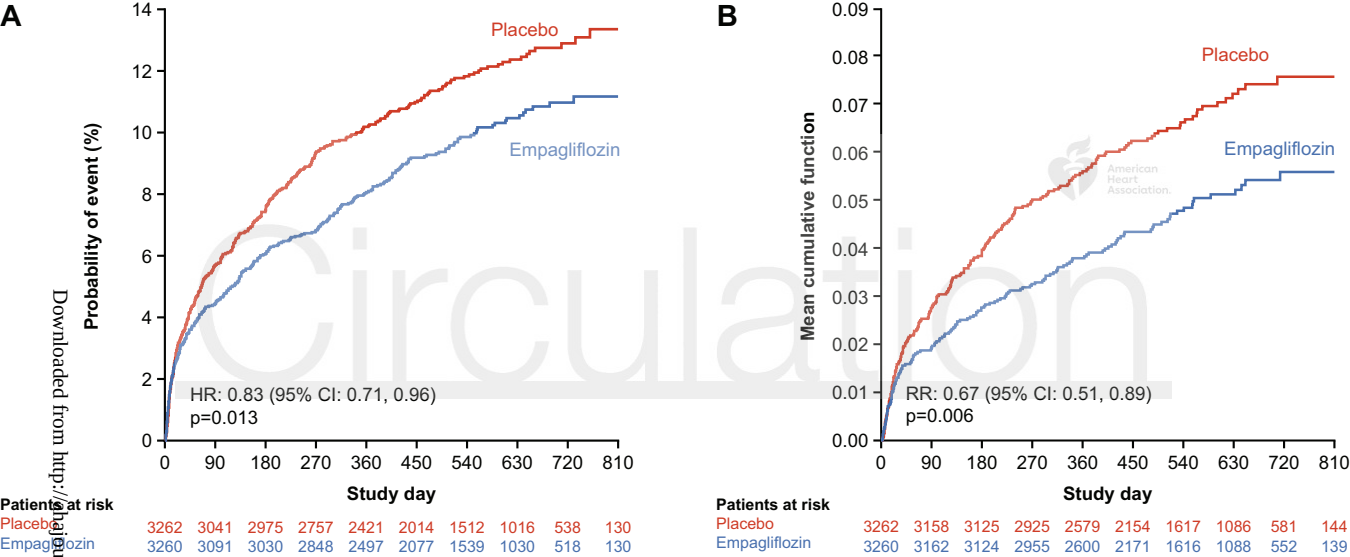
Figure 5. Total Number of Heart Failure Hospitalizations, According to Pre-specified Subgroups

*Median time from index MI diagnosis to randomisation: 5.0 days

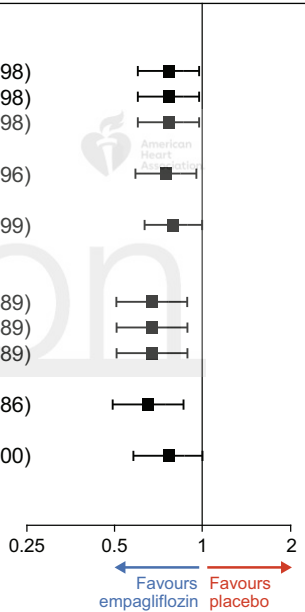
NC, Not calculated

Figure 6. Cumulative Incidence Function for Post-discharge Time to First Use of Heart Failure Therapies Until 6 Months: (A) Diuretics*; (B) ARNI; (C) ACEI, ARB or ARNI; (D) MRA

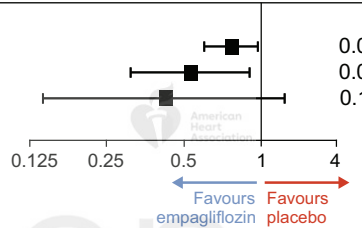
*Diuretics excluding MRA



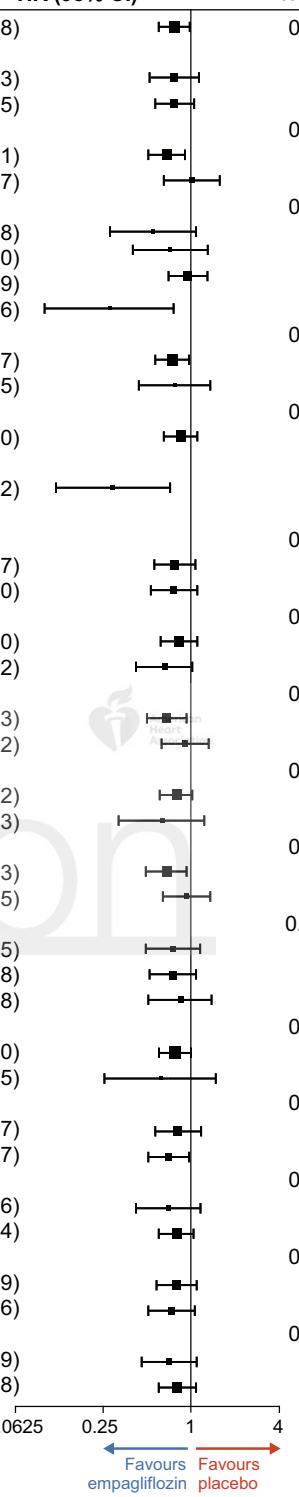
Variable	Empagliflozin (n=3260) N events*	Empagliflozin (n=3260) Events/ 100 py†	Placebo (n=3262) N events*	Placebo (n=3262) Events/ 100 py†	Hazard ratio or rate ratio‡	*p*-value
Hospitalizations with primary reason heart failure						
Time to first HHF	118	2.6	153	3.4	0.77 (0.60, 0.98)	0.031
Including elective HHF	119	2.6	154	3.4	0.77 (0.60, 0.98)	0.032
Including events without documented signs/symptoms of HF	118	2.6	153	3.4	0.77 (0.60, 0.98)	0.031
Including events without documented treatment for HF	121	2.7	160	3.5	0.75 (0.59, 0.96)	0.019
Including events without documented signs/symptoms or treatment for HF, including elective HHF	135	3.0	170	3.8	0.79 (0.63, 0.99)	0.039
Total number of HHF	148	2.4	207	3.6	0.67 (0.51, 0.89)	0.006
Including elective HHF	149	2.4	208	3.6	0.67 (0.51, 0.89)	0.006
Including events without documented signs/symptoms of HF	148	2.4	207	3.6	0.67 (0.51, 0.89)	0.006
Including events without documented treatment for HF	151	2.4	218	3.7	0.65 (0.49, 0.86)	0.003
Including events without documented signs/symptoms or treatment for HF, including elective HHF	181	3.2	234	4.2	0.76 (0.58, 1.00)	0.051



Variable	Number of patients (%) Empagliflozin (n=3260)	Placebo (n=3262)	Hazard ratio (95% CI)	*p*-value
Time to HHF by number of events (Wei-Lin-Weisfeld model)				
≥1 event	98 (3.0)	114 (3.5)	0.77 (0.60, 0.98)	0.032
≥2 events	15 (0.5)	27 (0.8)	0.53 (0.31, 0.91)	0.021
≥3 events	1 (<0.1)	9 (0.3)	0.42 (0.14, 1.24)	0.117
Test for consistency, *p*=0.290				



	Empagliflozin		Placebo			p-value for interaction
	n with event/ N analysed (%)	Incidence/ 100 py	n with event/ N analysed (%)	Incidence/ 100 py	HR (95% CI)	
Overall	118/3260 (3.6)	2.6	153/3262 (4.7)	3.4	0.77 (0.60, 0.98)	0.994
Age, years						
<65	46/1639 (2.8)	2.0	57/1623 (3.5)	2.4	0.77 (0.52, 1.13)	
≥65	72/1621 (4.4)	3.7	96/1639 (5.9)	4.4	0.77 (0.57, 1.05)	
Sex						0.136
Male	77/2448 (3.1)	2.2	113/2449 (4.6)	3.3	0.68 (0.51, 0.91)	
Female	41/812 (5.0)	3.3	40/813 (4.9)	3.6	1.01 (0.65, 1.57)	
Region						0.084
North America	13/431 (3.0)	2.0	26/433 (6.0)	4.0	0.55 (0.28, 1.08)	
Latin America	19/290 (6.6)	6.0	26/288 (9.0)	8.7	0.72 (0.40, 1.30)	
Europe	81/2153 (3.8)	2.6	83/2154 (3.9)	2.7	0.95 (0.70, 1.29)	
Asia	5/386 (1.3)	1.0	18/387 (4.7)	3.9	0.28 (0.10, 0.76)	
Ethnicity						0.902
Not Hispanic/Latino	93/2866 (3.2)	2.3	124/2859 (4.3)	3.1	0.74 (0.57, 0.97)	
Hispanic/Latino	22/338 (6.5)	5.8	28/331 (8.5)	7.8	0.77 (0.44, 1.35)	
Race						0.027
White	106/2730 (3.9)	2.7	123/2721 (4.5)	3.2	0.85 (0.65, 1.10)	
Black/African-American	3/44 (6.8)	6.2	8/48 (16.7)	14.4	NC	
Asian	6/421 (1.4)	1.1	20/413 (4.8)	4.0	0.29 (0.12, 0.72)	
Other (including mixed race)	0/9 (0.0)	0.0	1/7 (14.3)	10.4	NC	
Time from index MI diagnosis to randomization						0.958
≤median*	66/1870 (3.5)	2.5	85/1915 (4.4)	3.2	0.77 (0.56, 1.07)	
>median*	52/1388 (3.7)	2.7	68/1347 (5.0)	3.6	0.76 (0.53, 1.10)	
Type of index MI						0.397
STEMI	86/2444 (3.5)	2.5	100/2401 (4.2)	3.0	0.82 (0.62, 1.10)	
NSTEMI	32/814 (3.9)	2.8	53/861 (6.2)	4.5	0.66 (0.42, 1.02)	
T2D at baseline						0.249
No	68/2225 (3.1)	2.2	92/2216 (4.2)	3.0	0.68 (0.50, 0.93)	
Yes	50/1035 (4.8)	3.5	61/1046 (5.8)	4.3	0.91 (0.63, 1.32)	
History of MI						0.525
No	105/2872 (3.7)	2.6	128/2803 (4.6)	3.3	0.79 (0.61, 1.02)	
Yes	13/388 (3.4)	2.4	25/459 (5.4)	4.0	0.63 (0.32, 1.23)	
Baseline eGFR (CKD-EPI), mL/min/1.73 m²						0.197
≥60	65/2540 (2.6)	1.8	93/2524 (3.7)	2.6	0.68 (0.49, 0.93)	
<60	53/720 (7.4)	5.4	60/738 (8.1)	6.2	0.93 (0.64, 1.35)	
Baseline SBP (mmHg)						0.764†
<130	38/719 (5.3)	4.0	51/723 (7.1)	5.4	0.75 (0.49, 1.15)	
≥130 to <130	52/1605 (3.2)	2.3	68/1570 (4.3)	3.1	0.75 (0.52, 1.08)	
≥130	28/935 (3.0)	2.1	34/969 (3.5)	2.5	0.84 (0.51, 1.38)	
Atrial fibrillation at baseline						0.604
No	109/3154 (3.5)	2.5	140/3154 (4.4)	3.2	0.78 (0.61, 1.00)	
Yes	9/106 (8.5)	6.5	13/108 (12.0)	9.0	0.62 (0.26, 1.45)	
Baseline use of loop or high-ceiling diuretics						0.550
No	53/2126 (2.5)	1.8	68/2184 (3.1)	2.2	0.81 (0.57, 1.17)	
Yes	65/1134 (5.7)	4.2	85/1078 (7.9)	5.8	0.70 (0.51, 0.97)	
Baseline use of beta blocker						0.673
No	26/745 (3.5)	2.7	36/728 (4.9)	3.6	0.70 (0.42, 1.16)	
Yes	92/2515 (3.7)	2.6	117/2534 (4.6)	3.3	0.79 (0.60, 1.04)	
Baseline use of MRA						0.751
No	69/1992 (3.5)	2.5	83/1957 (4.2)	3.1	0.79 (0.58, 1.09)	
Yes	49/1268 (3.9)	2.7	70/1305 (5.4)	3.8	0.73 (0.51, 1.06)	
Baseline use of ACE inhibitor, ARB or ARNI						0.632
No	34/865 (3.9)	2.9	53/931 (5.7)	4.1	0.71 (0.46, 1.09)	
Yes	84/2395 (3.5)	2.5	100/2331 (4.3)	3.1	0.80 (0.60, 1.08)	



	Empagliflozin		Placebo			
	n events/ N analysed	Events/ 100 py	n events/ N analysed	Events/ 100 py	Event rate ratio (95% CI)	*p*-value for interaction
Overall	148/3260	2.4	207/3262	3.6	0.67 (0.51, 0.89)	
Age, years						0.355
<65	58/1639	2.2	78/1623	2.8	0.78 (0.51, 1.21)	
≥65	90/1621	2.7	129/1639	4.5	0.60 (0.41, 0.87)	
Sex						0.242
Male	93/2448	2.2	152/2449	3.6	0.60 (0.43, 0.84)	
Female	55/812	3.1	55/813	3.5	0.87 (0.51, 1.47)	
Region						0.333
North America	23/431	3.0	36/433	4.1	0.73 (0.35, 1.50)	
Latin America	20/290	4.4	35/288	8.5	0.52 (0.23, 1.18)	
Europe	99/2153	2.3	114/2154	3.0	0.77 (0.54, 1.09)	
Asia	6/386	1.2	22/387	4.0	0.29 (0.10, 0.84)	
Ethnicity						0.519
Not Hispanic/Latino	120/2866	2.3	168/2859	3.3	0.68 (0.50, 0.93)	
Hispanic/Latino	25/338	3.4	38/331	6.6	0.52 (0.24, 1.11)	
Race						0.270
White	131/2730	2.3	169/2721	3.3	0.71 (0.52, 0.96)	
Black/African-American	7/44	14.9	11/48	14.5	1.03 (0.21, 5.12)	
Asian	7/421	1.4	24/413	4.4	0.31 (0.12, 0.85)	
Other (including mixed race)	0/9	NC	2/7	NC	NC	
Time from index MI diagnosis to randomization						0.431
≤median*	77/1870	2.2	115/1915	3.6	0.61 (0.42, 0.89)	
>median*	71/1388	2.7	92/1347	3.5	0.77 (0.50, 1.18)	
Type of index MI						0.392
STEMI	109/2444	2.4	139/2401	3.3	0.73 (0.52, 1.02)	
NSTEMI	39/814	2.3	68/861	4.2	0.55 (0.32, 0.95)	
T2D at baseline						0.765
No	88/2225	2.1	121/2216	3.0	0.70 (0.48, 1.00)	
Yes	60/1035	3.3	86/1046	5.1	0.64 (0.40, 1.01)	
History of MI						0.855
No	134/2872	2.4	176/2803	3.6	0.68 (0.50, 0.92)	
Yes	14/388	2.1	31/459	3.3	0.63 (0.28, 1.42)	
Baseline eGFR (CKD-EPI), mL/min/1.73 m²						0.506
≥60	76/2540	1.9	118/2524	3.0	0.62 (0.44, 0.89)	
<60	72/720	5.5	89/738	7.2	0.76 (0.47, 1.24)	
Baseline SBP (mmHg)						0.560†
<130	54/719	4.0	71/723	6.2	0.64 (0.38, 1.08)	
≥130 to <130	60/1605	2.1	94/1570	3.3	0.63 (0.41, 0.96)	
≥130	34/935	1.8	42/969	2.2	0.81 (0.46, 1.43)	
Atrial fibrillation at baseline						0.382
No	139/3154	2.4	193/3154	3.4	0.69 (0.52, 0.93)	
Yes	9/106	3.0	14/108	7.9	0.39 (0.11, 1.38)	
Baseline use of loop or high-ceiling diuretics						0.604
No	67/2126	1.8	91/2184	2.4	0.73 (0.49, 1.08)	
Yes	81/1134	3.6	116/1078	5.8	0.62 (0.41, 0.95)	
Baseline use of beta blocker						0.371
No	31/745	2.1	48/728	4.0	0.53 (0.29, 0.97)	
Yes	117/2515	2.5	159/2534	3.4	0.72 (0.52, 1.00)	
Baseline use of MRA						0.092
No	87/1992	2.5	106/1957	3.0	0.84 (0.57, 1.22)	
Yes	61/1268	2.3	101/1305	4.4	0.51 (0.33, 0.79)	
Baseline use of ACE inhibitor, ARB or ARNI						0.874
No	45/865	2.8	67/931	4.0	0.70 (0.42, 1.18)	
Yes	103/2395	2.3	140/2331	3.4	0.67 (0.47, 0.93)