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# Effect of Empagliflozin on Worsening Heart Failure Events in Patients with Heart Failure and a Preserved Ejection Fraction: The EMPEROR-Preserved Trial

**Running Title:** *Packer, et al.; Empagliflozin on Worsening Heart Failure Events in HFpEF*

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## Abstract

**Background:** Empagliflozin reduces the risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, but additional data are needed about its effect on inpatient and outpatient heart failure events.

**Methods:** We randomly assigned 5988 patients with class II-IV heart failure with an ejection fraction of >40% to double-blind treatment with placebo or empagliflozin (10 mg once daily), in addition to usual therapy, for a median of 26 months. We prospectively collected information on inpatient and outpatient events reflecting worsening heart failure and prespecified their analysis in individual and composite endpoints.

**Results:** Empagliflozin reduced the combined risk of cardiovascular death, hospitalization for heart failure or an emergent/urgent heart failure visit requiring intravenous treatment (432 vs 546 patients; empagliflozin vs placebo, respectively; hazard ratio 0.77, 95% CI: 0.67-0.87),  $P < 0.0001$ . This benefit reached statistical significance at 18 days after randomization.

Empagliflozin reduced the total number of heart failure hospitalizations that required intensive care (hazard ratio 0.71, 95% CI 0.52-0.96,  $P=0.028$ ) and the total number of all hospitalizations that required a vasopressor or positive inotropic drug (hazard ratio 0.73, 95% CI: 0.55-0.97,  $P=0.033$ ). As compared with placebo, fewer patients in the empagliflozin group reported outpatient intensification of diuretics (482 vs 610, hazard ratio 0.76, 95% CI: 0.67-0.86,  $P < 0.0001$ ), and patients assigned to empagliflozin were 20-50% more likely to have a better NYHA functional class, with significant effects at 12 weeks that were maintained for at least 2 years. The benefit on total heart failure hospitalizations was similar in patients with an ejection fraction of >40- $<50\%$  and 50- $<60\%$ , but was attenuated at higher ejection fractions.

**Conclusions:** In patients with heart failure and a preserved ejection fraction, empagliflozin produced a meaningful, early and sustained reduction in the risk and severity of a broad range of inpatient and outpatient worsening heart failure events.

**Clinical Trial Registration:** The registration identifier at ClinicalTrials.gov is NCT03057977

**Key Words:** empagliflozin; heart failure; SGLT2 inhibitor

### Non-standard Abbreviations and Acronyms

CI	confidence interval
EMPEROR	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure
EMPEROR-Preserved	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction
EMPEROR-Reduced	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction
NTproBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
SGLT2	sodium-glucose cotransporter 2

## Clinical Perspective

### What is new?

- The EMPEROR-Preserved trial showed that — in patients with heart failure and a preserved ejection fraction — empagliflozin reduced the primary endpoint of cardiovascular death or hospitalization for heart failure, primarily related to a 29% lower risk of hospitalizations for heart failure.
- In the current analysis, we show that empagliflozin reduced the risk of severe hospitalizations, as reflected by admissions requiring the use of positive inotropic and vasopressor drugs and the need for intensive care.
- Empagliflozin also reduced the risk of outpatient worsening heart failure events, including need for urgent care visits, diuretic intensification and unfavorable changes in functional class.



### What are the clinical implications?

- Therapeutic options for patients with heart failure and a preserved ejection fraction are limited, since prior trials with various interventions have shown little or modest effects.
- The favorable effects of empagliflozin on inpatient and outpatient worsening heart failure events in patients with heart failure and a preserved ejection fraction in the EMPEROR-Preserved trial are similar to those reported with empagliflozin in patients with heart failure and a reduced ejection fraction in the EMPEROR-Reduced trial.

## Introduction

Heart failure is a progressive disorder, which is marked by ongoing or episodic worsening of symptoms, leading to a deterioration of functional capacity and requiring the intensification of treatment. Often, these episodes of clinical worsening can be managed as in an outpatient setting, which can involve an office, clinic, emergency department or urgent care setting. When severe or of rapid onset, worsening symptoms may require hospitalization, and if the patient becomes clinically unstable, admission to intensive care. Therefore, the clinical progression of heart failure can manifest itself in a broad range of clinical settings. Although the primary endpoint of clinical trials typically focuses only on hospitalizations,<sup>1,2</sup> these represent only a tiny proportion of a patient's journey,<sup>3,4</sup> and outpatient and inpatient worsening heart failure events can have similar adverse prognostic implications.<sup>5-7</sup>



In clinical trials in type 2 diabetes or chronic kidney disease, sodium-glucose cotransporter 2 (SGLT2) inhibitors reduced the risk of hospitalizations for heart failure.<sup>8-14</sup> However, these trials did not evaluate the effect of these drugs on the broad spectrum of both inpatient and outpatient heart failure events. We and others have reported that — in patients with heart failure and a reduced ejection fraction — empagliflozin, dapagliflozin and sotagliflozin not only lowered the risk of hospitalization for heart failure, but also diminished the risk of outpatient events, including emergent/urgent care visits and outpatient intensification of diuretics for worsening heart failure.<sup>15-18</sup> In this paper, we report on the effect of empagliflozin on inpatient and outpatient worsening heart failure events in patients with heart failure and an ejection fraction > 40%. Furthermore, since patients with heart failure and a preserved ejection fraction have comorbidities that can cause serious disability for reasons other than heart failure, we report

on the effect of empagliflozin using more comprehensive definitions of death and hospitalization.<sup>19-23</sup>

## Methods

The EMPEROR-Preserved trial was a randomized, double-blind, parallel-group, placebo-controlled and event-driven study, whose design has been described previously.<sup>24,25</sup> Ethics approval was obtained at each study site, and informed consent was obtained from all study participants; the registration identifier is NCT0305795 (clinicaltrials.gov). Data will be made available upon request in adherence with transparency conventions in medical research and through requests to the corresponding author. The Executive Committee of the EMPEROR trials has developed a comprehensive analysis plan and numerous prespecified analyses, which will be presented in future scientific meetings and publications. At a later time point, the full database will be made available in adherence with the transparency policy of the sponsor (available at [https://trials.boehringer-ingenelheim.com/transparency\\_policy.html](https://trials.boehringer-ingenelheim.com/transparency_policy.html)).

## Study Patients and Assessments

We enrolled men or women with chronic heart failure (New York Heart Association [NYHA] functional class II, III or IV) with a left ventricular ejection fraction > 40%, who had elevated levels of N-terminal prohormone B-type natriuretic peptide (NTproBNP) >300 pg/mL; this threshold was tripled in patients with atrial fibrillation at baseline. Patients who fulfilled prespecified inclusion and exclusion criteria were randomized double-blind (in a 1:1 ratio) to receive placebo or empagliflozin 10 mg daily, in addition to their usual therapy. Following randomization, all appropriate treatments for heart failure or other medical conditions could be initiated or altered at the discretion of each patient's physician. Patients were assessed at study

visits for major outcomes, functional capacity related to heart failure, changes in the utilization of diuretics, vital signs and biomarkers reflecting changes in the course of heart failure or the action of SGLT2 inhibitors; these assessments took place every 2-6 months, depending on the metric and the duration of follow-up. All randomized patients were to be followed for prespecified outcomes for the entire duration of the trial.

### **Trial Endpoints**

In a manner similar to that followed for the EMPEROR-Reduced trial,<sup>15</sup> we prospectively collected information on deaths, hospitalizations for any reason and emergent, urgent and outpatient events that reflect worsening heart failure. Hospitalizations were classified as cardiovascular or noncardiovascular based on the judgment of the investigator, but hospitalizations for heart failure were prospectively adjudicated by a clinical-event committee in a blinded manner using prespecified criteria. To qualify as an adjudicated heart failure hospitalization, patients were required to have meaningful worsening of their clinical status and intensification of treatment for heart failure. The duration of the in-hospital stay was at least 12 hours; if patient had not received intravenous medications for heart failure, the minimum stay of an adjudicated heart failure hospitalization was 24 hours. Investigators documented the clinical course of each hospital admission on a dedicated form, including the prescribing of medications used to treat episodes of clinical decompensation, and the utilization of intensive care.

In addition to the adjudication and characterization of hospitalizations for heart failure, at each scheduled study visit, patients were prospectively asked about interval events and about changes in the use of diuretics that were prescribed in response to worsening heart failure since the last visit. Events that were prospectively considered to reflect meaningful changes in clinical status included: (1) worsening heart failure that required the use of an intravenous drug for heart



failure in an emergency department or urgent care setting; (2) intensification of daily doses of diuretics for worsening symptoms; and (3) changes in New York Heart Association (NYHA) functional class. Events treated in an emergency department, urgent care setting or during a hospital stay shorter than that required for an adjudicated event were grouped together.

Physicians were not provided any specific guidance as to the degree or duration of diuretic intensification that would qualify as representing a clinically meaningful change. Ascertainment of these events and measures were prospectively collected in the case report form, and their inclusion in analyses of individual and composite endpoints was prespecified before the blind of the trial was broken. Outpatient worsening heart failure events were not adjudicated.

The endpoints selected for inclusion in this paper are very similar to those that we analyzed for the EMPEROR-Reduced trial,<sup>15</sup> and we prospectively planned to perform these analyses for the EMPEROR-Preserved trial.

### **Statistical Analysis**

For time-to-first-event analyses, differences between the placebo and empagliflozin groups were assessed using a Cox proportional hazards model, with prespecified covariates of age, gender, geographical region, diabetes status at baseline, left ventricular ejection fraction, and estimated glomerular filtration rate at baseline. To determine the time point when statistical significance was reached and maintained for the first time, the same Cox regression models were fitted and sequentially censoring at increasing number of days since randomization, yielding a continuous display of hazard ratios with confidence bands. For the analysis of total (first and repeated) events, between-group differences were assessed using a joint frailty model,<sup>26</sup> with cardiovascular death (for endpoints including heart failure events) or all-cause mortality (for

endpoints including all-cause hospitalisation) as competing risks and using the covariates that were used for the time-to-first event analyses.

Odds ratios were calculated for the effect of empagliflozin versus placebo on NYHA class at prespecified study visits using ordinal logistic regression assuming partial proportional odds adjusting for baseline NYHA class and using the same covariates as for the Cox regression models, without imputation for missing data. For the analysis of changes in vital signs and biomarkers, treatment effects were assessed based on changes from baseline using a mixed model for repeated measures that included age and baseline estimated glomerular filtration rate and ejection fraction as linear covariates and baseline score by visit, visit by treatment, sex, region, individual last projected visit based on dates of randomization and trial closure, and baseline diabetes status as fixed effects. The analysis of changes in N-terminal proBNP was performed on log-transformed data. Because the outcome measures were highly correlated, no adjustment was made for multiplicity of comparisons.

## Results

A total of 5988 patients were randomly assigned to placebo (n=2991) or to empagliflozin (n=2997). As previously reported,<sup>25</sup> the two groups had clinical features typical of patients with heart failure and a preserved ejection fraction, and they were well-balanced with respect to baseline characteristics.

### Effect on Combined Risk of Death or Hospitalization

There were 662 patients who died for any reason or were hospitalized for heart failure in the placebo group and 581 such patients in the empagliflozin group, reflecting a 15% lower risk with empagliflozin as compared with placebo (hazard ratio 0.85; 95% confidence interval (CI), 0.76–

0.95;  $P=0.005$ ), Table 1. There were 967 patients who died for any reason or were hospitalized for a cardiovascular reason in the placebo group and 888 such patients in the empagliflozin group, reflecting a 11% lower risk with empagliflozin than placebo (hazard ratio 0.89; 95% CI, 0.81–0.98;  $P=0.014$ ). There were 1431 patients who died or were hospitalized for any reason in the placebo group and 1356 such patients in the empagliflozin group, reflecting an 8% lower risk with empagliflozin than placebo (hazard ratio 0.92; 95% CI, 0.85–0.99;  $P=0.025$ ), Table 1.

### Effect of Empagliflozin on Hospitalizations

As compared with the placebo group, patients in the empagliflozin group had fewer total (first and recurrent) hospitalizations for heart failure (407 vs 541, hazard ratio 0.73; 95% CI, 0.61–0.88;  $P=0.0009$ ) and fewer total (first and recurrent) hospitalizations for a cardiovascular reason (1145 vs 1333, hazard ratio 0.84; 95% CI, 0.74–0.95;  $P=0.005$ ). Total (first and recurrent) hospitalizations for any reason were not significantly different in the two treatment groups (2566 vs 2769, empagliflozin vs placebo, respectively, hazard ratio 0.93; 95% CI, 0.85–1.01;  $P=0.10$ ), Table 1. However, among these, empagliflozin reduced the total number of hospitalizations requiring intravenous diuretics by 33% (hazard ratio 0.67; 95% CI, 0.57–0.79,  $P<0.0001$ ) and the total number of hospitalizations requiring intravenous vasopressor or positive inotropic agents by 27% (hazard ratio 0.73; 95% CI, 0.55–0.97),  $P=0.03$ , Figure 1.

The effect of empagliflozin on total hospitalizations for heart failure is described in Table 2. As compared with placebo, fewer patients in the empagliflozin group were hospitalized for heart failure once (181 vs 243), hospitalized for heart failure twice (49 vs 67), and hospitalized for heart failure three or more times (29 vs 42). The effect of empagliflozin on total (first and recurrent) hospitalizations for heart failure was consistent in most of the prespecified subgroups. For this endpoint, we observed a nominally significant interaction between treatment and the

baseline use of mineralocorticoid receptor antagonists (interaction  $P=0.038$ ) as well as an interaction between treatment and ejection fraction ( $P\text{-trend}=0.008$ ), with an attenuated response in patients with an ejection fraction  $\geq 60\%$  (Supplemental Figure I). When the analysis of hospitalizations was broadened to total (first and recurrent) cardiovascular hospitalizations, only the interaction between treatment and ejection fraction was still apparent ( $P\text{-trend}=0.02$ ), again with an attenuated response in patients with an ejection fraction  $\geq 60\%$  (Supplemental Figure II).

Empagliflozin also reduced the severity of heart failure admissions and the frequency of utilization of a broad range of interventions used for the management of decompensated heart failure. Empagliflozin decreased the time to the first heart failure hospitalization that required intensive care, and the drug also decreased the total number of such heart failure admissions (hazard ratio 0.71, 95% CI 0.52 to 0.96,  $P=0.03$ ), Table 1 and Figure 2. When compared with the placebo group, the empagliflozin group experienced fewer total hospitalizations for heart failure that required only oral or intravenous diuretics (297 vs 366), fewer hospitalizations for heart failure that required intravenous vasodilators but no vasopressor or positive inotropic agents (32 vs 65) and fewer admissions for heart failure that required a vasopressor or positive inotropic agent (45 vs 72), Table 2. When considering all hospitalizations for heart failure, the two groups were similar with respect to the mean duration of each admission for heart failure (10.8, 95% CI: 9.6-12.0 and 11.5 (95% CI: 10.0, 12.9) for placebo vs empagliflozin, respectively,  $P=0.50$ ).

### **Effect of Empagliflozin on Worsening Heart Failure Events Other Than Hospitalizations**

Patients in the empagliflozin group experienced fewer emergent/urgent care visits for worsening heart failure (298 events in the placebo group and 174 in the empagliflozin group, hazard ratio 0.55 (95% CI: 0.43–0.69),  $P< 0.0001$ ). When a worsening heart failure event is defined as

cardiovascular death, hospitalization for heart failure or an emergent/urgent heart failure visit requiring intravenous treatment, there were 546 events in the placebo group and 432 events in the empagliflozin group, reflecting a 23% lower risk of a worsening heart failure event with empagliflozin (hazard ratio 0.77, 95% CI 0.67 to 0.87),  $P < 0.0001$ , Table 1. The benefit of empagliflozin on this endpoint first reached statistical significance at 18 days after randomization and maintained significance thereafter, Figure 3.

As compared with placebo, fewer patients in the empagliflozin group reported outpatient intensification of diuretics since the prior study visit (482 vs 610), and there were fewer total study visits that reported interval outpatient diuretic intensification in the empagliflozin group (626 vs 838), Tables 1 and 2. Conversely, the empagliflozin group had more patients (424 vs 358) and more study visits (519 vs 445) where the dose of diuretics was reported to have been reduced. Empagliflozin prolonged the time to the first study visit that reported interval outpatient diuretic intensification (hazard ratio 0.76, 95% CI 0.67 to 0.86,  $P < 0.0001$ ) as well as the total number of study visits that reported interval outpatient intensification of diuretics since the prior visit (hazard ratio 0.73, 95% CI 0.65 to 0.82,  $P < 0.0001$ ), Table 1 and Figure 4.

In general, at each prespecified study visit, patients in the empagliflozin group were at 20-50% greater odds of having a less severe NYHA functional class than patients in the placebo group, Table 3. This treatment difference was nearly significant at week 4 ( $P=0.06$ ) and was statistically significant at all time points from 12 weeks through 148 weeks following randomization (Table 3).

Serial changes in laboratory tests and vital signs are shown in Figures III, IV, V, VI and VII in the Supplement. Treatment with empagliflozin was accompanied by small decreases in N-terminal proBNP after 4 weeks, and the effect increased in magnitude over time.

Empagliflozin produced significant increases in hematocrit and decreases in uric acid, which were apparent as early as 4 weeks after randomization and were maintained for more than 24 months. Patients treated with empagliflozin experienced an early and sustained decrease in body weight and systolic blood pressure, which averaged somewhat greater than 1 kg and 2 mm Hg, respectively.

## Discussion

As previously reported, in the EMPEROR-Preserved trial, empagliflozin reduced the risk of cardiovascular death or hospitalization for heart failure by 21% ( $P < 0.001$ ), an effect that was related primarily to reduction in hospitalizations for heart failure.<sup>25</sup> Herein, we show that, when the analysis is expanded to include all deaths and all hospitalizations regardless of attribution, the effect of empagliflozin on morbidity and mortality remained statistically significant ( $P = 0.025$ ). However, as expected, the magnitude of the effect on hospitalization diminished when the focus of the analysis broadened beyond heart failure events, decreasing from a 27% risk reduction for total heart failure hospitalizations to 16% risk reduction for total cardiovascular hospitalizations to 7% risk reduction for total hospitalizations for any reason. This decline is expected whenever hospitalizations that are not particularly influenced by a treatment are added in a stepwise manner to the analysis of events in a trial of patients with heart failure and a preserved ejection fraction, in whom only 46% of the hospital admissions are related to a cardiovascular reason and only 18% are related to worsening heart failure.

Empagliflozin reduced the risk of hospitalization for heart failure, whether the analysis was broadened to investigator-identified events or focused on adjudicated events. The hospitalizations that were prevented by treatment with empagliflozin involved admissions that

were treated only with oral or intravenous diuretics as well as hospitalizations that required therapy with intravenous vasopressors or positive inotropic agents or that necessitated intensive care. These benefits of SGLT2 inhibition were seen in time-to-first-event analyses and in the analysis of total (first and recurrent) events; the number of patients who were hospitalized once or multiple times was fewer in the empagliflozin group than in the placebo group. Empagliflozin reduced the total number of hospitalizations for heart failure that involved admission to intensive care by 29% (hazard ratio 0.71; 95% CI: 0.52 – 0.96) and the total number of admissions for any reason that required intravenous vasopressors or positive inotropic drugs by 27% (hazard ratio 0.73; 95% CI: 0.55 – 0.97). The lower risk of hospital admissions did not result in a longer length of stay when patients in the empagliflozin group were hospitalized for heart failure.

In addition to these inpatient events, treatment with empagliflozin had an important effect to mitigate worsening heart failure events in the outpatient setting. There were fewer emergent/urgent care visits for worsening heart failure in the empagliflozin group than in the placebo group. Additionally, SGLT2 inhibition reduced the number of study visits that reported diuretic intensification for worsening heart failure by 25%, and at the same time, empagliflozin led to a 17% increase in the number of study visits that reported a decrease in dose of diuretics. Moreover, patients in the empagliflozin group had a 20-50% higher odds of having a better NYHA functional class, and these benefits were apparent early in treatment and were sustained for the duration of double-blind therapy. An early symptom effect is concordant with our finding on clinical events, i.e., when worsening heart failure was defined in a manner similar to the primary endpoint of the DAPA-HF trial (e.g., cardiovascular death, hospitalization for heart failure or an emergent or urgent heart failure visit requiring intravenous treatment),<sup>27</sup> a benefit of empagliflozin was apparent (hazard ratio 0.77; 95% CI: 0.67–0.87) and first reached statistical

significance at 18 days after randomization and remained significant for the duration of follow-up. This finding of early benefits is similar to that which we and others have reported with SGLT2 inhibitors in patients with heart failure and a reduced ejection fraction.<sup>15,27</sup>

The effects of empagliflozin on inpatient and outpatient worsening heart failure events was largely consistent across our predefined subgroups. We noted a possible influence of concomitant treatment with mineralocorticoid receptor antagonists in an analysis of the effect of empagliflozin on total heart failure hospitalizations, but this interaction was no longer apparent when we broadened the analysis to all cardiovascular hospitalizations. In contrast, ejection fraction influenced the magnitude of the effect of empagliflozin when the analysis focused on total hospitalizations for heart failure (P-trend =0.008) or on all cardiovascular hospitalizations (P-trend =0.02). These findings are concordant with our yet-to-be-published observations that the effect of empagliflozin to reduce the risk of heart failure hospitalization is similar in magnitude across a broad range of ejection fractions ranging from < 25% to <65% but appears to be attenuated in patients with an ejection fraction of 65% or greater. Further characterization of patients with heart failure and high-normal ejection fractions is warranted.

The mechanisms by which empagliflozin reduces inpatient and outpatient worsening heart failure events are not well understood. Although the early benefits of empagliflozin to prevent clinical deterioration may suggest the possibility of a natriuretic effect,<sup>28</sup> the magnitude of such an action is typically modest and short-lived.<sup>29-31</sup> Conventional diuretics typically produce immediate declines in natriuretic peptides, generally without a change in hematocrit. In contrast, the early effect of empagliflozin on natriuretic peptides was very small in our trial, and hematocrit increased (presumably as a result of erythrocytosis<sup>32</sup>), a pattern similar to that seen with empagliflozin in patients with heart failure and a reduced ejection fraction.<sup>15</sup> Many patients



with heart failure and a preserved ejection fraction are hypertensive, and systolic blood pressure decreased modestly with empagliflozin. Yet, sacubitril/valsartan produces greater decreases in blood pressure, but more modest decreases in the risk of hospitalization and emergent/urgent care visits.<sup>33-35</sup> Obesity can play an important role in heart failure and a preserved ejection fraction,<sup>36,37</sup> but the decline in body weight with empagliflozin was too small to mitigate the influence of adiposity. Finally, inflammation and oxidative stress have been implicated in the pathogenesis of heart failure and a preserved ejection fraction,<sup>38,39</sup> and empagliflozin produced meaningful and sustained decreases in uric acid, a marker of oxidative stress.<sup>40</sup> SGLT2 inhibitors have been shown to ameliorate inflammation and oxidative stress in experimental heart failure and a preserved ejection fraction.<sup>41,42</sup> The importance of these mechanisms in the clinical setting remain to be fully explored.



The findings of the current study should be interpreted in light of its strengths and limitations. This trial is the largest randomized double-blind controlled trial in patients with heart failure and a preserved ejection fraction, and we prospectively collected information on inpatients and outpatient worsening heart failure events; the outpatient clinical course of these patients has not been well-characterized to date. However, noninvasive assessment of cardiac structure and function were not standardized or interpreted in a central laboratory. Thus, we were not able to explore the heterogeneity of this patient population, and our measurements of ejection fraction are subject to the variability typically seen in clinical practice.

In conclusion, in patients with heart failure and a preserved ejection fraction, SGLT2 inhibition with empagliflozin produced a meaningful, early and sustained reduction in the risk and severity of a broad range of inpatient and outpatient worsening heart failure events. These benefits included a decrease in the need for hospitalizations requiring aggressive therapy, a

diminution of worsening events requiring intensification of diuretics, and an increased likelihood of functional class improvement, effects that were maintained for more than 2 years of double-blind treatment.

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### Conflict of Interest Disclosures

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## Supplemental Material

### Supplemental Figure I

Total (first and recurrent) hospitalizations for worsening heart failure, by subgroups

### Supplemental Figure II

Total cardiovascular hospitalizations, by subgroups

### Supplemental Figure III

Changes in hematocrit during double-blind treatment in the placebo and empagliflozin groups

### Supplemental Figure IV

Changes in uric acid during double-blind treatment in the placebo and empagliflozin groups

### Supplemental Figure V

Changes in body weight during double-blind treatment in the placebo and empagliflozin groups

**Supplemental Figure VI**

Changes in N-terminal proBNP during double-blind treatment in the placebo and empagliflozin groups

**Supplemental Figure VII**

Changes in systolic blood pressure during double-blind treatment in the placebo and empagliflozin groups

**References**

1. Tyl B, Lopez Sendon J, Borer JS, Lopez De Sa E, Lerebours G, Varin C, De Montigny A, Pannaux M, Komajda M. Comparison of outcome adjudication by investigators and by a central end point committee in heart failure trials: experience of the SHIFT Heart Failure Study. *Circ Heart Fail.* 2020 Jul;13(7):e006720. doi: 10.1161/CIRCHEARTFAILURE.119.006720.
2. Carson P, Fiuzat M, O'Connor C, Anand I, Plehn J, Lindenfeld JA, Silver M, White M, Miller A, Davis G, et al. Determination of hospitalization type by investigator case report form or adjudication committee in a large heart failure clinical trial ( $\beta$ -Blocker Evaluation of Survival Trial [BEST]). *Am Heart J.* 2010;160:649-54.
3. Cleland JG. How to assess new treatments for the management of heart failure: composite scoring systems to assess the patients' clinical journey. *Eur J Heart Fail.* 2002;4:243-7.
4. Cleland JG, Charlesworth A, Lubsen J, Swedberg K, Remme WJ, Erhardt L, Di Lenarda A, Komajda M, Metra M, Torp-Pedersen C, et al. A comparison of the effects of carvedilol and metoprolol on well-being, morbidity, and mortality (the "patient journey") in patients with heart failure: a report from the Carvedilol Or Metoprolol European Trial (COMET). *J Am Coll Cardiol.* 2006;47:1603-11.
5. Mallick A, Gandhi PU, Gaggin HK, Ibrahim N, Januzzi JL. The importance of worsening heart failure in ambulatory patients: definition, characteristics, and effects of amino-terminal pro-B-type natriuretic peptide guided therapy. *JACC Heart Fail.* 2016;4:749-55.
6. Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Solomon SD, et al. Importance of clinical worsening of heart failure treated in the outpatient setting: evidence from the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF). *Circulation.* 2016 ;133:2254-62.
7. Skali H, Dwyer EM, Goldstein R, Haigney M, Krone R, Kukin M, Lichstein E, McNitt S, Moss AJ, Pfeffer MA, et al. Prognosis and response to therapy of first inpatient and outpatient heart failure event in a heart failure clinical trial: MADIT-CRT. *Eur J Heart Fail.* 2014;16:560-5.



8. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME trial investigators. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME trial. *Eur Heart J*. 2016;37:1526-34
9. Rådholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, Fulcher G, Barrett TD, Shaw W, Desai M, et al. canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS program. *Circulation*. 2018;138:458-468.
10. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, Kuder J, Murphy SA, Bhatt DL, Leiter LA, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation*. 2019;139:2528-2536.
11. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436-1446.
12. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295-2306.
13. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, Charbonnel B, Frederich R, Gallo S, Cosentino F, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020;383:1425-1435.
14. Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Inzucchi SE, Kosiborod MN, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med*. 2021;384:129-139.
15. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, Carson P, Anand I, Doehner W, Haass M, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. *Circulation*. 2021;143:326-336.
16. Docherty KF, Jhund PS, Anand I, Bengtsson O, Böhm M, de Boer RA, DeMets DL, Desai AS, Drozd J, Howlett J, et al. Effect of dapagliflozin on outpatient worsening of patients with heart failure and reduced ejection fraction: a prespecified analysis of DAPA-HF. *Circulation*. 2020;142:1623-1632.
17. Jackson AM, Dewan P, Anand IS, Bělohávek J, Bengtsson O, de Boer RA, Böhm M, Boulton DW, Chopra VK, DeMets DL, et al. Dapagliflozin and diuretic use in patients with heart failure and reduced ejection fraction in DAPA-HF. *Circulation*. 2020;142:1040-1054.
18. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Voors AA, Metra M, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384:117-128.
19. Desai RJ, Mahesri M, Chin K, Levin R, Lahoz R, Studer R, Vaduganathan M, Paterno E. Epidemiologic characterization of heart failure with reduced or preserved ejection fraction populations identified using Medicare claims. *Am J Med*. 2021;134:e241-e251. doi: 10.1016/j.amjmed.2020.09.038.
20. Kapłon-Cieślicka A, Laroche C, Crespo-Leiro MG, Coats AJS, Anker SD, Filippatos G, Maggioni AP, Hage C, Lara-Padrón A, Fucili A, et al; Heart Failure Association (HFA) of the European Society of Cardiology (ESC) and the ESC Heart Failure Long-Term Registry Investigators. Is heart failure misdiagnosed in hospitalized patients with

- preserved ejection fraction? From the European Society of Cardiology - Heart Failure Association EURObservational Research Programme Heart Failure Long-Term Registry. *ESC Heart Fail.* 2020;7:2098-2112.
21. Goyal P, Loop M, Chen L, Brown TM, Durant RW, Safford MM, Levitan EB. Causes and temporal patterns of 30-day readmission among older adults hospitalized with heart failure with preserved or reduced ejection fraction. *J Am Heart Assoc.* 2018 Apr 23;7(9):e007785. doi: 10.1161/JAHA.117.007785.
  22. Vaduganathan M, Patel RB, Michel A, Shah SJ, Senni M, Gheorghiade M, Butler J. Mode of death in heart failure with preserved ejection fraction. *J Am Coll Cardiol.* 2017;69:556-569.
  23. Lund LH, Donal E, Oger E, Hage C, Persson H, Haugen-Löfman I, Ennezat PV, Sportouch-Dukhan C, Drouet E, Daubert JC, et al. Association between cardiovascular vs. non-cardiovascular co-morbidities and outcomes in heart failure with preserved ejection fraction. *Eur J Heart Fail.* 2014;16:992-1001.
  24. Anker SD, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, Kimura K, Zeller C, George J, Brueckmann M, Zannad F, Packer M; EMPEROR-Preserved Trial Committees and Investigators. 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;21:1279-1287.
  25. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca H-P, Choi D-J, Chopra V, Chuquiure E, Giannetti N, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; DOI: 10.1056/NEJMoa2107038
  26. Rogers JK, Yaroshinsky A, Pocock SJ, Stokar D, Pogoda J. Analysis of recurrent events with an associated informative dropout time: application of the joint frailty model. *Stat Med* 2016;35:2195-2205.
  27. Berg DD, Jhund PS, Docherty KF, Murphy SA, Verma S, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sjöstrand M, Solomon SD, McMurray JJV, Sabatine MS. Time to clinical benefit of dapagliflozin and significance of prior heart failure hospitalization in patients with heart failure with reduced ejection fraction. *JAMA Cardiol.* 2021;6:499-507.
  28. Borges-Júnior FA, Silva Dos Santos D, Benetti A, Polidoro JZ, Wisnivesky ACT, Crajoinas RO, Antônio EL, Jensen L, Caramelli B, Malnic G, Tucci PJ, Girardi ACC. Empagliflozin inhibits proximal tubule NHE3 activity, preserves GFR, and restores euvolemia in nondiabetic rats with induced heart failure. *J Am Soc Nephrol.* 2021 Apr 12:ASN.2020071029. doi: 10.1681/ASN.2020071029.
  29. Yasui A, Lee G, Hirase T, Kaneko T, Kaspers S, von Eynatten M, Okamura T. Empagliflozin induces transient diuresis without changing long-term overall fluid balance in Japanese patients with type 2 diabetes. *Diabetes Ther.* 2018;9:863-871.
  30. Sha S, Polidori D, Heise T, Natarajan J, Farrell K, Wang SS, Sica D, Rothenberg P, Plum-Mörschel L. Effect of the sodium glucose co-transporter 2 inhibitor canagliflozin on plasma volume in patients with type 2 diabetes mellitus. *Diabetes Obes Metab.* 2014;16:1087-1095.
  31. Ohara K, Masuda T, Murakami T, Imai T, Yoshizawa H, Nakagawa S, Okada M, Miki A, Myoga A, Sugase T, et al. Effects of the sodium-glucose cotransporter 2 inhibitor

- dapagliflozin on fluid distribution: A comparison study with furosemide and tolvaptan. *Nephrology (Carlton)*. 2019;24:904-911.
32. Mazer CD, Hare GMT, Connelly PW, Gilbert RE, Shehata N, Quan A, Teoh H, Leiter LA, Verma S. Effect of empagliflozin on erythropoietin levels, iron stores, and red blood cell morphology in patients with type 2 diabetes mellitus and coronary artery disease. *Circulation*. 2020;141:704-707.
  33. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609-1620.
  34. Vaduganathan M, Cunningham JW, Claggett BL, Causland FM, Barkoudah E, Finn P, Zannad F, Pfeffer MA, Rizkala AR, Sabarwal S, et al. Worsening heart failure episodes outside a hospital setting in heart failure with preserved ejection fraction: the PARAGON-HF trial. *JACC Heart Fail*. 2021;9:374-382.
  35. Packer M, Zannad F, Anker SD. Heart failure and a preserved ejection fraction: a side-by-side examination of the PARAGON-HF and EMPEROR-Preserved trials. *Circulation*. 2021; DOI: 10.1161/CIRCULATIONAHA.121.056657
  36. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation*. 2017;136:6-19.
  37. Packer M, Kitzman DW. Obesity-related heart failure with a preserved ejection fraction: the mechanistic rationale for combining inhibitors of aldosterone, neprilysin, and sodium-glucose cotransporter-2. *JACC Heart Fail*. 2018;6:633-639.
  38. Packer M, Lam CSP, Lund LH, Maurer MS, Borlaug BA. Characterization of the inflammatory-metabolic phenotype of heart failure with a preserved ejection fraction: a hypothesis to explain influence of sex on the evolution and potential treatment of the disease. *Eur J Heart Fail*. 2020;22:1551-1567.
  39. Hage C, Löfgren L, Michopoulos F, Nilsson R, Davidsson P, Kumar C, Ekström M, Eriksson MJ, Lyngå P, Persson B, et al. Metabolomic profile in HFpEF vs HFrEF patients. *J Card Fail*. 2020;26:1050-1059.
  40. Packer M. Uric acid is a biomarker of oxidative stress in the failing heart: lessons learned from trials with allopurinol and SGLT2 inhibitors. *J Card Fail*. 2020;26:977-984.
  41. Cappetta D, De Angelis A, Ciuffreda LP, Coppini R, Cozzolino A, Micciché A, Dell'Aversana C, D'Amario D, Cianflone E, Scavone C, et al. Amelioration of diastolic dysfunction by dapagliflozin in a non-diabetic model involves coronary endothelium. *Pharmacol Res*. 2020 Jul;157:104781. doi: 10.1016/j.phrs.2020.104781.
  42. Juni RP, Kuster DWD, Goebel M, Helmes M, Musters RJP, van der Velden J, Koolwijk P, Paulus WJ, van Hinsbergh VWM. Cardiac microvascular endothelial enhancement of cardiomyocyte function is impaired by inflammation and restored by empagliflozin. *JACC Basic Transl Sci*. 2019;4:575-591.



**Table 1.** Major Outcomes and Worsening Heart Failure Events

Variable	Placebo (n=2991)		Empagliflozin (n=2997)		Hazard ratio (95% CI)	P value
		<i>Events/100 patient-yr</i>		<i>Events/100 patient-yr</i>		
<b>All-cause and cardiovascular outcomes</b>						
Time to all-cause mortality or hospitalization for heart failure	662 (22.1)	11.2	581 (19.4)	9.6	0.85 (0.76 – 0.95)	0.005
Time to all-cause mortality or cardiovascular hospitalization	967 (32.3)	18.1	888 (29.6)	16.1	0.89 (0.81 – 0.98)	0.014
Time to all-cause mortality or hospitalization for any reason	1431 (47.8)	31.2	1356 (45.2)	28.6	0.92 (0.85 – 0.99)	0.025
Time to first hospitalization for cardiovascular reason	765 (25.6)	14.3	669 (22.3)	12.2	0.85 (0.77 – 0.94)	0.002
Time to first hospitalization for any reason	1340 (44.8)	29.2	1271 (42.4)	26.8	0.92 (0.85 – 0.99)	0.032
Total (first and recurrent) number of cardiovascular hospitalizations	1333		1145		0.84 (0.74 – 0.95)	0.005
Total (first and recurrent) number of hospitalizations for any reason	2769		2566		0.93 (0.85 – 1.01)	0.101
Total hospitalizations requiring intravenous diuretics	727		516		0.67 (0.57 – 0.79)	<0.0001
Total hospitalizations requiring intravenous vasopressors or positive inotropic drugs	140		102		0.73 (0.55 – 0.97)	0.033
<b>Worsening heart failure events</b>						
<b><i>Worsening heart failure requiring hospitalization</i></b>						
Time to first adjudicated hospitalization for heart failure	352 (11.8)	6.0	259 (8.6)	4.3	0.71 (0.60 – 0.83)	<0.0001
Time to first adjudicated hospitalizations for heart failure requiring IV vasopressor or positive inotropic drugs	54 (1.8)	0.9	37 (1.2)	0.6	0.67 (0.44 – 1.02)	0.065
Time to first adjudicated hospitalization for heart failure requiring CCU/ICU care	94 (3.1)	1.5	68 (2.3)	1.1	0.71 (0.52 – 0.97)	0.032
Total (first and recurrent) number of adjudicated hospitalizations for heart failure	541		407		0.73 (0.61 – 0.88)	0.0009

Total adjudicated hospitalizations for heart failure requiring IV vasopressor or positive inotropic drugs	72		45		0.62 (0.41 – 0.92)	0.019
Total adjudicated hospitalizations for heart failure requiring CCU/ICU care	117		86		0.71 (0.52 – 0.96)	0.028
Time to first investigator-identified hospitalization for heart failure	485 (16.2)	8.5	362 (12.1)	6.1	0.72 (0.63 – 0.82)	<0.0001
<b><i>Worsening heart failure requiring emergency or urgent care</i></b>						
Time to first emergency or urgent care visit for worsening heart failure requiring IV therapy	215 (7.2)	3.5	136 (4.5)	2.2	0.61 (0.50 – 0.76)	<0.0001
Time to adjudicated hospitalization for heart failure or emergent or urgent care for heart failure requiring IV therapy	393 (13.1)	6.7	280 (9.3)	4.7	0.69 (0.59 – 0.80)	<0.0001
Time to cardiovascular mortality, adjudicated hospitalization for heart failure or emergent or urgent care for heart failure requiring IV therapy	546 (18.3)	9.3	432 (14.4)	7.2	0.77 (0.67 – 0.87)	<0.0001
<b><i>Worsening heart failure requiring outpatient intensification of diuretics</i></b>						
Time to first study visit that reported interval outpatient intensification of diuretics	610 (20.4)	11.1	482 (16.1)	8.5	0.76 (0.67 – 0.86)	<0.0001
Total (first and recurrent) study visits that reported interval outpatient intensification of diuretics	838		626		0.73 (0.65 – 0.82)	<0.0001
Time to adjudicated hospitalization for heart failure, emergent or urgent care for heart failure requiring IV therapy, or interval outpatient intensification of diuretics	813 (27.2)	15.5	635 (21.2)	11.5	0.74 (0.67 – 0.82)	<0.0001

To avoid double-counting, the total number of emergent/urgent care visits and hospitalizations for heart failure were not summated, since many emergent/urgent care were followed within 1-2 days by admission to a hospital for the same clinical event. All events that are not designated as being adjudicated were investigator-identified. For time-to-first-event analyses, differences between the placebo and empagliflozin groups were assessed using a Cox proportional hazards model, adjusting for covariates of age, gender, geographical region, diabetes status at baseline, left ventricular ejection fraction, and estimated glomerular filtration rate at baseline. For the analysis of total (first and repeated) events, between-group differences were assessed using a joint frailty model, with cardiovascular death (for endpoints including heart failure events) or all-cause mortality (for endpoints including all-cause hospitalisation) as competing risks and using the covariates that were used for the time-to-first event analyses. No adjustment was made for multiplicity of comparisons.

**Table 2.** Occurrence of Worsening Heart Failure Events

	Placebo	Empagliflozin
<b>Adjudicated hospitalizations for heart failure</b>		
Patients hospitalized once	243	181
Patients hospitalized twice	67	49
Patients hospitalized $\geq 3$ times	42	29
<b>Total (first and recurrent) adjudicated hospitalizations for heart failure</b>		
Number of hospitalizations requiring only oral or intravenous diuretics	366	297
Number of hospitalizations requiring IV vasodilators	65	32
Number of hospitalizations requiring IV vasopressors or positive inotropic drugs	72	45
<b>Total (first and recurrent) emergent or urgent care visits for heart failure requiring intravenous therapy</b>		
Patients who required emergent or urgent care once	165	110
Patients who required emergent or urgent care twice	31	20
Patients who required emergent or urgent care $\geq 3$ times	19	6
<b>Outpatient changes in diuretic dose since prior study visit</b>		
Number of patients who had diuretics were intensified since prior study visit	610	482
Total number of study visits that reported that the dose of diuretics had been intensified since prior study visit	838	626
Number of patients who had reduction in the dose of diuretics since prior study visit	358	424
Total number of study visits that reported that the dose of diuretics had been reduced since prior study visit	445	519

Categories are ordered according to severity of intervention, with each category including less intensive but excluding more intensive interventions, i.e., use of intravenous vasodilators includes the use of diuretics, but excludes the use of intravenous positive inotropic drugs or vasopressors. A total of 38 patients in the placebo group and 32 in empagliflozin group did not have complete information on the utilization of drug or non-drug interventions during hospitalization or received only non-drug treatments during hospitalization.

**Table 3.** Odds Ratios (Empagliflozin: Placebo) for a Less Severe New York Heart Association Functional Class at Planned Study Visits (Partial Proportional Odds Model), Without Imputation

	Placebo (n=2991)	Empagliflozin (n=2997)	Odds ratio (95% CI) P value
At 4 weeks	2945	2967	1.17 (0.99, 1.37) P=0.063
At 12 weeks	2896	2924	1.23 (1.07, 1.41) P=0.004
At 32 weeks	2780	2792	1.30 (1.14, 1.49) P< 0.0001
At 52 weeks	2683	2689	1.37 (1.20, 1.57) P< 0.0001
At 76 weeks	2423	2390	1.43 (1.24, 1.64) P< 0.0001
At 100 weeks	1857	1833	1.21 (1.04, 1.41) P=0.016
At 124 weeks	1306	1319	1.33 (1.11, 1.60) P=0.002
At 148 weeks	778	779	1.48 (1.17, 1.88) P=0.001

Shown are odds ratios, 95% confidence intervals and P values for each study visit. No imputation was used for patients who died, were lost to follow-up or withdrew consent.



Circulation

## Figure Legends

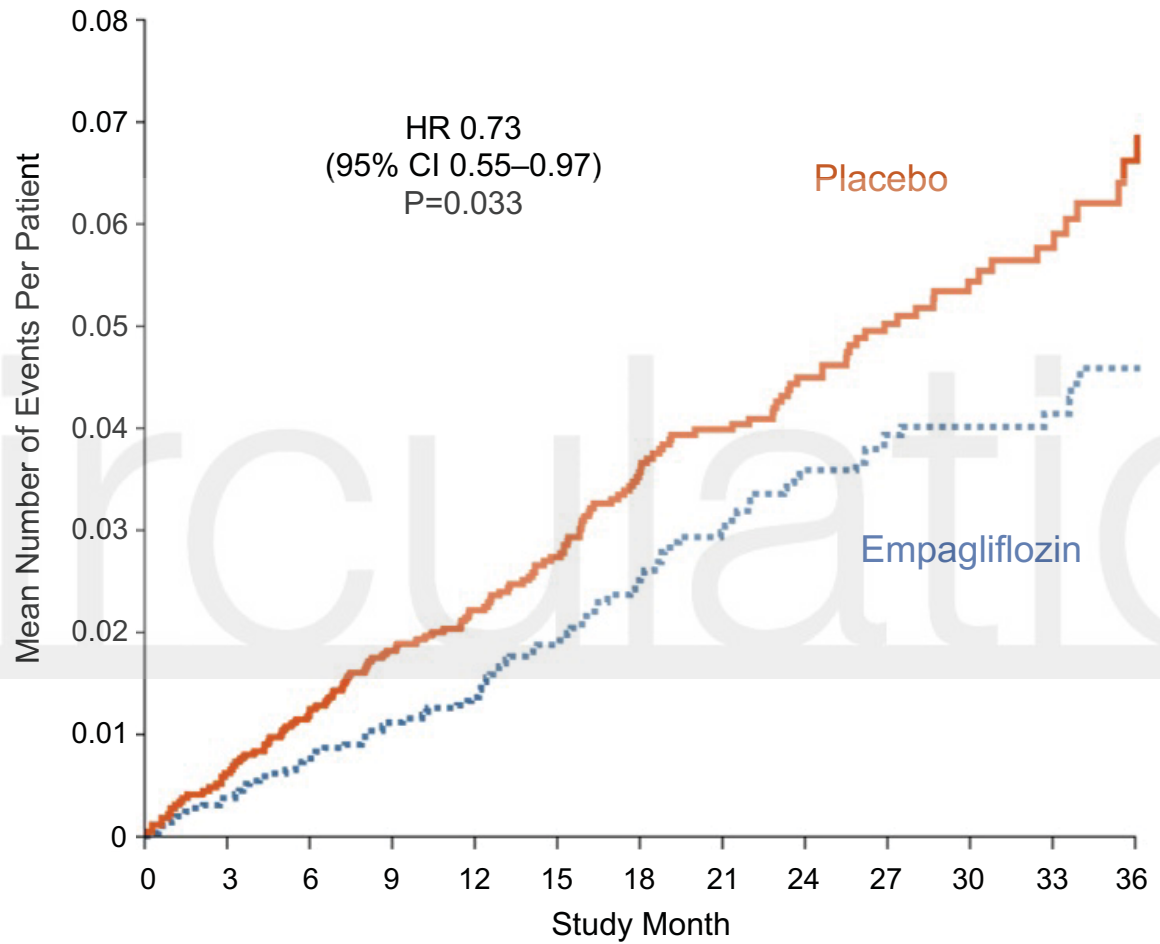
**Figure 1. Total (first and recurrent) hospitalizations for any reason that required intravenous vasopressors or positive inotropic agents.** Shown are mean cumulative function curves for placebo (shown in red) and for empagliflozin (shown in blue). CI = confidence interval; HR = hazard ratio.

**Figure 2. Total (first and recurrent) adjudicated heart failure hospitalizations requiring admission to CCU or ICU in in the placebo and empagliflozin groups.** Shown are mean cumulative function curves for placebo (shown in red) and for empagliflozin (shown in blue). CCU = cardiac care unit; CI = confidence interval; HR = hazard ratio; ICU = intensive care unit.

**Figure 3. Time of first statistical significance in time-to-first-event analysis of cardiovascular death, hospitalization for heart failure or emergent/urgent heart failure visit requiring intravenous treatment for worsening heart failure.** To determine the time point when statistical significance was reached and maintained for the first time, Cox regression models were fitted and sequentially censoring at increasing number of days since randomization, yielding a continuous display of hazard ratios with confidence bands.

**Figure 4. Total number of outpatient visits reporting interval intensification of diuretics for worsening heart failure.** Shown are mean cumulative function curves for placebo (shown in red) and for empagliflozin (shown in blue). CCU = cardiac care unit; CI = confidence interval; HR = hazard ratio; ICU = intensive care unit.

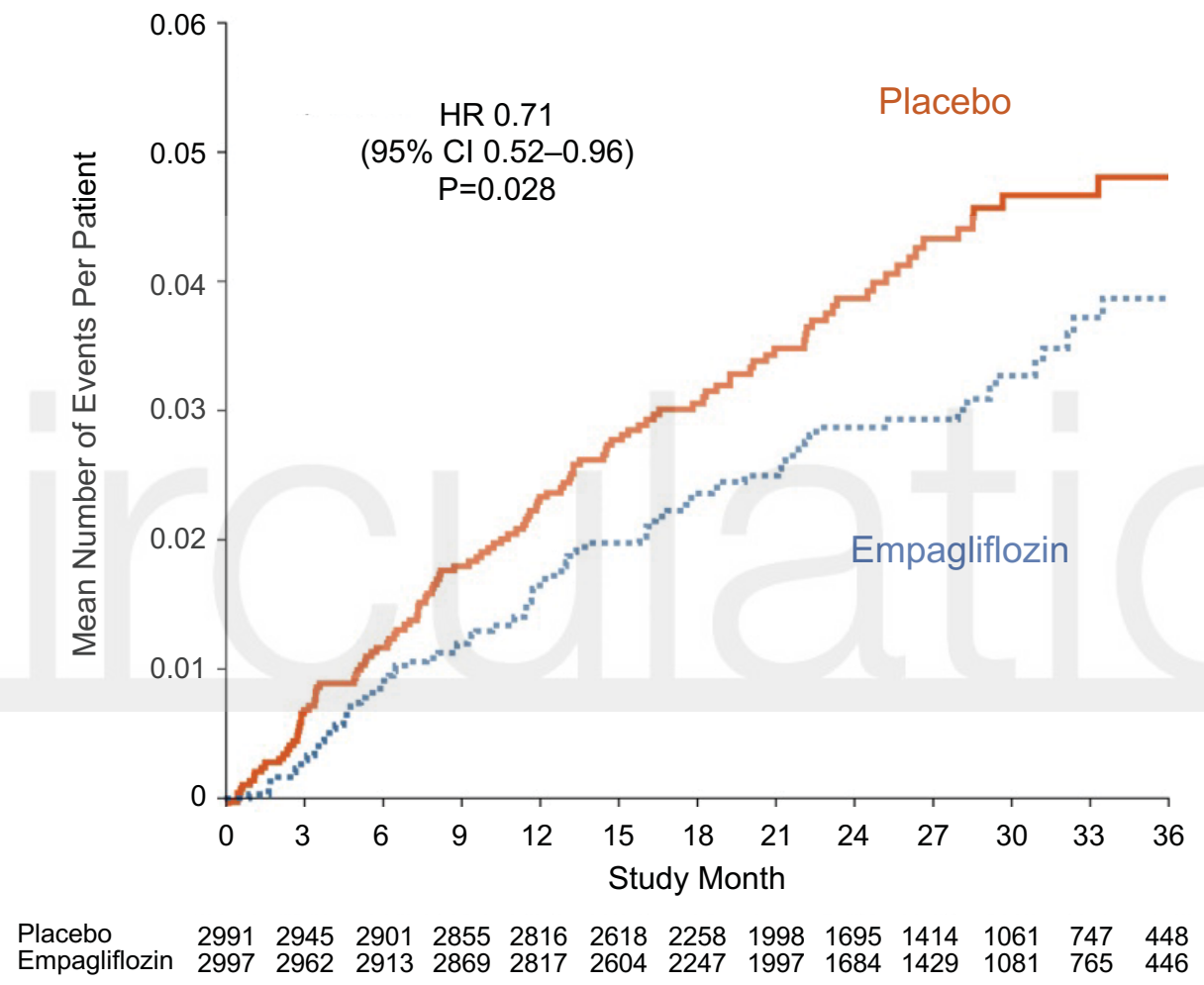
Figure 1



Circulation

Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1997	1684	1429	1081	765	446

Figure 2



Circulation

Figure 3

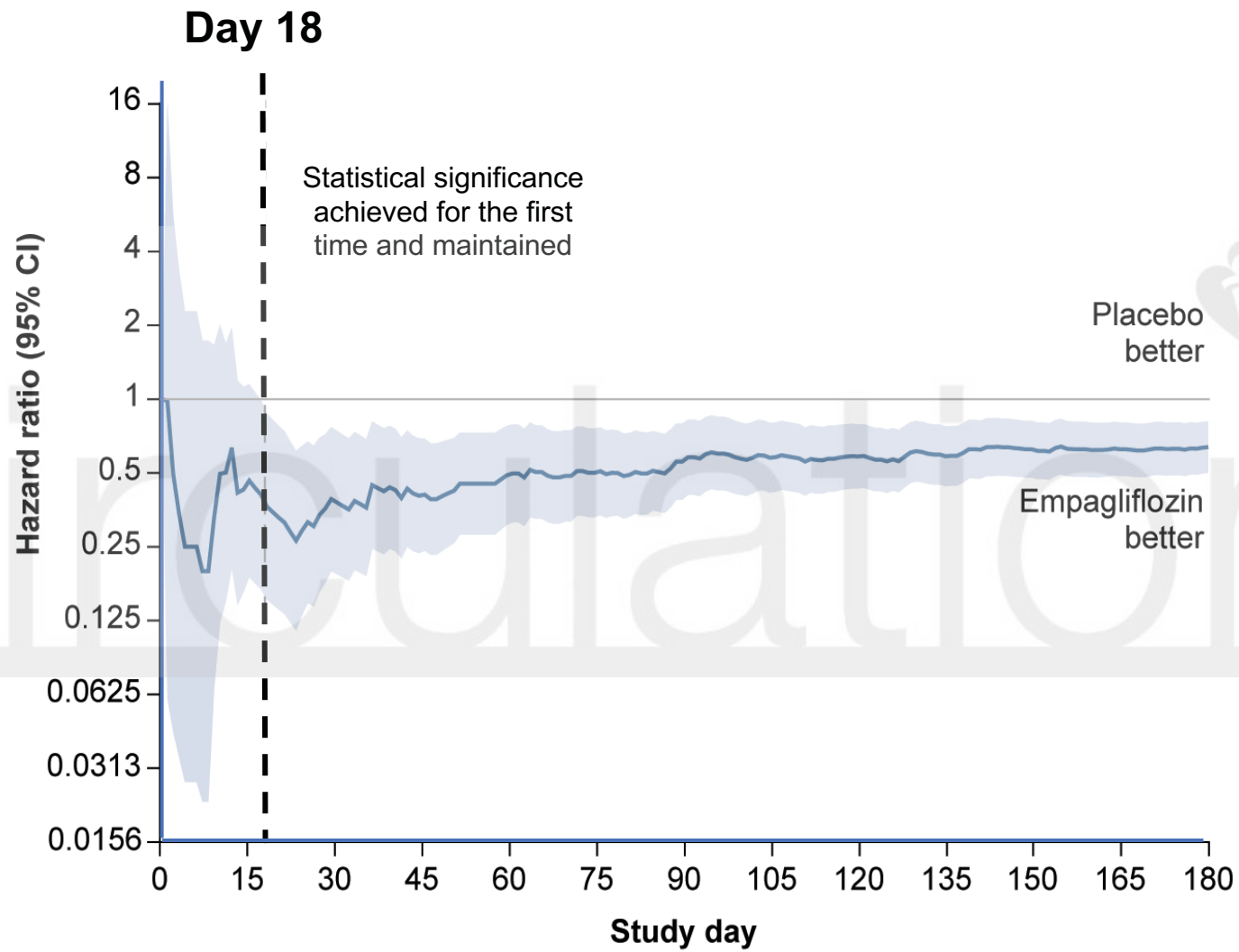
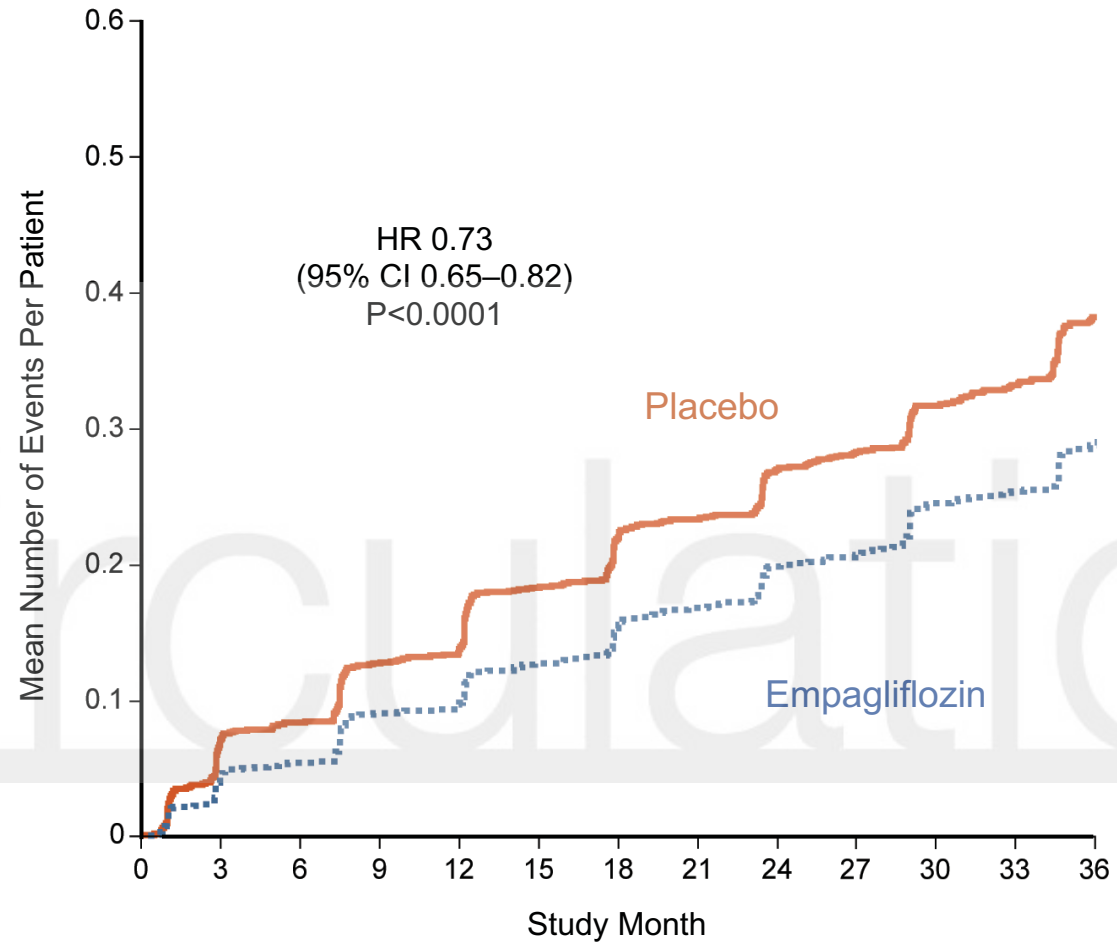




Figure 4



Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1997	1684	1429	1081	765	446



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