ORIGINAL ARTICLE

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

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ABSTRACT

BACKGROUND

Sodium–glucose cotransporter 2 inhibitors reduce the risk of hospitalization for heart failure in patients with heart failure and a reduced ejection fraction, but their effects in patients with heart failure and a preserved ejection fraction are uncertain.

METHODS

In this double-blind trial, we randomly assigned 5988 patients with class II–IV heart failure and an ejection fraction of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

RESULTS

Over a median of 26.2 months, a primary outcome event occurred in 415 of 2997 patients (13.8%) in the empagliflozin group and in 511 of 2991 patients (17.1%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001). This effect was mainly related to a lower risk of hospitalization for heart failure in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001). Uncomplicated genital and urinary tract infections and hypotension were reported more frequently with empagliflozin.

CONCLUSIONS

Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Preserved ClinicalTrials.gov number, NCT03057951).

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*The EMPEROR-Preserved Trial Investigators are listed in the Supplementary Appendix, available at NEJM.org.

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Patients with heart failure present with either a reduced or a preserved ejection fraction. Whereas heart failure with a reduced ejection fraction can be treated with drugs that act to attenuate the overactivation of endogenous neurohormonal systems,[1] therapeutic options for patients with heart failure and a preserved ejection fraction are limited. Although some benefits have been reported with mineralocorticoid-receptor antagonists and neprilysin inhibitors, the magnitude of the effects has been modest and the benefits have been apparent only in subgroups of patients.[2-4]

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been shown to reduce the development and progression of heart failure in patients with type 2 diabetes and in those with heart failure and a reduced ejection fraction.[5,6] However, the effect of these drugs in patients with heart failure and a preserved ejection fraction has not been well studied. Post hoc analyses of a large-scale trial of dapagliflozin in type 2 diabetes indicated that SGLT2 inhibition might not reduce the incidence of serious adverse heart failure outcomes in patients with heart failure and a preserved ejection fraction.[7] In contrast, benefits in such patients were reported in a trial with sotagliflozin, but the number of events was too small to allow for a reliable estimate of a treatment effect.[8]

The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) was carried out to evaluate the effects of SGLT2 inhibition with empagliflozin on major heart failure outcomes in patients with heart failure and a preserved ejection fraction.

Methods

Trial Design and Oversight

EMPEROR-Preserved was a randomized, double-blind, parallel-group, placebo-controlled, event-driven trial. The trial protocol and the statistical analysis plan are available with the full text of this article at NEJM.org. The ethics committee at each center approved the trial, and all patients provided written informed consent. The sponsors were Boehringer Ingelheim and Eli Lilly.

The executive committee, which included representatives of Boehringer Ingelheim, developed the protocol and statistical analysis plan, oversaw the recruitment of patients, and supervised the analysis of the data. An independent data monitoring committee reviewed the safety data and the results of an interim analysis according to prespecified stopping boundaries. A clinical events committee adjudicated outcomes in a blinded manner according to prespecified definitions. Boehringer Ingelheim was responsible for data collection and storage. An independent statistician replicated and verified the analyses. The academic members of the executive committee provided an independent interpretation of the results. The authors made the decision to submit the manuscript for publication, assume full responsibility for the accuracy and completeness of the data, and attest to the fidelity of the trial to the protocol (see the Supplementary Appendix, available at NEJM.org).

Patients

The trial design has been previously described in detail.[9] Participants were men or women, 18 years of age or older, who had New York Heart Association functional class II–IV chronic heart failure and a left ventricular ejection fraction of more than 40%. The protocol required patients to have an N-terminal pro–B-type natriuretic peptide (NT-proBNP) level of more than 300 pg per milliliter or, for patients with atrial fibrillation at baseline, an NT-proBNP level of more than 900 pg per milliliter.

Patients were excluded if they had a disorder that could change their clinical course, independent of heart failure, or if they had any condition that might jeopardize patient safety or limit their participation in the trial. The key inclusion and exclusion criteria are listed in the Supplementary Appendix.

Trial Visits and Follow-up

After a screening period of 4 to 28 days, eligible patients were randomly assigned in a 1:1 ratio and in double-blind fashion to receive either placebo or empagliflozin, 10 mg per day, in addition to usual therapy. Randomization was performed with a permuted block design and was stratified by geographic region, diabetes status, estimated glomerular filtration rate (eGFR) of less than 60 ml per minute per 1.73 m^2 of body-surface area or 60 ml or more per minute per 1.73 m^2, and left ventricular ejection fraction of less than 50% or 50% or more, all measured at screening. We anticipated that half the patients would not have diabetes at enrollment. After randomization,

all appropriate treatments for heart failure or other medical conditions could be initiated or altered at the discretion of the clinician.

Patients were evaluated periodically at trial visits for symptoms, health status (assessed with the Kansas City Cardiomyopathy Questionnaire), and adverse events. Vital signs, body weight, glycated hemoglobin level, NT-proBNP level, eGFR, and uric acid level were also assessed. All patients who had undergone randomization were to be followed for the occurrence of prespecified outcomes for the entire duration of the trial, whether or not they were taking the study medications or adhering to protocol-specified procedures.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome and the first two secondary outcomes were included in a hierarchical testing procedure, as described in Statistical Analysis, below. The primary outcome was a composite of adjudicated cardiovascular death or hospitalization for heart failure, analyzed as the time to the first event. The first secondary outcome was the occurrence of all adjudicated hospitalizations for heart failure, including first and recurrent events. The second secondary outcome was the rate of decline in the eGFR during double-blind treatment. Additional prespecified outcomes outside the testing hierarchy are described and adjudicated outcome event definitions provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The primary outcome, the combined risk of cardiovascular death or hospitalization for heart failure, was assessed in a time-to-event analysis. According to the intention-to-treat principle, the primary analysis for all patients who underwent randomization includes information through the end of the planned treatment period. Differences between the placebo and empagliflozin groups for the primary outcome were assessed for statistical significance at an alpha level of 0.0497, adjusted for one interim analysis, with the use of a Cox proportional-hazards model, with adjustment for prespecified baseline covariates of age, sex, geographic region, diabetes status, left ventricular ejection fraction, and eGFR. The effect of empagliflozin on the individual components of the primary outcome was also analyzed. Treatment effects were expressed as hazard ratios with 95% confidence intervals.

If the between-group difference in results for the primary outcome was significant, the two key secondary outcomes were to be analyzed in a prespecified stepwise, hierarchical manner, to preserve the overall type I error rate. The first secondary outcome — total (first and recurrent) hospitalizations for heart failure — was evaluated (alpha level, 0.0497) with the use of a joint frailty model that included cardiovascular death as the source of informative censoring. The second secondary outcome — the slope of the change in eGFR — was analyzed on the basis of on-treatment data with a random-coefficient model that included age, eGFR, and left ventricular ejection fraction at baseline as linear covariates and sex, geographic region, baseline diabetes status, and baseline-by-time and treatment-by-time interactions as fixed effects; the model allows for randomly varying slope and intercept between patients. The analysis of eGFR was assigned an alpha level of 0.001. The remaining alpha after hierarchical testing was applied to an analysis of pooled patient-level data from the current trial and a concurrent trial in patients with a reduced ejection fraction, which specified serious adverse renal events as the primary outcome variable.[10] Safety analyses were based on data from patients who had received at least one dose of the trial medication. For all hazard ratios or treatment differences not included in the testing hierarchy, no adjustment has been made for multiple comparisons, so the intervals should not be used to infer definitive treatment effects.

No imputation was used for missing data. For time-to-event analyses, data were censored at the end of treatment for patients who completed the planned treatment period or at the last available follow-up visit for patients who discontinued treatment early. For the analysis of eGFR, all available on-treatment data for the change from baseline were used. We explored the proportional hazards assumption for the primary outcome by plotting the log of the negative log of the estimated survival function against the log of time by treatment group and checking for parallelism. In addition, an interaction of treatment with log of time was included in the Cox regression model for an exploratory analysis.

For this event-driven study, we determined that a target number of 841 adjudicated primary outcome events would provide 90% power to detect a hazard ratio of 0.8 for the primary outcome at a

two-sided alpha level of 0.05. Assuming an annual 10% event rate in the placebo group, a recruitment period of 18 months, and a follow-up period of 20 months, we established a planned enrollment of 4126 patients, with the option of enrolling up to 6000 patients if the accumulation of primary outcome events was slower than expected. Accordingly, on the basis of monitoring of the primary outcome event rate during the trial, the number of patients who underwent randomization was increased to at least 5750, without any change in the target number of events.[9] The increase in sample size was made without any knowledge of unblinded trial data. Subsequently, the data monitoring committee carried out one prespecified interim efficacy analysis after the occurrence of approximately 500 primary outcome events, with the possibility of recommending early termination of the trial if the one-sided alpha level of approximately 0.001 for a benefit of empagliflozin was achieved for both the primary outcome and cardiovascular death alone. The committee did not recommend early termination.

RESULTS

PATIENT CHARACTERISTICS AND RANDOMIZATION

Between March 27, 2017, and April 13, 2020, a total of 11,583 patients were screened for eligibility, and 5988 patients were randomly assigned to receive either empagliflozin (2997 patients) or placebo (2991 patients) at 622 centers in 23 countries (Fig. S1 in the Supplementary Appendix). The reasons for screening failure are described in Table S1. The characteristics of the patients at baseline were similar in the two treatment groups (Table 1 and Table S2). Nearly half the patients had diabetes and half had an eGFR of less than 60 ml per minute per 1.73 m^2. Two thirds of the patients had a left ventricular ejection fraction of 50% or more; the median left ventricular ejection fraction was 54%.

The final date of follow-up for data collection was April 26, 2021. The trial medication was stopped for reasons other than death in 696 patients (23.2%) receiving empagliflozin and in 699 patients (23.4%) receiving placebo; 10.6% of the patients discontinued treatment owing to an adverse event. A total of 17 patients (0.6%) in the empagliflozin group and 19 patients (0.6%) in the placebo group had unknown vital status at the end of the trial (Fig. S1). The median duration of follow-up for the primary outcome was 26.2 months (interquartile range, 18.1 to 33.1).

PRIMARY OUTCOME

A primary composite outcome event (death from cardiovascular causes or hospitalization for heart failure) occurred in 415 patients (13.8%) in the empagliflozin group and in 511 patients (17.1%) in the placebo group (6.9 vs. 8.7 events per 100 patient-years; hazard ratio, 0.79; 95% CI, 0.69 to 0.90; P<0.001) (Fig. 1 and Table 2). During a median trial period of 26 months, the number of patients treated with empagliflozin needed to prevent one primary outcome event was 31 (95% CI, 20 to 69). The results for the assessment of the proportional hazards assumption are shown in the Supplementary Appendix.

Hospitalization for heart failure occurred in 259 patients (8.6%) in the empagliflozin group and in 352 patients (11.8%) in the placebo group (hazard ratio, 0.71; 95% CI, 0.60 to 0.83) (Fig. S2). Death from cardiovascular causes occurred in 219 patients (7.3%) in the empagliflozin group and in 244 patients (8.2%) in the placebo group (hazard ratio, 0.91; 95% CI, 0.76 to 1.09) (Fig. S3). The causes of death among patients in the two treatment groups are summarized in Table S3.

The effect of empagliflozin on the incidence of primary outcome events was generally consistent across prespecified subgroups, including patients with or without diabetes at baseline (Fig. 2 and Fig. S3).

SECONDARY OUTCOMES AND OTHER PRESPECIFIED ANALYSES

The total number of hospitalizations for heart failure was lower with empagliflozin than with placebo (hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001; Fig. 3 and Table S4). The rate of decline in the eGFR was slower in the empagliflozin group than in the placebo group (–1.25 vs. –2.62 ml per minute per 1.73 m^2 per year; P<0.001) (Fig. S4). A total of 422 patients (14.1%) in the empagliflozin group and 427 patients (14.3%) in the placebo group died from any cause (hazard ratio, 1.00; 95% CI, 0.87 to 1.15) (Fig. S5). Outcomes outside the hierarchical testing procedure are shown in Table 2. Table S5 shows changes in glycated hemoglobin level, hematocrit level, NT-proBNP, systolic blood pressure, body weight, and uric acid level from baseline to 52 weeks.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Empagliflozin (N=2997)	Placebo (N=2991)
Age — yr	71.8±9.3	71.9±9.6
Female sex — no. (%)	1338 (44.6)	1338 (44.7)
Race — no. (%)†		
White	2286 (76.3)	2256 (75.4)
Black	133 (4.4)	125 (4.2)
Asian	413 (13.8)	411 (13.7)
Other or missing	165 (5.5)	199 (6.7)
Geographic region — no. (%)		
North America	360 (12.0)	359 (12.0)
Latin America	758 (25.3)	757 (25.3)
Europe	1346 (44.9)	1343 (44.9)
Asia	343 (11.4)	343 (11.5)
Other	190 (6.3)	189 (6.3)
NYHA functional classification — no. (%)		
Class I	3 (0.1)	1 (<0.1)
Class II	2432 (81.1)	2451 (81.9)
Class III	552 (18.4)	531 (17.8)
Class IV	10 (0.3)	8 (0.3)
Body-mass index‡	29.77±5.8	29.90±5.9
Heart rate — beats per minute	70.4±12.0	70.3±11.80
Systolic blood pressure — mm Hg	131.8±15.6	131.9±15.7
Left ventricular ejection fraction		
Mean left ventricular ejection fraction — %	54.3±8.8	54.3±8.8
Left ventricular ejection fraction >40% to <50% — no. (%)§	995 (33.2)	988 (33.0)
Left ventricular ejection fraction ≥50% to <60% — no. (%)	1028 (34.3)	1030 (34.4)
Left ventricular ejection fraction ≥60% — no. (%)	974 (32.5)	973 (32.5)
Median NT-proBNP (interquartile range) — pg/ml	994 (501–1740)	946 (498–1725)
Heart failure category — no. (%)		
Ischemic	1079 (36.0)	1038 (34.7)
Nonischemic	1917 (64.0)	1953 (65.3)
Cardiovascular history — no. (%)		
Hospitalization for heart failure during previous 12 mo	699 (23.3)	670 (22.4)
Atrial fibrillation	1543 (51.5)	1514 (50.6)
Diabetes mellitus	1466 (48.9)	1472 (49.2)
Hypertension	2721 (90.8)	2703 (90.4)
Mean eGFR — ml/min/1.73 m^2	60.6±19.8	60.6±19.9
eGFR <60 ml/min/1.73 m^2 — no./total no. (%)	1504/2997 (50.2)	1484/2989 (49.6)

* Plus–minus values are means ±SD. The abbreviation eGFR denotes estimated glomerular filtration rate, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.
† Race was reported by the patient; patients who identified with more than one race or with no race were classified as other.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Two patients with an ejection fraction of exactly 40% underwent randomization and were included in the analysis.

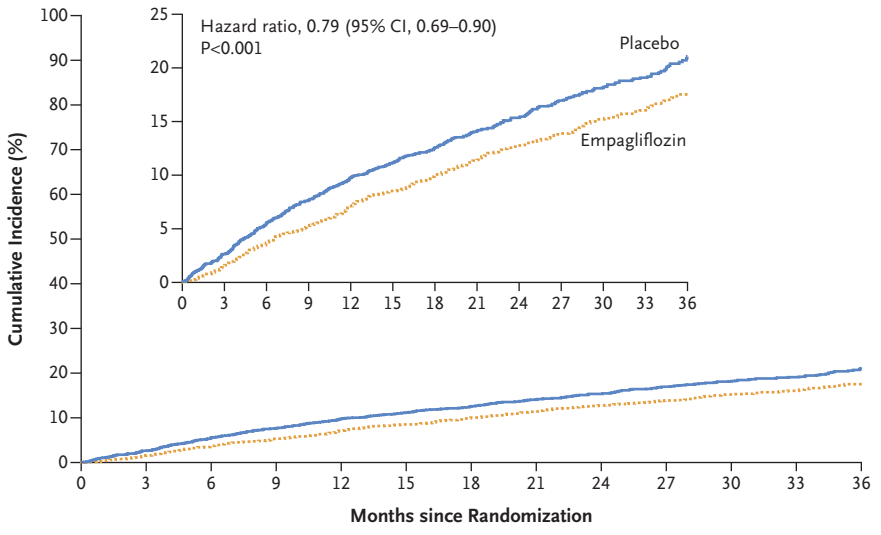

Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.
The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

SAFETY

Three patients (one in the empagliflozin group and two in the placebo group) did not receive the study medication and were excluded from the safety analyses. Serious adverse events occurred in 1436 patients (47.9%) in the empagliflozin group and in 1543 patients (51.6%) in the placebo group. Adverse events leading to discontinuation of treatment occurred in 571 patients (19.1%) in the empagliflozin group and in 551 patients (18.4%) in the placebo group. Specific adverse events are listed in Table S6. Uncomplicated genital and urinary tract infections and hypotension were more common in patients treated with empagliflozin.

DISCUSSION

In patients with heart failure and a preserved ejection fraction, SGLT2 inhibition with empagliflozin led to a 21% lower relative risk in the composite of cardiovascular death or hospitalization for heart failure, which was mainly related to a 29% lower risk of hospitalization for heart failure with empagliflozin. The effects on the incidence of primary outcome events were generally seen consistently across all prespecified subgroups, including patients with or without diabetes.

Empagliflozin also led to a lower total number of hospitalizations for heart failure and a longer time to first hospitalization for heart failure. The pattern of benefits shown in Table 2 is similar to that reported with empagliflozin in a similarly designed parallel trial of patients with heart failure and a reduced ejection fraction (EMPEROR-Reduced),[11] which suggests that the effects of SGLT2 inhibition on heart failure events do not vary meaningfully with the heart failure phenotype.

The effects of empagliflozin in patients with heart failure and a preserved ejection fraction are consistent with findings in previous reports that SGLT2 inhibitors reduce the risk of hospitalization for heart failure in patients with type 2 diabetes.[5] However, in these earlier trials, most patients did not have heart failure at the time of enrollment. Post hoc characterization of the heart failure phenotype, either at the time of randomization or at the onset of a post-randomization heart failure event, suggested that patients with heart failure and a preserved ejection fraction

Table 2. Primary and Secondary Cardiovascular Outcomes.*

Variable	Empagliflozin (N=2997)		Placebo (N=2991)		Hazard Ratio or Difference (95% CI)	P Value
		events per 100 patient-yr		*events per 100 patient-yr*		
Primary composite outcome — no. (%)	415 (13.8)	6.9	511 (17.1)	8.7	0.79 (0.69–0.90)	<0.001
Hospitalization for heart failure	259 (8.6)	4.3	352 (11.8)	6.0	0.71 (0.60–0.83)	
Cardiovascular death	219 (7.3)	3.4	244 (8.2)	3.8	0.91 (0.76–1.09)	
Secondary outcomes specified in hierarchical testing procedure						
Total no. of hospitalizations for heart failure	407	—	541	—	0.73 (0.61–0.88)	<0.001
eGFR (CKD-EPI) mean slope change per year — ml/min/1.73 m^2†	−1.25±0.11	—	−2.62±0.11	—	1.36 (1.06–1.66)	<0.001
Other prespecified analyses						
Change in KCCQ clinical summary score at 52 wk‡	4.51±0.31	—	3.18±0.31	—	1.32 (0.45–2.19)	
Total no. of hospitalizations for any cause	2566	—	2769	—	0.93 (0.85–1.01)	
Composite renal outcome — no. (%)	108 (3.6)	2.1	112 (3.7)	2.2	0.95 (0.73–1.24)	
Onset of new diabetes in patients with prediabetes — no. (%)	120 (12.0)	6.1	137 (14.0)	7.4	0.84 (0.65–1.07)	
Death from any cause — no. (%)	422 (14.1)	6.6	427 (14.3)	6.7	1.00 (0.87–1.15)	

* All treatment effects are shown as hazard ratios, except for the slope of the change in the eGFR and the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score. For all hazard ratios or treatment differences without P values, no adjustment has been made for multiple comparisons, so the intervals should not be used to infer definitive treatment effects.

† The eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) slope is analyzed on the basis of on-treatment data, using a random intercept–random slope model including age, baseline eGFR, and baseline left ventricular ejection fraction as linear covariates and sex, geographic region, baseline diabetes status, and baseline-by-time and treatment-by-time interactions as fixed effects; the model allows for randomly varying slope and intercept between patients.

‡ Change from baseline in KCCQ clinical summary score (scores range from 0 to 100, with higher scores indicating fewer or less severe symptoms or physical limitations) was analyzed with a mixed model for repeated measures, including age, baseline eGFR (CKD-EPI formula based on creatinine), and baseline left ventricular ejection fraction as linear covariates and baseline score-by-visit, visit-by-treatment, sex, geographic region, last projected visit based on dates of randomization and trial closure, and baseline diabetes status as fixed effects. The analysis is based on on-treatment data. The number of patients with available measurements for the KCCQ at week 52 in the empagliflozin and placebo groups are 2333 and 2335, respectively.

Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)
≥60%	132/974	145/973	0.87 (0.69–1.10)
Age			
<70 yr	134/1066	152/1084	0.88 (0.70–1.11)
≥70 yr	281/1931	359/1907	0.75 (0.64–0.87)
Sex			
Male	253/1659	297/1653	0.81 (0.69–0.96)
Female	162/1338	214/1338	0.75 (0.61–0.92)
Race			
White	310/2286	370/2256	0.81 (0.69–0.94)
Black	24/133	28/125	0.73 (0.42–1.25)
Asian	54/413	77/411	0.65 (0.46–0.92)
Other	27/164	36/198	0.95 (0.58–1.57)
BMI at baseline			
<30	223/1654	292/1642	0.74 (0.62–0.88)
≥30	192/1343	219/1349	0.85 (0.70–1.03)
Estimated GFR (CKD-EPI) at baseline			
≥60 ml/min/1.73 m^2	152/1493	189/1505	0.81 (0.65–1.00)
<60 ml/min/1.73 m^2	263/1504	321/1484	0.78 (0.66–0.91)
Systolic blood pressure at baseline			
<Median	200/1496	249/1474	0.76 (0.63–0.91)
≥Median	215/1501	262/1517	0.82 (0.68–0.98)
History of atrial fibrillation or atrial flutter			
No	170/1417	219/1427	0.78 (0.64–0.95)
Yes	244/1576	292/1559	0.78 (0.66–0.93)
Hospitalization for heart failure ≤12 mo			
No	258/2298	319/2321	0.81 (0.68–0.95)
Yes	157/699	192/670	0.73 (0.59–0.90)
NYHA class at baseline			
II	275/2435	361/2452	0.75 (0.64–0.87)
III or IV	140/562	150/539	0.86 (0.68–1.09)
NT-proBNP at baseline (calculated by atrial fibrillation/flutter status)			
<Median	126/1477	168/1508	0.76 (0.61–0.96)
≥Median	288/1516	341/1476	0.78 (0.67–0.91)
Uric acid, in thirds, at baseline			
<T1	96/963	147/975	0.65 (0.50–0.84)
≥T1 to <T2	130/1032	132/966	0.92 (0.72–1.17)
≥T2	184/970	226/1018	0.81 (0.67–0.98)
Use of ACE-inhibitor, ARB, or ARNI at baseline			
No	90/569	121/587	0.75 (0.57–0.99)
Yes	325/2428	390/2404	0.80 (0.69–0.93)
Use of MRA at baseline			
No	233/1878	306/1866	0.73 (0.62–0.87)
Yes	182/1119	205/1125	0.87 (0.71–1.06)

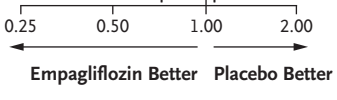

Figure 2 (facing page). Primary Composite Outcome in Prespecified Subgroups.

Results for the primary outcome of the trial — a composite of cardiovascular death or hospitalization for heart failure — are shown according to subgroups that were prespecified in the protocol. Race was reported by the patient. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. New York Heart Association (NYHA) class II includes 4 patients with NYHA class I. Baseline uric acid was calculated separately for male and female patients. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, ARNI angiotensin receptor–neprilysin inhibitor, CKD-EPI Chronic Kidney Disease Epidemiology Collaboration, GFR glomerular filtration rate, LVEF left ventricular ejection fraction, MRA mineralocorticoid receptor antagonist, and NT-proBNP N-terminal pro–B-type natriuretic peptide.

might have benefited from treatment,[7,8,12] but these analyses had a small number of events and substantial missing data. The current analysis — based on a large number of adjudicated events — shows a meaningful benefit of empagliflozin on major heart failure outcomes in patients with heart failure and a preserved ejection fraction. In addition, we show that the favorable effects in this heart failure phenotype were also seen in patients without diabetes.

Previous large-scale trials of drug interventions in patients with heart failure and a preserved ejection fraction have failed to demonstrate unequivocal benefits of treatment on the primary heart failure outcome. Trials of candesartan, spironolactone, and sacubitril–valsartan reported effects on cardiovascular death and hospitalizations for heart failure that were modest in size (i.e., a 10 to 15% reduction in risk) and of borderline statistical significance.[2,4,13] Subgroup analyses suggested that any benefit may have been preferentially seen in patients with an ejection fraction of 40 to 49%,[3,4,14] but patients with such mid-range ejection fractions have clinical features that are often more akin to those of patients with heart failure and a reduced ejection fraction than to patients with a preserved ejection fraction.[15,16] On the basis of these prior observations, we prespecified ejection fraction values of 50% and 60% as relevant thresholds for our subgroup analyses. In contrast with findings in earlier trials of candesartan, spironolactone, and sacubitril–valsartan, the

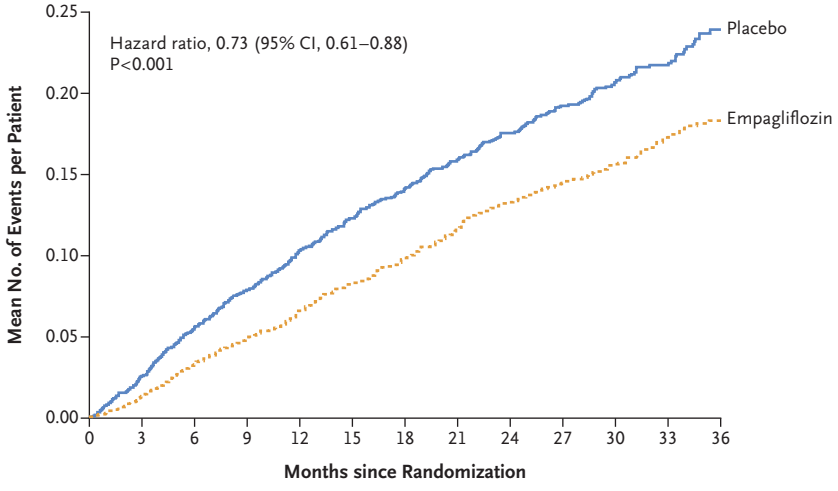

Figure 3. Hospitalizations for Heart Failure.

The mean number of events per patient for the first secondary outcome (total [first and recurrent] hospitalizations for heart failure) in the two groups is shown.

results favored empagliflozin, with hazard ratios less than 1 for the primary outcome in each of the ejection fraction subgroups.[3,4,14]

Treatment with empagliflozin led to a lower incidence of hospitalization for heart failure, but it did not appear to affect the number of deaths from cardiovascular or other causes in the current trial. It is noteworthy that the percentage of patients who discontinued treatment for reasons other than death was 23% overall and was similar in the two treatment groups; this high rate of discontinuation may have driven the effect size toward the null hypothesis. Nevertheless, a similar dissociation between treatment effects on hospitalizations for heart failure and cardiovascular mortality was seen in a previous trial with sacubitril–valsartan, which was conducted in a similar patient population that was followed for a similar period of time.[4]

Our findings show that empagliflozin reduced the risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction. This benefit was consistent across prespecified ejection fraction subgroups and was seen in patients with or without diabetes.

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APPENDIX

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REFERENCES

1. Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet 2020;396:121-8.
2. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383-92.
3. Solomon SD, Claggett B, Lewis EF, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J 2016;37:455-62.
4. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019;381:1609-20.
5. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31-9.
6. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet 2020;396:819-29.
7. Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation 2019;139:2528-36.
8. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2021;384:117-28.
9. Anker SD, Butler J, Filippatos GS, et al. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial. Eur J Heart Fail 2019;21:1279-87.
10. Packer M, Butler J, Filippatos G, et al. Design of a prospective patient-level pooled analysis of two parallel trials of empagliflozin in patients with established heart failure. Eur J Heart Fail 2020;22:2393-8.
11. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413-24.
12. Figtree GA, Rådholm K, Barrett TD, et al. Effects of canagliflozin on heart failure outcomes associated with preserved and reduced ejection fraction in type 2 diabetes mellitus. Circulation 2019;139:2591-3.
13. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-81.
14. Lund LH, Claggett B, Liu J, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail 2018;20:1230-9.
15. Butler J, Anker SD, Packer M. Redefining heart failure with a reduced ejection fraction. JAMA 2019;322:1761-2.
16. Pascual-Figal DA, Ferrero-Gregori A, Gomez-Otero I, et al. Mid-range left ventricular ejection fraction: Clinical profile and cause of death in ambulatory patients with chronic heart failure. Int J Cardiol 2017;240:265-70.