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Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

ABSTRACT

BACKGROUND

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure in patients regardless of the presence or absence of diabetes. More evidence is needed regarding the effects of these drugs in patients across the broad spectrum of heart failure, including those with a markedly reduced ejection fraction.

METHODS

In this double-blind trial, we randomly assigned 3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure.

RESULTS

During a median of 16 months, a primary outcome event occurred in 361 of 1863 patients (19.4%) in the empagliflozin group and in 462 of 1867 patients (24.7%) in the placebo group (hazard ratio for cardiovascular death or hospitalization for heart failure, 0.75; 95% confidence interval [CI], 0.65 to 0.86; P<0.001). The effect of empagliflozin on the primary outcome was consistent in patients regardless of the presence or absence of diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.70; 95% CI, 0.58 to 0.85; P<0.001). The annual rate of decline in the estimated glomerular filtration rate was slower in the empagliflozin group than in the placebo group (–0.55 vs. –2.28 ml per minute per 1.73 m^2 of body-surface area per year, P<0.001), and empagliflozin-treated patients had a lower risk of serious renal outcomes. Uncomplicated genital tract infection was reported more frequently with empagliflozin.

CONCLUSIONS

Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Reduced ClinicalTrials.gov number, NCT03057977.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Packer at Baylor Heart and Vascular Institute, 621 N. Hall St., Dallas, TX 75226, or at milton.packer@baylorhealth.edu.

*A complete list of the EMPEROR-Reduced investigators is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

In patients with type 2 diabetes, sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure and the risk of serious adverse renal events, benefits that are not seen with other antihyperglycemic drugs. In large-scale, randomized, placebo-controlled trials, the risk of hospitalization for heart failure was 30 to 35% lower among patients who received SGLT2 inhibitors than among those who received placebo[1]; this benefit was most striking in patients who had a left ventricular ejection fraction of 30% or less before treatment.[2] In addition, the risk of progression of renal disease (including the occurrence of renal death or the need for dialysis or renal transplantation) was 35 to 50% lower among patients who received SGLT2 inhibitors than among those who received placebo.[1] These cardiorenal benefits cannot be explained by an action of SGLT2 inhibitors to lower blood glucose, since similar effects have not been seen with other antidiabetic drugs that have greater antihyperglycemic actions.[3]

These observations are consistent with the hypothesis that SGLT2 inhibitors may slow the progression of cardiac and renal disease, regardless of cause and independent of the presence or absence of diabetes.[3] The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial showed a reduction in the risk of cardiovascular death or hospitalization for heart failure with dapagliflozin in patients regardless of the presence or absence of diabetes[4]; this trial primarily enrolled patients with mild-to-moderate degrees of left ventricular systolic dysfunction and increases in natriuretic peptide levels. In the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced), we evaluated empagliflozin in a population of patients with chronic heart failure and a reduced ejection fraction (with or without diabetes) that was enriched for patients with a greater severity of left ventricular systolic dysfunction.

Methods

Trial Design and Oversight

Details regarding the design of this randomized, double-blind, parallel-group, placebo-controlled, event-driven trial have been reported previously.[5] The trial was performed at 520 centers in 20 countries. The protocol and the statistical analysis plan are available (as a single PDF file) with the full text of this article at NEJM.org. The ethics committee at each trial center approved the trial, and all the patients provided written informed consent. The sponsors were Boehringer Ingelheim and Eli Lilly.

The executive committee developed and amended the protocol and had scientific oversight on the development of the statistical analysis plan, the case report forms, the recruitment of patients, the quality and thoroughness of follow-up, and the analysis of data. The academic members of the executive committee provided an independent interpretation of the results. An independent data and safety monitoring committee reviewed the safety data and the results of an interim analysis according to prespecified stopping boundaries. The statistical analyses were performed by employees of the sponsor with the oversight of the academic trial leadership, and an independent statistician replicated and verified the analyses. The first author, who had unrestricted access to the data, prepared the first draft of the manuscript, which was then reviewed and edited by all the authors. The authors made the decision to submit the manuscript for publication, assume full responsibility for the accuracy and completeness of the analyses, and attest to the fidelity of the trial to the protocol and the statistical analysis plan.

Patients

Adults (≥18 years of age) who had chronic heart failure (functional class II, III, or IV) with a left ventricular ejection fraction of 40% or less were eligible to participate in the trial. All the patients were receiving appropriate treatments for heart failure, including diuretics, inhibitors of the renin–angiotensin system and neprilysin, beta-blockers, mineralocorticoid receptor antagonists, and, when indicated, cardiac devices.

The intent of the trial was to enroll patients with heart failure who were at increased risk for a serious heart failure event. We limited the number of patients who had an ejection fraction of more than 30% by requiring a history of hospitalization for heart failure within the previous 12 months or a particularly high level of N-terminal prohormone of brain natriuretic peptide

(NT-proBNP), including a level of at least 1000 pg per milliliter in those with an ejection fraction of 31 to 35% or a level of at least 2500 pg per milliliter in those with an ejection fraction of 36 to 40%, as compared with a level of at least 600 pg per milliliter in those with an ejection fraction of 30% or less.[6] These NT-proBNP thresholds were doubled in patients with atrial fibrillation.[5] The key inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

TRIAL VISITS AND FOLLOW-UP

After a screening period of 4 to 28 days, patients who fulfilled the eligibility criteria were randomly assigned in a 1:1 ratio to receive either empagliflozin (at a dose of 10 mg daily) or placebo in addition to their usual therapy for heart failure. The dose of empagliflozin was selected on the basis of the reduction in the risk of cardiovascular death or hospitalization for heart failure that had been previously reported with this dose in patients with type 2 diabetes.[7] Randomization was performed with an interactive-response system that used a permuted-block design and was stratified according to geographical region (North America, Latin America, Europe, Asia, or other), diabetes status at screening, and the estimated glomerular filtration rate (GFR) at screening (<60 or ≥60 ml per minute per 1.73 m^2 of body-surface area), according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. After randomization, all appropriate treatments for heart failure or other medical conditions could be initiated or altered at the clinical discretion of the health care provider, according to each patient's needs.

Every 2 to 3 months, we evaluated patients at trial visits to assess outcomes and adverse events. We periodically evaluated vital signs, body weight, glycated hemoglobin level, NT-proBNP level, and renal function. In addition, we assessed the patients' quality of life using the Kansas City Cardiomyopathy Questionnaire. We reevaluated the estimated GFR 23 to 45 days after the discontinuation of empagliflozin or placebo in order to allow for an evaluation of the effect of treatment independent of the presence of the SGLT2 inhibitor. All the patients were followed for the occurrence of prespecified outcomes for the entire duration of the trial, regardless of whether they were adherent to the trial regimens or procedures.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome and the first two secondary outcomes were included in a hierarchical testing procedure, as described in the Statistical Analysis section. 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 the decline in the estimated GFR during double-blind treatment.

Additional prespecified efficacy outcomes that were not part of the testing hierarchy (including a composite renal outcome, total hospitalizations for any reason, and quality of life) are described in the Supplementary Appendix. Safety analyses included all the patients who had received at least one dose of empagliflozin or placebo. A clinical-events committee adjudicated fatal and nonfatal events in a blinded manner according to prespecified definitions, which are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We determined that a target number of 841 adjudicated primary outcome events would provide a power of 90% to detect a 20% lower relative risk of the primary outcome in the empagliflozin group than in the placebo group at a two-sided alpha level of 0.05. Assuming an annual incidence of the primary outcome of at least 15% per year in the placebo group and a recruitment period of 18 months, we established a planned enrollment of 2850 patients, with the option of increasing the enrollment to 4000 patients if the accumulation of primary outcome events was slower than expected. Accordingly, the number of patients undergoing randomization was increased to 3600 with no change to the target number of events. This increase in sample size was made without any knowledge of unblinded trial data and before the planned formal interim analysis of efficacy by the data and safety monitoring committee. This committee carried out one prespecified interim efficacy analysis after the occurrence of approximately 500 primary outcome events, with

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Empagliflozin (N=1863)	Placebo (N=1867)
Age — yr	67.2±10.8	66.5±11.2
Female sex — no. (%)	437 (23.5)	456 (24.4)
Race — no. (%)†		
White	1325 (71.1)	1304 (69.8)
Black	123 (6.6)	134 (7.2)
Asian	337 (18.1)	335 (17.9)
Other or missing	78 (4.2)	94 (5.0)
Region — no. (%)		
North America	212 (11.4)	213 (11.4)
Latin America	641 (34.4)	645 (34.5)
Europe	676 (36.3)	677 (36.3)
Asia	248 (13.3)	245 (13.1)
Other	86 (4.6)	87 (4.7)
NYHA functional class — no. (%)		
II	1399 (75.1)	1401 (75.0)
III	455 (24.4)	455 (24.4)
IV	9 (0.5)	11 (0.6)
Body-mass index‡	28.0±5.5	27.8±5.3
Heart rate — beats/min	71.0±11.7	71.5±11.8
Systolic blood pressure — mm Hg	122.6±15.9	121.4±15.4
Left ventricular ejection fraction		
Mean value	27.7±6.0	27.2±6.1
Value of ≤30% — no. (%)	1337 (71.8)	1392 (74.6)
NT-proBNP		
Median value (IQR) — pg/ml	1887 (1077–3429)	1926 (1153–3525)
Value of ≥1000 pg/ml — no./total no. (%)	1463/1862 (78.6)	1488/1866 (79.7)
Cause of heart failure — no. (%)		
Ischemic	983 (52.8)	946 (50.7)
Nonischemic	880 (47.2)	921 (49.3)
Cardiovascular history — no. (%)		
Hospitalization for heart failure in ≤12 mo	577 (31.0)	574 (30.7)
Atrial fibrillation	664 (35.6)	705 (37.8)
Diabetes mellitus	927 (49.8)	929 (49.8)
Hypertension	1349 (72.4)	1349 (72.3)
Estimated glomerular filtration rate		
Mean value — ml/min/1.73 m^2	61.8±21.7	62.2±21.5
Value of <60 ml/min/1.73 m^2 — no./total no. (%)	893/1862 (48.0)	906/1866 (48.6)

Table 1. (Continued.)

Characteristic	Empagliflozin (N=1863)	Placebo (N=1867)
Heart failure medication — no. (%)		
Renin–angiotensin inhibitor§		
Without neprilysin inhibitor	1314 (70.5)	1286 (68.9)
With neprilysin inhibitor	340 (18.3)	387 (20.7)
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)
Beta-blocker	1765 (94.7)	1768 (94.7)
Device therapy — no. (%)		
Implantable cardioverter–defibrillator¶	578 (31.0)	593 (31.8)
Cardiac resynchronization therapy‖	220 (11.8)	222 (11.9)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range, NT-proBNP N-terminal prohormone of brain natriuretic peptide, and NYHA New York Heart Association.
† Race was reported by the patients. Those 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.
§ Inhibitors of the renin–angiotensin system include angiotensin-converting–enzyme inhibitors and angiotensin-receptor blockers.
¶ This category includes all the patients with an implantable cardioverter–defibrillator regardless of the presence or absence of cardiac resynchronization therapy.
‖ This category includes all the patients who were receiving cardiac resynchronization therapy regardless of the presence or absence of a defibrillator.

the possibility of recommending early termination of the trial if a benefit associated with empagliflozin was significant at a one-sided alpha level of approximately 0.001 with respect to both the primary outcome and cardiovascular death alone.

The primary analysis was performed according to the intention-to-treat principle and included all the data that had been obtained up to the end of the planned treatment period for all the patients who had undergone randomization. Between-group differences in the primary outcome were assessed for statistical significance with the use of a Cox proportional-hazards model, with prespecified covariates of age, sex, geographical region, diabetes status at baseline, left ventricular ejection fraction, and estimated GFR at baseline.

If the between-group difference in the primary outcome was significant, the two key secondary outcomes were prespecified to be analyzed in a stepwise hierarchical manner to preserve the overall type I error rate at 0.0496 (two-sided) after accounting for one interim analysis. The first secondary outcome — total (first and recurrent) hospitalizations for heart failure — was evaluated with the use of a joint frailty model that accounted for informative censoring because of cardiovascular death. The second secondary outcome (the slope of the change in the estimated GFR) was evaluated at an alpha level of 0.001. The remaining alpha level after hierarchical testing will be applied to a patient-level meta-analysis that will be performed on the data sets from the current trial and from a parallel trial, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Preserved Ejection Fraction (EMPEROR-Preserved).

RESULTS

PATIENTS

From April 2017 through November 2019, a total of 7220 patients were screened for eligibility, and 3730 were randomly assigned to receive either empagliflozin (1863 patients) or placebo

Table 2. Primary and Secondary Cardiovascular Outcomes.*

Variable	Empagliflozin (N=1863)		Placebo (N=1867)		Hazard Ratio or Absolute Difference (95% CI)†	P Value
		events/100 patient-yr		*events/100 patient-yr*		
Primary composite outcome — no. (%)	361 (19.4)	15.8	462 (24.7)	21.0	0.75 (0.65 to 0.86)	<0.001
Hospitalization for heart failure	246 (13.2)	10.7	342 (18.3)	15.5	0.69 (0.59 to 0.81)	
Cardiovascular death	187 (10.0)	7.6	202 (10.8)	8.1	0.92 (0.75 to 1.12)	
Secondary outcomes specified in hierarchical testing procedure						
Total no. of hospitalizations for heart failure	388	—	553	—	0.70 (0.58 to 0.85)	<0.001
Mean slope of change in eGFR — ml/min/1.73 m^2 per year‡	−0.55±0.23	—	−2.28±0.23	—	1.73 (1.10 to 2.37)	<0.001
Other prespecified analyses						
Composite renal outcome — no. (%)§	30 (1.6)	1.6	58 (3.1)	3.1	0.50 (0.32 to 0.77)	
Change in quality-of-life score on KCCQ at 52 weeks¶	5.8±0.4	—	4.1±0.4	—	1.7 (0.5 to 3.0)	
No. of hospitalizations for any cause	1364	—	1570	—	0.85 (0.75 to 0.95)	
Death from any cause — no. (%)	249 (13.4)	10.1	266 (14.2)	10.7	0.92 (0.77 to 1.10)	
Onset of new diabetes in patients with prediabetes — no./total no. (%)	71/632 (11.2)	9.3	80/636 (12.6)	10.6	0.86 (0.62 to 1.19)	
Laboratory and other measurements (adjusted change from baseline to 52 wk)						
Glycated hemoglobin in patients with diabetes — %	−0.28±0.03	—	−0.12±0.03	—	−0.16 (−0.25 to −0.08)	
Hematocrit (%)	1.98±0.10	—	−0.38±0.10	—	2.36 (2.08 to 2.63)	
Median NT-proBNP (IQR) — pg/ml‖	−244 (−890 to 260)		−141 (−784 to 585)	—	0.87 (0.82 to 0.93)	
Body weight — kg	−0.73±0.13	—	0.08±0.13	—	−0.82 (−1.18 to −0.45)	
Systolic blood pressure — mm Hg	−2.4±0.4	—	−1.7±0.4	—	−0.7 (−1.8 to 0.4)	

* Plus–minus values are means ±SE. IQR denotes interquartile range.

† All treatment effects are shown as hazard ratios, except for the slope of the change in the estimated glomerular filtration rate (GFR), the quality-of-life score, and the variables listed under laboratory and other measurements. For all hazard ratios or treatment differences without P values, the widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects.

‡ The slope of the estimated GFR was analyzed on the basis of on-treatment data with a random coefficient model that included age and baseline estimated GFR as linear covariates and sex, region, baseline left ventricular ejection fraction, baseline diabetes status, baseline estimated GFR according to time, and treatment according to time interactions as fixed effects; the model allows for randomly varying slope and intercept between patients.

§ The composite renal outcome includes chronic dialysis or renal transplantation or a sustained reduction of 40% or more in the estimated GFR or a sustained estimated GFR of less than 15 ml per minute per 1.73 m^2 in patients with a baseline estimated GFR of 30 ml per minute per 1.73 m^2 or more or a sustained estimated GFR of less than 10 ml per minute per 1.73 m^2 in those with a baseline estimated GFR of less than 30 ml per minute per 1.73 m^2.

¶ The clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) ranges from 0 to 100, with higher scores indicating a better quality of life.

‖ NT-proBNP was analyzed with the use of a geometric mean ratio because modeling was performed on log-transformed data.

(1867 patients) (Fig. S1 in the Supplementary Appendix). The reasons for screening failure are described in Table S1. The baseline characteristics of the patients in the two trial groups were similar (Table 1). Half the patients had a history of diabetes, 73% had a left ventricular ejection fraction of 30% or less, 79% had a NT-proBNP level of at least 1000 pg per milliliter, 48% had an estimated GFR of less than 60 ml per minute per 1.73 m^2, and nearly 20% were receiving an angiotensin receptor–neprilysin inhibitor.

The final date of follow-up data collection for the double-blind treatment period was April 29, 2020. Four patients in the placebo group did not receive placebo. In addition, empagliflozin or placebo was stopped prematurely for reasons other than death in 303 patients (16.3%) in the empagliflozin group and in 335 patients (18.0%) in the placebo group. A total of 21 patients (0.6%) had unknown vital status at the end of the trial, in part related to operational challenges associated with coronavirus disease 2019 (Covid-19); 42 patients (20 in the placebo group and 22 in the empagliflozin group), including those with unknown vital status, were lost to follow-up at various times before the data cutoff. The median duration of follow-up was 16 months.

PRIMARY OUTCOME

The primary composite outcome of death from cardiovascular causes or hospitalization for heart failure occurred in 361 patients (19.4%) in the empagliflozin group and in 462 patients (24.7%) in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.65 to 0.86; P<0.001) (Table 2 and Fig. 1A). The hazard ratios for the effect of empagliflozin on cardiovascular death and on the first hospitalization for heart failure were 0.92 (95% CI, 0.75 to 1.12) and 0.69 (95% CI, 0.59 to 0.81), respectively (Table 2 and Figs. S2 and S3). During the trial period, the number of patients who would need to have been treated with empagliflozin to prevent one primary event was 19 (95% CI, 13 to 37).

The effect of empagliflozin on the primary outcome was consistent across prespecified subgroups, including patients with diabetes and those without diabetes at baseline (Fig. 2 and Fig. S4). Among the patients who were receiving sacubitril–valsartan at baseline, the hazard ratio for the comparison between empagliflozin and placebo for the primary outcome was 0.64 (95% CI, 0.45 to 0.89), as compared with 0.77 (95% CI, 0.66 to 0.90) among those who were not receiving sacubitril–valsartan.

SECONDARY OUTCOMES

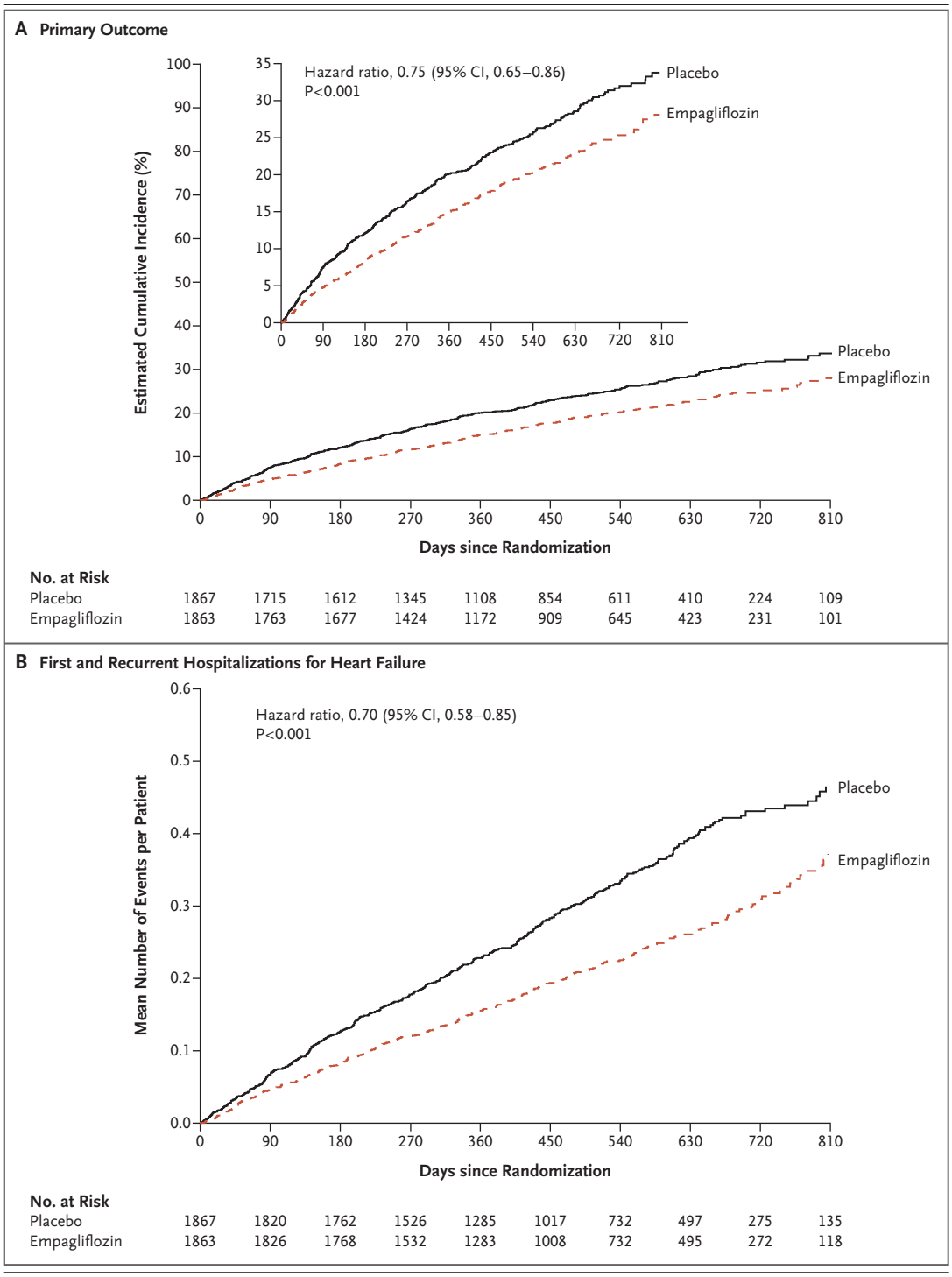
Empagliflozin also favorably influenced the two prespecified secondary outcomes that were included in the hierarchical testing procedure. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group, with 388 events and 553 events, respectively (hazard ratio, 0.70; 95% CI, 0.58 to 0.85; P<0.001) (Table 2 and Fig. 1B). The rate of the decline in the estimated GFR over the duration of the double-blind treatment period was slower in the empagliflozin group than in the placebo group (–0.55 ml per minute per 1.73 m^2 per year vs. –2.28 ml per minute per 1.73 m^2 per year), for a between-group difference of 1.73 ml per minute per 1.73 m^2 per year (95% CI, 1.10 to 2.37; P<0.001) (Table 2 and Fig. 3).

OTHER PRESPECIFIED OUTCOMES

In prespecified analyses that were not included in the testing hierarchy, a composite renal outcome (chronic dialysis or renal transplantation or a profound, sustained reduction in the estimated GFR) occurred in 30 patients (1.6%) in the empagliflozin group and in 58 patients (3.1%) in the placebo group (hazard ratio, 0.50; 95% CI, 0.32 to 0.77). In 966 patients with paired measurements before treatment and 23 to 45 days after the discontinuation of the trial regimens (which enabled assessment of the effects of empagliflozin independent of the presence of the drug), the estimated GFR declined by –0.93 ml per minute per 1.73 m^2 (95% CI, –1.97 to 0.11) in the empagliflozin group and by –4.21 ml per minute per 1.73 m^2 (95% CI, –5.26 to –3.17) in the placebo group. The effects of empagliflozin on patients' quality of life, total hospitalizations for any reason, and the frequency of new-onset diabetes are described in Table 2. A total of 249 patients (13.4%) in the empagliflozin group and 266 patients (14.2%) in the placebo group died from any cause (hazard ratio, 0.92; 95% CI, 0.77 to 1.10) (Fig. S5).

BIOMARKERS, SAFETY, AND SENSITIVITY ANALYSES

Changes from baseline to 52 weeks in values for glycated hemoglobin, hematocrit, NT-proBNP, body weight, and systolic blood pressure in the



two groups are shown in Table 2. The 4 patients in the placebo group who did not receive placebo were excluded from the safety analyses. Uncomplicated genital tract infection was reported more frequently with empagliflozin than with placebo. Adverse events of interest are listed in Table S2.

Several sensitivity analyses were performed to account for missing follow-up data in 42 patients

Figure 1 (facing page). Primary Outcome and Total Hospitalizations for Heart Failure.

Shown is the cumulative incidence of the primary composite outcome of cardiovascular death or hospitalization for heart failure (Panel A) and the total (first and recurrent) hospitalizations for heart failure, expressed as the mean number per patient (Panel B) in the empagliflozin group and the placebo group. The inset graph shows the data on an expanded y axis. The primary analysis was performed according to the intention-to-treat principle and included all the data that had been obtained up to the end of the planned treatment period for all the patients who had undergone randomization. The two outcomes were based on the central blinded adjudication of events reported by the investigators. For the analysis of the primary outcome, the assumption of proportional hazards was investigated, and no violations were observed.

and to consider competing risk. The results of these analyses, which are provided in Table S3, were similar to the results of the main analyses reported above.

DISCUSSION

In our trial, the combined risk of cardiovascular death or hospitalization for heart failure was 25% lower among the patients who received empagliflozin than among those who received placebo, a difference that was primarily related to a 31% lower risk of hospitalization for heart failure. These benefits were seen in patients receiving any of the currently recommended drugs for heart failure, including sacubitril–valsartan, and were seen regardless of the presence or absence of diabetes. In addition, empagliflozin was associated with a lower number of hospitalizations for heart failure and with a slower rate of decline in the estimated GFR; the latter effect was accompanied by a lower risk of serious renal outcomes.

Our findings with empagliflozin can be compared with the effects of dapagliflozin in the DAPA-HF trial.[5] The current trial was enriched for patients with a markedly reduced ejection fraction and increased levels of natriuretic peptides, as compared with the patients in the DAPA-HF trial (Table S4). Consequently, the incidence of the primary outcome was approximately 40% higher in the current trial than in the DAPA-HF trial. Our trial thus extends the benefits of SGLT2 inhibitors to patients with more advanced but stable heart failure.

In both the current trial and the DAPA-HF trial, the benefit of the SGLT2 inhibitor on the primary composite outcome was driven mainly by a reduction in hospitalizations for heart failure. The risk of cardiovascular death was 8% lower with empagliflozin than with placebo in our trial (hazard ratio, 0.92; 95% CI, 0.75 to 1.12) and was 18% lower with dapagliflozin in the DAPA-HF trial (hazard ratio, 0.82; 95% CI, 0.69 to 0.98). Of note, in large-scale trials involving patients with type 2 diabetes, the risk reductions in cardiovascular death among patients with similar cardiovascular histories (i.e., those with a prior myocardial infarction) were 41% for empagliflozin (hazard ratio, 0.59; 95% CI, 0.44 to 0.79) and 8% for dapagliflozin (hazard ratio, 0.92; 95% CI, 0.69 to 1.23).[7,8] Therefore, as noted by other investigators,[1] the effect of SGLT2 inhibitors on mortality appears to be heterogeneous, with no consistent evidence that one member of the drug class is superior to another with respect to the effects on survival.

In addition to the observed cardiovascular benefits, empagliflozin slowed the rate of decline in the estimated GFR during double-blind treatment, and the risk of the composite renal outcome was lower in the empagliflozin group than in the placebo group. When measurements were compared at the start and the end of the trial after the discontinuation of both empagliflozin and placebo, the estimated GFR declined more in the placebo group than in the empagliflozin group. These observations are consistent with the benefit observed in trials of SGLT2 inhibitors in patients with type 2 diabetes who largely did not have heart failure.[1] Accordingly, the ability of empagliflozin to favorably influence renal function is apparent in patients with diabetes, in those with heart failure, and in those with both conditions.

Uncomplicated genital tract infection was reported more frequently in the empagliflozin group. The frequency of hypoglycemia, lower limb amputation, and bone fracture did not differ between the two groups, even though these adverse events have been associated with the use of certain SGLT2 inhibitors in trials involving patients with type 2 diabetes.[9,10] Safety concerns that have been seen with other drugs for heart

Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	361/1863	462/1867	0.75 (0.65–0.86)
Baseline diabetes status			
Diabetes	200/927	265/929	0.72 (0.60–0.87)
No diabetes	161/936	197/938	0.78 (0.64–0.97)
Age			
<65 yr	128/675	193/740	0.71 (0.57–0.89)
≥65 yr	233/1188	269/1127	0.78 (0.66–0.93)
Sex			
Male	294/1426	353/1411	0.80 (0.68–0.93)
Female	67/437	109/456	0.59 (0.44–0.80)
Race			
White	264/1325	289/1304	0.88 (0.75–1.04)
Black	24/123	48/134	0.46 (0.28–0.75)
Asian	62/337	99/335	0.57 (0.41–0.78)
Other	5/51	14/63	0.41 (0.15–1.14)
Baseline body-mass index			
<30	226/1263	322/1300	0.70 (0.59–0.83)
≥30	135/600	140/567	0.85 (0.67–1.08)
Baseline eGFR (CKD-EPI)			
≥60	159/969	224/960	0.67 (0.55–0.83)
<60	202/893	237/906	0.83 (0.69–1.00)
HF hospitalization in ≤12 mo			
No	208/1286	285/1293	0.71 (0.60–0.85)
Yes	153/577	177/574	0.79 (0.64–0.99)
Cause of heart failure			
Ischemic	207/983	236/946	0.82 (0.68–0.99)
Nonischemic	154/880	226/921	0.67 (0.55–0.82)
Baseline NYHA class			
II	220/1399	299/1401	0.71 (0.59–0.84)
III or IV	141/464	163/466	0.83 (0.66–1.04)
Heart failure physiology			
LVEF ≤30% and NT-proBNP <median	80/699	115/724	0.70 (0.53–0.93)
LVEF ≤30% and NT-proBNP ≥median	169/631	249/661	0.65 (0.53–0.79)
LVEF >30%	108/526	97/475	0.99 (0.76–1.31)
Baseline use of MRA			
No	118/557	132/512	0.76 (0.59–0.97)
Yes	243/1306	330/1355	0.75 (0.63–0.88)
Baseline use of ARNi			
No	310/1523	369/1480	0.77 (0.66–0.90)
Yes	51/340	93/387	0.64 (0.45–0.89)

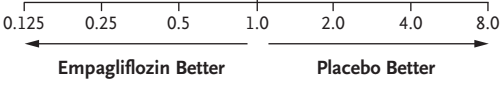


Figure 2. Primary Outcome in Prespecified Subgroups.

Shown is the risk of the primary outcome in key subgroups of patients. The size of the squares for the hazard ratios is proportional to the size of the subgroup. The body-mass index is the weight in kilograms divided by the square of the height in meters. Race was reported by the patients. ARNi denotes angiotensin receptor–neprilysin inhibitor, CKD-EPI Chronic Kidney Disease Epidemiology Collaboration, HF heart failure, eGFR estimated glomerular filtration rate, LVEF left ventricular ejection fraction, MRA mineralocorticoid receptor antagonist, NT-proBNP N-terminal prohormone of brain natriuretic peptide, and NYHA New York Heart Association.

failure (e.g., hypotension, volume depletion, renal dysfunction, bradycardia, and hyperkalemia) were not evident with empagliflozin in the current trial.

Overall, in this trial, empagliflozin was associated with a lower combined risk of cardiovascular death or hospitalization for heart failure than placebo and with a slower progressive

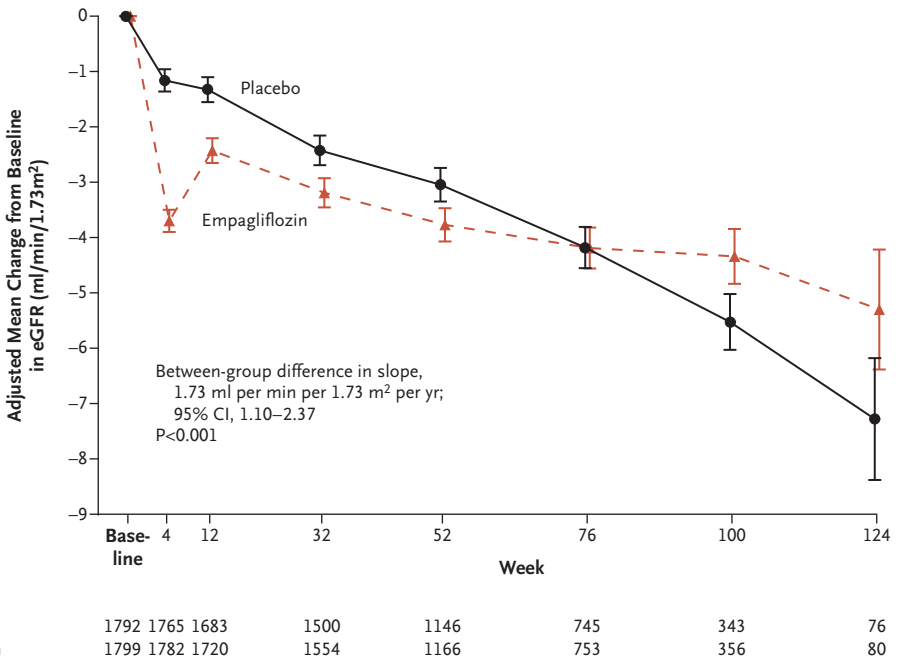


Figure 3. Changes in the Estimated Glomerular Filtration Rate.

Shown are the adjusted mean changes from baseline in the estimated GFR, as calculated with the Chronic Kidney Disease Epidemiology Collaboration equation. The I bars indicate the standard error. The on-treatment data were analyzed with the use of a mixed model for repeated measures that included age and baseline estimated GFR as linear covariates and sex, region, baseline left ventricular ejection fraction, baseline diabetes status, last projected visit based on dates of randomization and trial closure, baseline estimated GFR according to visit, and visit according to treatment interactions as fixed effects. A different model was used to analyze the slope of the change in the estimated GFR during double-blind treatment, as described in Table 2.

decline in renal function in patients with chronic heart failure and a reduced ejection fraction, regardless of the presence or absence of diabetes.

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

APPENDIX

The authors' full names and academic degrees are as follows: Milton Packer, M.D., Stefan D. Anker, M.D., Ph.D., Javed Butler, M.D., Gerasimos Filippatos, M.D., Stuart J. Pocock, Ph.D., Peter Carson, M.D., James Januzzi, M.D., Subodh Verma, M.D., Ph.D., Hiroyuki Tsutsui, M.D., Martina Brueckmann, M.D., Waheed Jamal, M.D., Karen Kimura, Ph.D., Janet Schnee, M.D., Cordula Zeller, Dipl.Math., Daniel Cotton, M.S., Edimar Bocchi, M.D., Michael Böhm, M.D., Ph.D., Dong-Ju Choi, M.D., Vijay Chopra, M.D., Eduardo Chuquiure, M.D., Nadia Giannetti, M.D., Stefan Janssens, M.D., Ph.D., Jian Zhang, M.D., Ph.D., Jose R. Gonzalez Juanatey, M.D., Sanjay Kaul, M.D., Hans-Peter Brunner-La Rocca, M.D., Bela Merkely, M.D., Stephen J. Nicholls, M.D., Sergio Perrone, M.D., Ileana Pina, M.D., Piotr Ponikowski, M.D., Naveed Sattar, M.D., Michele Senni, M.D., Marie-France Seronde, M.D., Jindrich Spinar, M.D., Iain Squire, M.D., Stefano Taddei, M.D., Christoph Wanner, M.D., and Faiez Zannad, M.D., Ph.D.

The authors' affiliations are as follows: Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas (M.P.); Imperial College (M.P.) and the Department of Medical Statistics, London School of Hygiene and Tropical Medicine (S.J.P.), London, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow (N.S.), and the Department of Cardiovascular Sciences, University of Leicester and National Institute for Health Research Biomedical Research Centre, Glenfield Hospital, Leicester (I.S.) — all in the United Kingdom; the Department of Cardiology and Berlin Institute of Health Center for Regenerative Therapies, German Center for Cardiovascular Research Partner Site Berlin, Charité Universitätsmedizin, Berlin (S.D.A.), Boehringer Ingelheim International, Ingelheim (M. Brueckmann, W.J.), Faculty of Medicine Mannheim, University of Heidelberg, Mannheim (M. Brueckmann), Boehringer Ingelheim Pharma, Biberach (C.Z.), Klinik für Innere Medizin III, Saarland University, Homburg–Saar (M. Böhm), and the Department of Medicine, University Hospital of Würzburg, Würzburg (C.W.) — all in Germany; the Department of Medicine, University of Missis-

sippi School of Medicine, Jackson (J.B.); National and Kapodistrian University of Athens School of Medicine, Athens University Hospital Attikon, Athens (G.F.); Washington DC Veterans Affairs Medical Center, Washington DC (P.C.); the Division of Cardiology, Harvard Medical School and Massachusetts General Hospital, Boston (J.J.); the Division of Cardiac Surgery, St. Michael's Hospital, University of Toronto, Toronto (S.V.), Boehringer Ingelheim Canada, Burlington, ON (K.K.), and the Division of Cardiology, McGill University and Health Centre, Montreal (N.G.) — all in Canada; the Department of Cardiovascular Medicine, Kyushu University, Higashi-ku, Fukuoka, Japan (H.T.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (J. Schnee, D.C.); Heart Institute, São Paulo University Medical School, São Paulo (E.B.); the Department of Medicine, Seoul National University, Seoul, South Korea (D.-J.C.); the Department of Cardiology, Max Super Speciality Hospital, Saket, New Delhi, India (V.C.); the Department of Clinical Cardiology, National Institute of Cardiology, Mexico City (E.C.); the Department of Cardiology, University Hospital Gasthuisberg of Leuven, Leuven, Belgium (S.J.); Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing (J.Z.); the Cardiology Department, University Hospital, Santiago de Compostela, Spain (J.R.G.J.); the Department of Cardiology, Cedars–Sinai Medical Center, Los Angeles (S.K.); Maastricht Heart and Vascular Center, Maastricht, the Netherlands (H.P.B.-L.R.); the Heart and Vascular Center, Semmelweis University, Budapest, Hungary (B.M.); Victorian Heart Institute and Monash University, Melbourne, VIC, Australia (S.J.N.); Fleni Institute and Hospital El Cruce–Nestor Kirchner, Buenos Aires (S.P.); the Department of Medicine, Wayne State and Central Michigan Universities, Detroit (I.P.); the Center for Heart Diseases, Wrocław Medical University, Wrocław, Poland (P.P.); the Cardiovascular Department, Papa Giovanni XXIII Hospital, Bergamo (M.S.), and the Department of Clinical and Experimental Medicine, University of Pisa, Pisa (S.T.) — both in Italy; the Department of Cardiology, University Hospital Jean Minjoz, Besançon (M.-F.S.), and Université de Lorraine, INSERM Investigation Network Initiative–Cardiovascular and Renal Clinical Trialists, Centre Hospitalier Régional Universitaire, Nancy (F.Z.) — both in France; and Internal Cardiology, University Hospital Brno, Brno, Czech Republic (J. Spinar).

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