The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 25, 2024 VOL. 390 NO. 16

Empagliflozin after Acute Myocardial Infarction

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ABSTRACT

BACKGROUND

Empagliflozin improves cardiovascular outcomes in patients with heart failure, patients with type 2 diabetes who are at high cardiovascular risk, and patients with chronic kidney disease. The safety and efficacy of empagliflozin in patients who have had acute myocardial infarction are unknown.

METHODS

In this event-driven, double-blind, randomized, placebo-controlled trial, we assigned, in a 1:1 ratio, patients who had been hospitalized for acute myocardial infarction and were at risk for heart failure to receive empagliflozin at a dose of 10 mg daily or placebo in addition to standard care within 14 days after admission. The primary end point was a composite of hospitalization for heart failure or death from any cause as assessed in a time-to-first-event analysis.

RESULTS

A total of 3260 patients were assigned to receive empagliflozin and 3262 to receive placebo. During a median follow-up of 17.9 months, a first hospitalization for heart failure or death from any cause occurred in 267 patients (8.2%) in the empagliflozin group and in 298 patients (9.1%) in the placebo group, with incidence rates of 5.9 and 6.6 events, respectively, per 100 patient-years (hazard ratio, 0.90; 95% confidence interval [CI], 0.76 to 1.06; P=0.21). With respect to the individual components of the primary end point, a first hospitalization for heart failure occurred in 118 patients (3.6%) in the empagliflozin group and in 153 patients (4.7%) in the placebo group (hazard ratio, 0.77; 95% CI, 0.60 to 0.98), and death from any cause occurred in 169 (5.2%) and 178 (5.5%), respectively (hazard ratio, 0.96; 95% CI, 0.78 to 1.19). Adverse events were consistent with the known safety profile of empagliflozin and were similar in the two trial groups.

CONCLUSIONS

Among patients at increased risk for heart failure after acute myocardial infarction, treatment with empagliflozin did not lead to a significantly lower risk of a first hospitalization for heart failure or death from any cause than placebo. (Funded by Boehringer Ingelheim and Eli Lilly; EMPACT-MI ClinicalTrials.gov number, NCT04509674.)

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This article was published on April 6, 2024, at NEJM.org.

N Engl J Med 2024;390:1455-66.
DOI: 10.1056/NEJMoa2314051

CME

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After acute myocardial infarction, patients are at increased risk for heart failure and death, particularly if they present with congestion or a decreased left ventricular ejection fraction.[1-3] Treatment with sodium–glucose cotransporter 2 (SGLT2) inhibitors improves cardiovascular outcomes in high-risk patients with type 2 diabetes, those with chronic kidney disease, and those with heart failure with a reduced or preserved left ventricular ejection fraction.[4] In the EMMY trial (Impact of Empagliflozin on Cardiac Function and Biomarkers of Heart Failure in Patients with Acute Myocardial Infarction), patients who received empagliflozin after an acute myocardial infarction had a reduced natriuretic peptide concentration, an increased left ventricular ejection fraction, and a decreased cardiac volume; however, this trial was not designed to assess clinical outcomes.[5] The DAPA-MI trial (Dapagliflozin Effects on Cardiometabolic Outcomes in Patients with an Acute Heart Attack) was limited by the small number of clinical events during the trial and therefore was unable to assess the effects of SGLT2 inhibitor therapy after myocardial infarction on rates of death or hospitalizations for heart failure.[6]

Here, we report the results of the EMPACT-MI trial (Study to Evaluate the Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients with Acute Myocardial Infarction), in which empagliflozin was compared with placebo with respect to the risk of hospitalization for heart failure or death among patients with acute myocardial infarction and either a new reduction in left ventricular ejection fraction or signs or symptoms of congestion (or both).

Methods

Trial Oversight

The EMPACT-MI trial was an international, event-driven, double-blind, randomized, placebo-controlled trial. The trial design has been described previously.[7] The trial was approved by the ethics committee at each trial site, and all the patients provided written informed consent. The trial sponsors were Boehringer Ingelheim and Eli Lilly. The trial protocol (available with the full text of this article at NEJM.org) was developed and amended by the executive and steering committees, which included employees of Boehringer Ingelheim (who represented the sponsors) and provided scientific oversight on the development of the statistical analysis plan (available with the protocol), patient recruitment and follow-up, and data analysis. An independent data monitoring committee reviewed the safety data. Statistical analyses were performed by employees of Boehringer Ingelheim with oversight by the executive committee, and key analyses were verified by an independent statistician. The first author prepared the first draft of the submitted manuscript, which was reviewed and edited by all the authors. The first and last authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and the statistical analysis plan.

Patients

Patients were men and women 18 years of age or older who had been hospitalized with an acute myocardial infarction within 14 days before randomization and had either evidence of a newly developed left ventricular ejection fraction of less than 45% or signs or symptoms of congestion that resulted in treatment during the index hospitalization (or both). Patients needed to have at least one additional enrichment factor (a clinical factor that was known to be associated with hospitalization for heart failure or death from any cause), including an age of 65 years or older; a newly developed ejection fraction of less than 35%; a history of myocardial infarction, atrial fibrillation, or type 2 diabetes; an estimated glomerular filtration rate (GFR) of less than 60 ml per minute per 1.73 m^2 of body-surface area; an elevated natriuretic peptide or uric acid level; an elevated pulmonary artery or right ventricular systolic pressure; three-vessel coronary artery disease; peripheral artery disease; or no revascularization for the index myocardial infarction. Patients with a previous diagnosis of heart failure, as well as those who were taking or planning to take SGLT2 inhibitors, were excluded. A full list of eligibility criteria is provided in the Supplementary Appendix (available at NEJM.org) and was published previously.[7]

Trial Design

Patients who met the eligibility criteria were randomly assigned in a 1:1 ratio to receive empa-

gliflozin at a dose of 10 mg daily or placebo in addition to standard care. Randomization was performed with the use of interactive response technology and was stratified according to type 2 diabetes status and geographic region (North America, Latin America, Europe, or Asia). The EMPACT-MI trial had a streamlined design, with the collection of essential data only, including information about specific safety events, and mainly remote follow-up of patients (by means of a Web-based application or a telephone call) with only a few face-to-face visits; the trial assessed investigator-reported end-point events rather than centrally adjudicated end-point events.

After randomization, patients had a remote visit at 2 weeks, a face-to-face visit at 6 months, and remote visits every 6 months thereafter until the end of the trial, when a final telephone call was performed. During these visits, data on prespecified end points, safety events, and adherence to the trial regimen were collected. Data on all concomitant medications were collected for 6 months after randomization; thereafter, medication data were collected only on open-label initiation of treatment with SGLT2 inhibitors or combined treatment with SGLT1 and SGLT2 inhibitors. Because of the established safety profile of empagliflozin,[8-10] we used focused safety reporting, in which the investigators reported only serious adverse events, adverse events that led to discontinuation of the trial regimen for at least 7 consecutive days, and adverse events of special interest. All the patients who underwent randomization were followed for the duration of the trial, regardless of whether they received empagliflozin or placebo.

TRIAL END POINTS

The primary end point was a composite of hospitalization for heart failure or death from any cause as assessed in a time-to-first-event analysis. The key secondary end points in the prespecified hierarchical testing strategy were the total number of hospitalizations for heart failure or death from any cause, the total number of nonelective cardiovascular hospitalizations or death from any cause, the total number of nonelective hospitalizations for any cause or death from any cause, and the total number of hospitalizations for myocardial infarction or death from any cause. Additional prespecified end points are described in the Supplementary Appendix. In lieu of central adjudication, end-point events were reviewed and categorized according to prespecified definitions by investigators at the trial sites who were unaware of trial-group assignment and had received training in reviewing end-point events. Investigator-reported end-point events were verified according to the algorithm described in the Supplementary Appendix.

STATISTICAL ANALYSIS

In this event-driven trial, we estimated that 532 patients with a primary end-point event would provide the trial with 85% power to detect a 23% lower risk of an event in the empagliflozin group than in the placebo group, with a two-sided type I error of 0.05. The original protocol planned for the enrollment of 3312 patients, with an option to increase enrollment to 5000 patients if the accrual of events was slower than expected. The sample size was further increased to 6500. These decisions were made on the basis of blinded trial data, with no change to the target number of events or revisions to effect-size projections or power calculations. No interim efficacy analyses were performed.

The analyses of the primary composite end point and its components were performed according to the intention-to-treat principle and included all the patients who underwent randomization. The differences between the empagliflozin and placebo groups in the risk of a primary end-point event were assessed with the use of a Cox proportional-hazards model that included the baseline covariates of age, geographic region, estimated GFR (<45, 45 to <60, 60 to <90, or ≥90 ml per minute per 1.73 m^2 according to the Chronic Kidney Disease Epidemiology Collaboration formula), left ventricular ejection fraction (<35% or ≥35%), type 2 diabetes status, persistent or permanent atrial fibrillation, previous myocardial infarction, peripheral artery disease, and smoking status. Data for patients who did not have a primary end-point event were censored on the last day they were known to have been free of the event, which may have been the last time point before the patient was lost to follow-up (under the assumption of noninformative censoring).

A prespecified hierarchical testing procedure was used, beginning with the primary end point and then proceeding to the set of key secondary end points. A Hochberg step-up procedure was

used to assess the first and second key secondary end points at the same level of hierarchy, with the next two key secondary end points subsequently tested in a hierarchical manner.

All key secondary end points were analyzed with the use of a negative binomial regression model that included the same covariates as the primary model and the logarithm of time as an adjustment for observation time. The observation time started on the day of randomization and ended on the last day when information about end-point events was collected for an individual patient, which may have been the last time point before the patient was lost to follow-up. Post hoc sensitivity analyses that accounted for the competing risks of death from any cause and death from cardiovascular causes were performed with the use of Fine and Gray models for time to a first hospitalization for heart failure, time to death from cardiovascular causes, and time to a first hospitalization for heart failure or death from cardiovascular causes. Safety analyses included all the patients who received at least one dose of empagliflozin or placebo. The confidence intervals for the secondary and exploratory end points were not adjusted for multiplicity and should be interpreted as exploratory.

RESULTS

PATIENTS

From December 2020 through March 2023, a total of 6610 patients at 451 sites in 22 countries were screened, of whom 6522 were randomly assigned to receive empagliflozin at a dose of 10 mg daily (3260 patients) or placebo (3262 patients). The median time from admission to randomization was 5 days (interquartile range, 3 to 8). The characteristics of the patients at baseline were similar in the two trial groups (Table 1).[11] A total of 78.4% of the patients had a left ventricular ejection fraction of less than 45%, and 57.0% had signs or symptoms of congestion that resulted in treatment during the index hospitalization. Among the patients with signs or symptoms of congestion, 20.6% had a left ventricular ejection fraction of at least 45%. The most common enrichment factors included an age of 65 years or older (in 50.0% of the patients), type 2 diabetes (in 31.9%), and three-vessel coronary artery disease (in 31.0%); 70.5% of the patients had more than one enrichment factor (Table S1 in the Supplementary Appendix). Nearly 75% of the patients who underwent randomization presented with ST-segment elevation myocardial infarction (STEMI), and revascularization for the index myocardial infarction was performed in 89.3%.

The trial regimen was stopped prematurely for reasons other than death in 684 patients (21.2%) in the empagliflozin group and in 716 patients (22.2%) in the placebo group. A total of 436 patients (6.7%) started treatment with an open-label SGLT2 inhibitor during the trial, including 201 (6.2%) in the empagliflozin group and 235 (7.2%) in the placebo group. A total of 6328 patients (97.0%) were followed until the end of the trial for the occurrence of a primary end-point event, and 6467 patients (99.2%) had data on vital status available at the end of the trial (Fig. S1). The median duration of follow-up was 17.9 months, and the median duration of exposure to empagliflozin or placebo was similar in the two trial groups (Table S4). Adherence to the trial regimen is shown in Table S5.

END POINTS

A primary end-point event — a first hospitalization for heart failure or death from any cause — occurred in 267 of 3260 patients (8.2%) in the empagliflozin group and in 298 of 3262 patients (9.1%) in the placebo group, with incidence rates of 5.9 and 6.6 events, respectively, per 100 patient-years (hazard ratio, 0.90; 95% confidence interval [CI], 0.76 to 1.06; P=0.21). With respect to the individual components of the primary end point, a first hospitalization for heart failure occurred in 118 patients (3.6%) in the empagliflozin group and in 153 patients (4.7%) in the placebo group (hazard ratio, 0.77; 95% CI, 0.60 to 0.98), and death from any cause occurred in 169 (5.2%) and 178 (5.5%), respectively (hazard ratio, 0.96; 95% CI, 0.78 to 1.19) (Table 2 and Fig. 1). Results for the primary end point, a first hospitalization for heart failure, and death from any cause were consistent across subgroups (Fig. 2 and Figs. S2 and S3). Results for the primary end point were consistent across sensitivity analyses, which included additional categories of hospitalization for heart failure (Fig. S4). Causes of death are shown in Table S6.

Results for key secondary end points are shown in Table 2. The rate ratio (empagliflozin vs. placebo) was 0.87 (95% CI, 0.68 to 1.10) for the total number of hospitalizations for heart failure

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Empagliflozin Group (N=3260)	Placebo Group (N=3262)
Age — yr	63.6±11.0	63.7±10.8
Female sex — no. (%)	812 (24.9)	813 (24.9)
Race or ethnic group — no. (%)†		
White	2730 (83.7)	2721 (83.4)
Black	44 (1.3)	48 (1.5)
Asian	421 (12.9)	413 (12.7)
Other or missing	65 (2.0)	80 (2.5)
Geographic region — no. (%)		
North America	431 (13.2)	433 (13.3)
Latin America	290 (8.9)	288 (8.8)
Europe	2153 (66.0)	2154 (66.0)
Asia	386 (11.8)	387 (11.9)
Index myocardial infarction type — no. (%)‡		
STEMI	2444 (75.0)	2401 (73.6)
NSTEMI	814 (25.0)	861 (26.4)
Revascularization for the index myocardial infarction — no. (%)	2911 (89.3)	2911 (89.2)
Thrombolytic therapy for the index myocardial infarction — no. (%)	345 (10.6)	355 (10.9)
Lowest left ventricular ejection fraction — no. (%)§		
<25%	126 (3.9)	126 (3.9)
≥25 to <35%	721 (22.1)	699 (21.4)
≥35 to <45%	1724 (52.9)	1716 (52.6)
≥45 to <55%	438 (13.4)	468 (14.3)
≥55%	227 (7.0)	225 (6.9)
Signs or symptoms of congestion that resulted in treatment — no. (%)		
Overall	1852 (56.8)	1863 (57.1)
Lowest left ventricular ejection fraction of <45%¶	1172 (36.0)	1151 (35.3)
Lowest left ventricular ejection fraction of ≥45%¶	657 (20.2)	684 (21.0)
Cardiovascular disease history and risk factors — no. (%)		
Previous myocardial infarction	388 (11.9)	459 (14.1)
Atrial fibrillation	358 (11.0)	361 (11.1)
Diabetes mellitus type 2	1035 (31.7)	1046 (32.1)
Hypertension	2262 (69.4)	2276 (69.8)
Peripheral artery disease	172 (5.3)	180 (5.5)

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding. The trial groups are composed of patients hospitalized for acute myocardial infarction and at risk for heart failure who were randomly assigned within 14 days after admission to receive empagliflozin at a dose of 10 mg daily or placebo in addition to standard care. NSTEMI denotes non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

† Race and ethnic group were reported by the patients; "other" includes patients who reported mixed race. Data were missing for 56 patients in the empagliflozin group and 73 patients in the placebo group.

‡ Data on index myocardial infarction type were missing for 2 patients in the empagliflozin group.

§ Data on lowest left ventricular ejection fraction were missing for 24 patients in the empagliflozin group and 28 patients in the placebo group.

¶ Data on lowest left ventricular ejection fraction (<45% or ≥45%) among patients with signs or symptoms of congestion that resulted in treatment were missing for 23 patients in the empagliflozin group.

Table 2. Primary, Secondary, and Other End Points.

End Point	Empagliflozin Group (N=3260)		Placebo Group (N=3262)		Effect (95% CI)*
	Value	Incidence	Value	Incidence	
		no. of events per 100 patient-yr†		*no. of events per 100 patient-yr*†	
Primary composite end point					
A first hospitalization for heart failure or death from any cause — no. (%)	267 (8.2)	5.9	298 (9.1)	6.6	0.90 (0.76–1.06)‡
A first hospitalization for heart failure	118 (3.6)	2.6	153 (4.7)	3.4	0.77 (0.60–0.98)
Death from any cause	169 (5.2)	3.6	178 (5.5)	3.8	0.96 (0.78–1.19)
Key secondary end points§					
Total no. of hospitalizations for heart failure or death from any cause	317	7.1¶	385	8.3¶	0.87 (0.68–1.10)‖
Total no. of nonelective cardiovascular hospitalizations or death from any cause	666	15.5¶	730	16.9¶	0.92 (0.78–1.07)‖
Total no. of nonelective hospitalizations for any cause or death from any cause	998	23.0¶	1138	26.3¶	0.87 (0.77–1.0)‖
Total no. of hospitalizations for myocardial infarction or death from any cause	276	6.7¶	274	6.3¶	1.06 (0.83–1.35)‖
Other secondary and prespecified exploratory end points					
Death from cardiovascular causes — no. (%)	132 (4.0)	2.8	131 (4.0)	2.8	1.03 (0.81–1.31)
A first hospitalization for heart failure or death from cardiovascular causes — no. (%)	231 (7.1)	5.1	259 (7.9)	5.7	0.90 (0.75–1.07)
Total no. of hospitalizations for heart failure	148	2.4¶	207	3.6¶	0.67 (0.51–0.89)‖

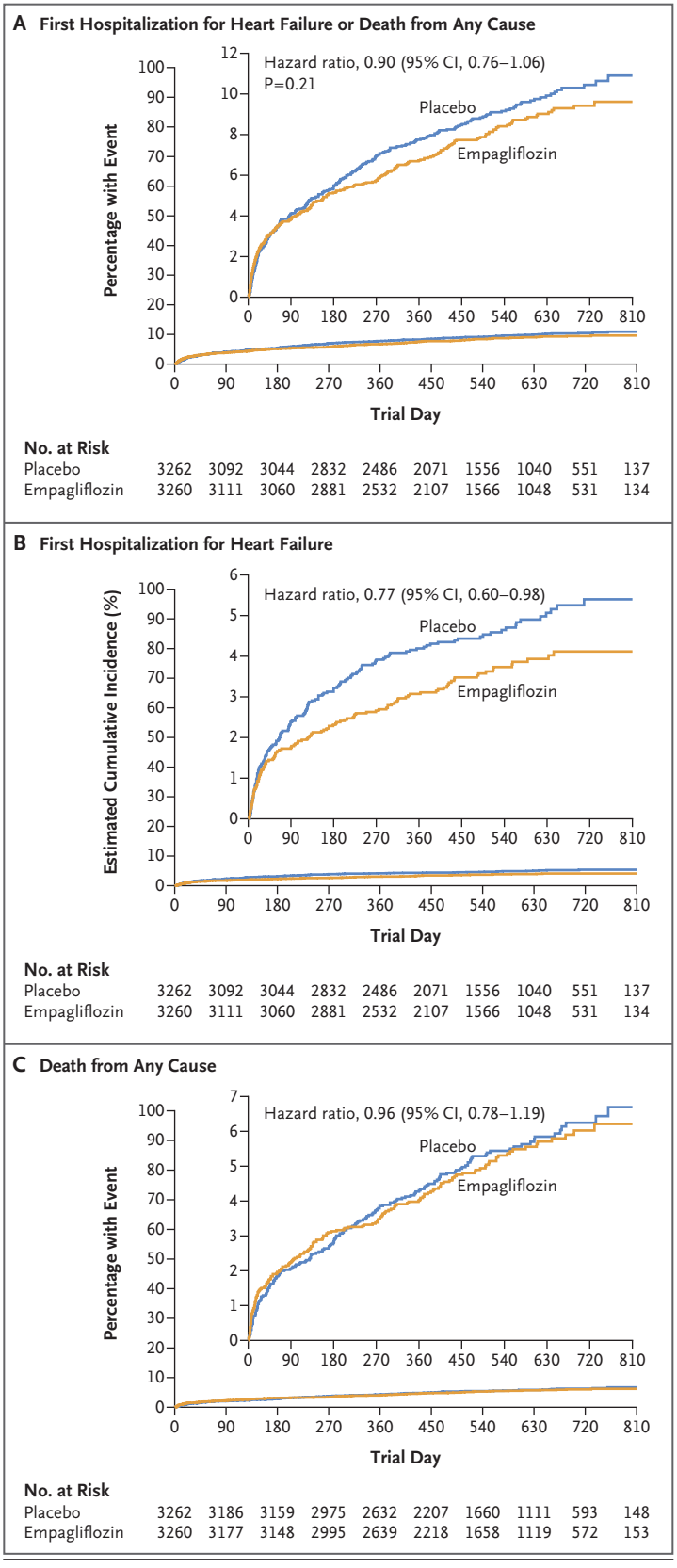
* The effects are presented as hazard ratios estimated with the use of a Cox proportional-hazards model unless indicated otherwise. The confidence intervals for secondary and exploratory outcomes were not adjusted for multiplicity and should be interpreted as exploratory.
† Values are the number of patients with an end-point event per 100 patient-years (as calculated by dividing the number of patients with at least one event by the time at risk and multiplying the quotient by 100), unless indicated otherwise.
‡ P=0.21 for the comparison of the empagliflozin group with the placebo group.
§ The key secondary end points were assessed as part of a hierarchical confirmatory testing procedure.
¶ Shown is the adjusted number of events per 100 patient-years, as calculated with the use of negative binomial regression analysis.
‖ The effect is presented as the rate ratio estimated with the use of negative binomial regression analysis.

or death from any cause, 0.92 (95% CI, 0.78 to 1.07) for the total number of nonelective cardiovascular hospitalizations or death from any cause, 0.87 (95% CI, 0.77 to 1.0) for the total number of nonelective hospitalizations for any cause or death from any cause, and 1.06 (95% CI, 0.83 to 1.35) for the total number of hospitalizations for myocardial infarction or death from any cause.

With respect to exploratory end points, death from cardiovascular causes occurred in 132 patients (4.0%) in the empagliflozin group and in 131 patients (4.0%) in the placebo group (hazard ratio, 1.03; 95% CI, 0.81 to 1.31). The time to death from cardiovascular causes and the time to a first hospitalization for heart failure or death from cardiovascular causes were similar in the two trial groups (Figs. S5 and S6). The total number of hospitalizations for heart failure was 148 in the empagliflozin group and 207 in the placebo group, with a rate of 2.4 and

Figure 1. Kaplan–Meier Estimates and Cumulative Incidence Function for the Composite Primary End Point and Its Components.

Shown are the time to a first hospitalization for heart failure or death from any cause (composite primary end point; Panel A), the time to a first hospitalization for heart failure (Panel B), and the time to death from any cause (Panel C). Patients hospitalized for acute myocardial infarction and at risk for heart failure were randomly assigned within 14 days after admission to receive empagliflozin at a dose of 10 mg daily or placebo in addition to standard care. The insets show the same data on an expanded y axis.



3.6 events, respectively, per 100 patient-years (rate ratio, 0.67; 95% CI, 0.51 to 0.89). Results of sensitivity analyses that accounted for the competing risks of death from any cause or death from noncardiovascular causes were consistent with those from Cox regression models (data not shown).

SAFETY

A similar percentage of patients in the two trial groups had a serious adverse event (23.7% in the empagliflozin group and 24.7% in the placebo group) or an adverse event that resulted in permanent discontinuation of the trial regimen (3.8% in each group) (Table 3). Contrast-induced acute kidney injury occurred in 8 patients (0.2%) in the empagliflozin group and in 9 patients (0.3%) in the placebo group.

DISCUSSION

In the EMPACT-MI trial, empagliflozin treatment did not lead to a significantly lower risk of a composite primary end-point event — a first hospitalization for heart failure or death from any cause — than placebo among patients presenting with an acute myocardial infarction and an increased risk of heart failure. The rates of prespecified key secondary end-point events did not differ substantially in the two trial groups.

Recently, the DAPA-MI trial, which excluded patients with diabetes, did not show a lower risk of death from cardiovascular causes or hospitalization for heart failure with dapagliflozin therapy than with placebo after acute myocardial infarction.[6] The prespecified composite primary end point in the DAPA-MI trial was changed to a seven-level win ratio. The actual numbers of heart-failure events or deaths were too few to allow for any meaningful conclusion.[12] The

Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with event/total no. (%)		
Overall	267/3260 (8.2)	298/3262 (9.1)	0.90 (0.76–1.06)
Age			
<65 yr	92/1639 (5.6)	102/1623 (6.3)	0.88 (0.66–1.16)
≥65 yr	175/1621 (10.8)	196/1639 (12.0)	0.92 (0.75–1.13)
Sex			
Male	176/2448 (7.2)	219/2449 (8.9)	0.81 (0.66–0.99)
Female	91/812 (11.2)	79/813 (9.7)	1.14 (0.85–1.55)
Geographic region			
North America	34/431 (7.9)	42/433 (9.7)	0.91 (0.58–1.43)
Latin America	38/290 (13.1)	52/288 (18.1)	0.74 (0.49–1.13)
Europe	179/2153 (8.3)	177/2154 (8.2)	0.99 (0.80–1.22)
Asia	16/386 (4.1)	27/387 (7.0)	0.58 (0.31–1.08)
Ethnic group			
Not Hispanic or Latinx	223/2866 (7.8)	237/2859 (8.3)	0.94 (0.78–1.13)
Hispanic or Latinx	40/338 (11.8)	55/331 (16.6)	0.73 (0.48–1.10)
Race			
White	236/2730 (8.6)	249/2721 (9.2)	0.94 (0.79–1.13)
Black	7/44 (15.9)	11/48 (22.9)	0.86 (0.33–2.23)
Asian	20/421 (4.8)	30/413 (7.3)	0.64 (0.36–1.13)
Other, including mixed race	0/9	2/7 (28.6)	NC
Median time from index myocardial infarction diagnosis to randomization			
≤5 days	140/1870 (7.5)	163/1915 (8.5)	0.86 (0.68–1.08)
>5 days	127/1388 (9.1)	135/1347 (10.0)	0.95 (0.74–1.21)
Index myocardial infarction type			
STEMI	194/2444 (7.9)	195/2401 (8.1)	0.96 (0.79–1.18)
NSTEMI	73/814 (9.0)	103/861 (12.0)	0.77 (0.57–1.04)
Type 2 diabetes at baseline			
No	159/2225 (7.1)	175/2216 (7.9)	0.85 (0.69–1.06)
Yes	108/1035 (10.4)	123/1046 (11.8)	0.97 (0.75–1.25)
History of myocardial infarction			
No	225/2872 (7.8)	239/2803 (8.5)	0.91 (0.76–1.10)
Yes	42/388 (10.8)	59/459 (12.9)	0.83 (0.56–1.24)
Baseline estimated GFR			
≥60 ml/min/1.73 m^2	156/2540 (6.1)	171/2524 (6.8)	0.89 (0.72–1.11)
<60 ml/min/1.73 m^2	111/720 (15.4)	127/738 (17.2)	0.92 (0.71–1.18)
Baseline systolic blood pressure			
<110 mm Hg	73/719 (10.2)	82/723 (11.3)	0.91 (0.66–1.24)
110 to <130 mm Hg	115/1605 (7.2)	136/1570 (8.7)	0.84 (0.65–1.08)
≥130 mm Hg	79/935 (8.4)	80/969 (8.3)	1.00 (0.73–1.37)
Baseline LVEF			
<35%	101/705 (14.3)	109/688 (15.8)	0.93 (0.71–1.22)
≥35%	163/2531 (6.4)	188/2546 (7.4)	0.87 (0.71–1.07)
Lowest LVEF during index hospitalization			
<45%	222/2571 (8.6)	243/2541 (9.6)	0.92 (0.76–1.10)
≥45%	42/665 (6.3)	54/693 (7.8)	0.78 (0.52–1.17)
Signs or symptoms of congestion that resulted in treatment during index hospitalization			
No	79/1408 (5.6)	89/1399 (6.4)	0.84 (0.62–1.14)
Yes	188/1852 (10.2)	209/1863 (11.2)	0.93 (0.77–1.14)
Lowest LVEF and signs or symptoms of congestion that resulted in treatment during index hospitalization			
Lowest LVEF of <45% and congestion	143/1172 (12.2)	154/1151 (13.4)	0.97 (0.77–1.22)
Lowest LVEF of <45% and no congestion	79/1399 (5.6)	89/1390 (6.4)	0.85 (0.63–1.15)
Lowest LVEF of ≥45%	42/665 (6.3)	54/693 (7.8)	0.78 (0.52–1.17)
Baseline use of loop or high-ceiling diuretics			
No	118/2126 (5.6)	149/2184 (6.8)	0.84 (0.66–1.06)
Yes	149/1134 (13.1)	149/1078 (13.8)	0.93 (0.74–1.17)
Baseline use of beta-blocker			
No	64/745 (8.6)	74/728 (10.2)	0.85 (0.61–1.18)
Yes	203/2515 (8.1)	224/2534 (8.8)	0.92 (0.76–1.11)
Baseline use of mineralocorticoid-receptor antagonist			
No	149/1992 (7.5)	165/1957 (8.4)	0.87 (0.69–1.08)
Yes	118/1268 (9.3)	133/1305 (10.2)	0.95 (0.74–1.22)
Baseline use of ACE inhibitor, ARB, or ARNI			
No	86/865 (9.9)	106/931 (11.4)	0.88 (0.66–1.17)
Yes	181/2395 (7.6)	192/2331 (8.2)	0.92 (0.75–1.13)

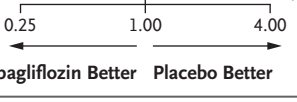


Figure 2 (facing page). Composite Primary End Point, According to Prespecified Subgroups.

Shown is the risk of a first hospitalization for heart failure or death from any cause in the trial groups. Ethnic group and race were reported by the patient. The glomerular filtration rate (GFR) was estimated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula. The size of the boxes indicates the size of the subgroup. The confidence intervals were not adjusted for multiplicity and should be interpreted as exploratory. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, ARNI angiotensin receptor–neprilysin inhibitor, LVEF left ventricular ejection fraction, NC not calculated, NSTEMI non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

data from the EMPACT-MI trial help fill the gap in knowledge about the effect of SGLT2 inhibitors in patients after acute myocardial infarction.

Certain factors may have contributed to the lack of an effect of empagliflozin on the primary composite end point in the EMPACT-MI trial. Deaths from any cause composed 52% of the primary end-point events and occurred in a similar percentage of patients in the two trial groups. By design, we enrolled patients soon after acute myocardial infarction, a time when several mechanisms that may not be amenable to modification with SGLT2 inhibition, which include cardiac causes (e.g., stent thrombosis, recurrent myocardial infarction, mechanical complications, and scar-related ventricular arrhythmias) and noncardiac causes within the first 30 days, contribute to mortality.[13]

As in our trial, the sample size in the PARADISE-MI trial (Prospective ARNI versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction) was increased because of low rates of primary end-point events — 6.7 and 7.4 events per 100 patient-years in the valsartan–sacubitril and ramipril groups, respectively.[14,15] These rates and the rates in our trial are lower than those observed in previous trials and observational studies.[16,17] The reasons for this may be related to multiple factors, including the widespread use of medical therapies, timely access to revascularization after myocardial infarction, and the coronavirus disease 2019 (Covid-19) pandemic, as well as regional wars in the case of the EMPACT-MI trial.[18]

The number and percentage of heart-failure events that contributed to the primary end point may have been affected by several factors. Our trial was conducted during the Covid-19 pandemic, when the number of hospitalizations for heart failure decreased substantially.[19] Patients with less severe symptoms may not have sought care or may have been treated in the outpatient setting. In addition, two of the regions where our trial was conducted were affected by war.[20] Heart-failure events other than hospitalization were not included in the primary end point. In some other trials, outpatient heart-failure events have contributed meaningfully to the total burden of heart-failure events. For example, of the 4744 patients randomly assigned to receive dapagliflozin or placebo in the DAPA-HF trial (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), 549 were hospitalized for heart failure, 33 had a heart-failure event that resulted in the receipt of intravenous diuretic therapy in the outpatient setting, and 604 had a worsening heart-failure event that resulted in the initiation or intensification of oral diuretic therapy in the outpatient setting.[21] Whether the inclusion of a broader measure of the burden of heart failure in the primary end point would have affected the results of our trial is unclear.

In our trial, some of the patients with a lower left ventricular ejection fraction or congestion at the time of randomization may have had a stunned myocardium that was reversible; further improvement after revascularization is unlikely in this lower-risk population.[3,22,23] This might be the case particularly in patients with STEMI, who composed nearly 75% of the patients in the EMPACT-MI trial, in which approximately 90% of the patients underwent early revascularization.

Previous trials involving patients with established heart failure or with type 2 diabetes and atherosclerotic cardiovascular disease have shown reductions of 29 to 35% in the relative risk of hospitalization for heart failure among patients treated with SGLT2 inhibitors as compared with patients who received placebo.[8-10,24,25] The findings of our exploratory analyses of a first hospitalization for heart failure and the total number of hospitalizations for heart failure in the empagliflozin group as compared with the placebo group appear to be consistent with the results of these previous trials, and further study of the

Table 3. Adverse Events in the Safety Population.*

Event	Empagliflozin Group (N=3234)		Placebo Group (N=3229)	
	Value	Incidence	Value	Incidence
		no. of events per 100 patient-yr		*no. of events per 100 patient-yr*
Any adverse event — no. (%)	891 (27.6)	25.37	883 (27.3)	25.38
Serious adverse event — no. (%)	765 (23.7)	21.43	798 (24.7)	22.69
Adverse event that led to permanent discontinuation of empagliflozin or placebo — no. (%)	122 (3.8)	2.93	122 (3.8)	2.96
Adverse events of special interest				
Ketoacidosis				
Overall — no. (%)	2 (0.1)	0.05	1 (<0.1)	0.02
Type 2 diabetes present at baseline — no./total no. (%)	2/1024 (0.2)	0.16	1/1032 (0.1)	0.08
Type 2 diabetes absent at baseline — no./total no. (%)	0/2210	0	0/2197	0
Adverse event that led to lower-limb amputation — no. (%)	9 (0.3)	0.19	5 (0.2)	0.11
Hepatic injury — no. (%)†	8 (0.2)	0.19	2 (0.1)	0.05
Contrast-induced kidney injury — no. (%)	8 (0.2)	0.19	9 (0.3)	0.22
Other relevant adverse events				
Acute renal failure — no. (%)‡	43 (1.3)	1.04	59 (1.8)	1.44
Acute kidney injury — no. (%)§	27 (0.8)	0.65	43 (1.3)	1.05
Volume depletion — no. (%)¶	35 (1.1)	0.84	40 (1.2)	0.98
Hypoglycemia‡				
Overall — no. (%)	4 (0.1)	0.10	5 (0.2)	0.12
Type 2 diabetes present at baseline — no./total no. (%)	4/1024 (0.4)	0.31	5/1032 (0.5)	0.39
Type 2 diabetes absent at baseline — no./total no. (%)	0/2210	0	0/2197	0

* Patients who received at least one dose of empagliflozin or placebo were included in the safety population. Shown are adverse events analyzed up to 7 days after the discontinuation of the trial regimen, except for lower-limb amputations, which were analyzed up to the end of the trial. Adverse events that were to be reported in the trial included serious adverse events, adverse events that led to discontinuation of the trial regimen for at least 7 days, and adverse events of special interest, defined as ketoacidosis, adverse events leading to lower-limb amputation, hepatic injury, and contrast-induced kidney injury.

† Hepatic injury was defined as an aspartate aminotransferase (AST) level or an alanine aminotransferase level (ALT) (or both) of at least 3 times the upper limit of the normal range, combined with a total bilirubin level of at least 2 times the upper limit of the normal range, as measured in the same blood sample or in blood samples obtained within 30 days of each other; or an ALT level or AST level (or both) of at least 10 times the upper limit of the normal range. Hepatic injury as defined by these criteria and reported by the investigator occurred in three patients in the empagliflozin group and in no patients in the placebo group.

‡ Events were identified with the use of a standardized *Medical Dictionary for Regulatory Activities* (MedDRA), version 26.1, query.

§ "Acute kidney injury" is a MedDRA, version 26.1, preferred term.

¶ Events were identified with the use of a Boehringer Ingelheim–customized MedDRA, version 26.1, query.

effects of SLGT2 inhibitors on heart-failure outcomes in high-risk patients after myocardial infarction may be warranted.

We did not observe evidence of increased rates of serious adverse events, adverse events that resulted in permanent discontinuation of the trial

regimen, or adverse events of special interest. The data from EMPACT-MI trial further build on the safety profile of SGLT2 inhibitors in patients across the spectrum of cardiovascular risks and provide evidence for the safety of these agents in hospitalized patients.[8,26,27]

Our trial has limitations. The end-point events were not centrally adjudicated but were assessed by site investigators according to prespecified definitions. Outpatient heart-failure events were not analyzed as clinical end points. Despite our attempts to improve the representation of women, older adults, and historically underrepresented racial and ethnic minorities in this trial, their representation remained suboptimal. Some patients in these groups are at increased risk for heart failure after myocardial infarction, and further work is needed to improve their representation (Table S3).[1,28] Only focused safety data were collected.

In the current trial, empagliflozin did not reduce the risk of the composite primary end-point event — a first hospitalization for heart failure or death from any cause — in patients with acute myocardial infarction who were at increased risk for heart failure.

Supported by Boehringer Ingelheim and Eli Lilly.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients for participating in the trial and the investigators and staff at the trial sites, the members of EMPACT-MI trial committees, and the trial personnel from the Duke Clinical Research Institute, Fortrea, and Boehringer Ingelheim.

APPENDIX

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