10.1161/CIRCULATIONAHA.120.051824

Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status – Results from the EMPEROR-Reduced Trial

Running Title: *Anker et al,; Empagliflozin in HFrEF with or without Diabetes*

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*This manuscript was sent to Jeffrey M. Testani, MD, MTR, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Abstract

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors improve outcomes in patients with heart failure with reduced ejection fraction, but additional information is needed about whether glycemic status influences the magnitude of their benefits on heart failure and renal events.

Methods: Patients with class II–IV heart failure and a left ventricular ejection fraction ≤40% were randomized to receive empagliflozin (10 mg daily) or placebo in addition to recommended therapy. We prespecified a comparison of the effect of empagliflozin in patients with and without diabetes.

Results: Of the 3730 patients enrolled, 1856 (50%) had diabetes, 1268 (34%) had prediabetes (HbA1c 5.7–6.4%), and 606 (16%) had normoglycemia (HbA1c <5.7%). The risks of the primary outcome (cardiovascular death or hospitalization for heart failure), total hospitalizations for heart failure, and adverse renal outcomes were higher in patients with diabetes, but were similar between patients with prediabetes and normoglycemia. Empagliflozin reduced the risk of the primary outcome in patients with and without diabetes (hazard ratio 0.72 [95% CI 0.60–0.87] and 0.78 [95% CI 0.64–0.97], respectively, interaction P =0.57). Patients with and without diabetes also did not differ with respect to the effect of empagliflozin on total hospitalizations for heart failure, on the decline in estimated glomerular filtration rate over time, and on the risk of serious adverse renal outcomes. Among these endpoints, the effects of the drug did not differ in patients with prediabetes or normoglycemia. When analyzed as a continuous variable, baseline HbA1c did not significantly modify the benefits of empagliflozin on the primary outcome (P-interaction=0.40). Empagliflozin did not lower HbA1c in patients with prediabetes or normoglycemia and was not associated with increased risk of hypoglycemia.

Conclusions: In the EMPEROR-Reduced trial, empagliflozin significantly improved cardiovascular and renal outcomes in patients with heart failure and a reduced ejection fraction, independent of baseline diabetes status and across the continuum of HbA1c.

Clinical Trial Registration: URL: https://www.clinicaltrials.gov. Unique identifier: NCT03057977

Key Words: empagliflozin; heart failure; diabetes; cardio-renal outcomes

Non-Standard Abbreviations and Acronyms

SGLT2	sodium-glucose co-transporter 2
DAPA-HF trial	Dapagliflozin And Prevention of Adverse Outcomes in Heart Failure trial
EMPEROR-Reduced	The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction
HbA1c	glycated hemoglobin
NYHA	New York Heart Association
NT-proBNP	N-terminal pro-hormone B-type natriuretic peptide
eGFR	estimated glomerular filtration rate
CKD-EPI	the Chronic Kidney Disease Epidemiology Collaboration
KCCQ	Kansas City Cardiomyopathy Questionnaire
CV	cardiovascular
MMRM	mixed model for repeated measures

Clinical Perspective

What is new?

- In the placebo-controlled EMPEROR-Reduced trial, the addition of empagliflozin to recommended heart failure therapy reduced the risk of cardiorenal outcomes in patients with heart failure with reduced ejection fraction with and without diabetes.
- The risks of these cardiorenal outcomes were higher in patients with diabetes, but were similar between patients with prediabetes and normoglycemia.
- These favorable heart failure and renal effects of empagliflozin were consistent in patients with or without diabetes and across the spectrum of A1C.
- Empagliflozin did not lower HbA1c in patients without diabetes and was not associated with increased risk of hypoglycemia.

What are the clinical implications?

- The heart failure and renal benefits of empagliflozin in patients with heart failure and a reduced ejection fraction are present both in patients with and without diabetes and are not influenced by baseline levels of glycated hemoglobin.
- Decisions regarding the use of empagliflozin for the treatment of heart failure and a reduced ejection fraction should not be driven by the glycemic status of individual patients.

Introduction

Unlike other anti-hyperglycemic agents, sodium-glucose co-transporter 2 (SGLT2) inhibitors have consistently shown to reduce the risk of heart failure hospitalizations and serious renal outcomes among patients with diabetes.[1-3] These substantial cardio-renal benefits cannot be explained by the anti-hyperglycemic action of SGLT2 inhibitors. Therefore, it has been suggested that SGLT2 inhibitors exert broad cardioprotective and nephroprotective effects, which would be apparent in patients with or without diabetes.[4]

In the Dapagliflozin And Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, dapagliflozin was shown to reduce the risk of worsening heart failure events and cardiovascular death independent of diabetes status.[5,6] However, the DAPA-HF trial did not comprehensively report the influence of diabetes on the renal effects of dapagliflozin or on the influence of prediabetes; furthermore, the trial enrolled primarily patients who had mild-to-moderate left ventricular systolic dysfunction and increases in natriuretic peptides. The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trial evaluated the effect of empagliflozin in patients with heart failure, including those with more severe left ventricular systolic dysfunction and more severely impaired kidney function, and the trial identified the effect of the drug on renal outcomes as a major outcome variable.[7] Empagliflozin reduced the risk of major adverse heart failure and renal outcomes, when added to inhibitors of the renin-angiotensin system and beta-blockers and regardless of background therapy with mineralocorticoid receptor antagonists and angiotensin receptor/neprilysin inhibitors.[8]

In this pre-specified analysis of the EMPEROR-Reduced trial, we analyzed the efficacy and safety of empagliflozin on heart failure and renal events by baseline diabetes status and across the range of baseline values of glycated hemoglobin (HbA1c).

Methods

Trial Design

The EMPEROR-Reduced trial was a randomized, double-blind, parallel-group, placebo-controlled, event-driven study. Patients were recruited into EMPEROR-Reduced between April 25, 2017 and November 8, 2019 at 520 centers in 20 countries. The design and conduct of this trial have been published previously .[7] The trial was approved by the ethics committee at each study site, and all patients provided written informed consent. The registration identifier at ClinicalTrials.gov is NCT03057977.

Study Patients

Participants included patients ≥18 years or older who had chronic heart failure (New York Heart Association (NYHA) functional class II, III or IV) with a left ventricular ejection fraction ≤40%. To enroll patients at increased risk of events, the number of patients with an ejection fraction >30% was limited by requiring that they had been hospitalized for heart failure within 12 months or had exceptionally high levels of N-terminal pro-hormone B-type natriuretic peptide (NT-proBNP), i.e., >1000 pg/mL or >2500 pg/mL in those with an ejection fraction of 31-35% or 36-40%, respectively; these thresholds were doubled in patients with atrial fibrillation. Patients were receiving all appropriate treatments for heart failure as available and tolerated. Exclusion criteria included symptomatic hypotension, systolic blood pressure of <100 mm Hg or ≥180 mm Hg, or an estimated glomerular filtration rate (eGFR) <20 mL/min/1.73m^2. Following a 4-28 day

screening period, patients who fulfilled eligibility criteria were randomized double-blind (in a 1:1 manner) to receive placebo or empagliflozin 10 mg daily, in addition to their usual therapy for heart failure.

For this prespecified subgroup analysis, patients were categorized as having diabetes, if they had a history of the diagnosis or if one pre-treatment HbA1c was at least 6.5% (≥48 mmol/mol). Among those without diabetes, patients were classified as having prediabetes if they had an HbA1c of 5.7 to 6.4%, and they were considered to have normoglycemia if they had all pretreatment HbA1c of <5.7%. Randomization was stratified based on glycemic status at screening (diabetes, prediabetes or normoglycemia), geographical region (North America, Latin America, Europe, Asia, other), and estimated glomerular filtration rate (eGFR by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) at screening (< or ≥60 mL/min/1.73 m^2). Following randomization, patients were periodically evaluated for efficacy, vital signs, laboratory tests and adverse events. These assessments included the Kansas City Cardiomyopathy Questionnaire (KCCQ), systolic blood pressure, hemoglobin, body weight, HbA1c, NT-proBNP and renal function.

Trial Endpoints

The primary endpoint of the EMPEROR-Reduced trial was the time-to-first-event analysis of the combined risk of cardiovascular death or hospitalization for heart failure. This analysis was based on adjudicated events, as assessed by a clinical event committee, which applied prespecified definitions and was blinded to the treatment assignment. The key secondary endpoints of the study were (1) the total number of adjudicated hospitalizations for heart failure (including first and recurrent events); and (2) the slope of the change in eGFR during double-blind treatment. We prespecified two additional assessments of renal function. First, in 966

patients, we analyzed eGFR 23-45 days following the withdrawal of the study medication at the end of double-blind treatment. Changes in eGFR from pre-randomization to the off-treatment visit allowed for an assessment of the long-term effects of treatment on renal function unconfounded by the presence of an SGLT2 inhibitor. Second, a composite renal endpoint was defined as the need for chronic dialysis or renal transplant or a ≥40% decrease in eGFR $(CKD\text{-}EPI)_{cr}$ or a sustained eGFR <15 mL/min/1.73m^2 (if the baseline eGFR was ≥30) or <10 mL/min/1.73m^2 (if the baseline eGFR was <30 mL/min/1.73m^2). In addition, we evaluated the effects of treatment on the individual components of the primary endpoint.

Changes between the treatment groups in the KCCQ clinical summary score, body weight, blood pressure, hemoglobin and glycated hemoglobin, and NT-proBNP were assessed at 52 weeks. Safety analyses included serious adverse events, adverse events leading to discontinuation of study drug, and specified adverse events of interest (hypotension, volume depletion, hypoglycemia, diabetic ketoacidosis, limb amputations, fractures, acute renal failure and genital and urinary tract infections).

Statistical Analyses

For time-to-first-event analyses, differences between the placebo and empagliflozin groups for the primary end point were assessed for statistical significance 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. These analyses were performed according to the intention-to-treat principle for all randomized patients, and included data up to the end of the planned treatment period. For the analysis of total (first and repeated) events, between-group differences were assessed using a joint frailty model, with cardiovascular (CV) death as a competing risk. For the analysis of changes in eGFR,

KCCQ scores, vital signs and laboratory measurements, treatment effects were assessed based on changes from baseline using a mixed model for repeated measures (MMRM). Between-group difference in the slope of change in eGFR were analyzed using a random intercept random slope model. KCCQ as well as eGFR slope and MMRM are analyzed using on-treatment data. The MMRM, the slope model and the joint frailty model included the same covariates as the Cox model. To assess the consistency of effects across subgroups, subgroup-by-treatment interaction terms were added in the models. Analyses for safety were performed including all the patients who had received at least one dose of empagliflozin or placebo.

According to our pre-specified statistical plan, analyses of the influence of glycemic status on the effect of empagliflozin on various outcomes and measurements were made primarily by comparing patients with or without diabetes. Additionally, analyses were performed to evaluate and compare the effect of empagliflozin in patients with diabetes, prediabetes and no glycemic disorder (which were stratification variables in the trial). We also evaluated in exploratory analyses the effect of baseline HbA1c (as a continuous variable) on the effect of empagliflozin on first heart failure hospitalization or CV death assuming a linear relationship.

All analyses were performed using SAS, version 9.4 (SAS Institute). All *P* values reported are 2-sided, and $P < 0.05$ was considered as statistically significant in all cases. No adjustments for multiple testing was made.

Data sharing

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 EMPEROR 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-ingelheim.com/transparency_policy.html).

Results

Of the 3730 patients who were randomly assigned to receive either placebo or empagliflozin, 1856 (50%) had diabetes, and of the patients without diabetes, 1268 (34%) had prediabetes and 606 (16%) were normoglycemic. When compared with patients without diabetes, those with diabetes were more likely to have a history of prior hospitalization for heart failure, NYHA functional class III symptoms, a history of hypertension, and a higher proportion of patients with eGFR<60 mL/min/1.73 m^2 (**Table 1**). Patients with prediabetes had baseline characteristics similar to those with no glycemic disorder (**Supplemental Table I**). The mean HbA1c was 7.4 ± 1.6% in patients with patients with diabetes, 5.9 ± 0.2% in patients with prediabetes, and 5.3 ± 0.3% in normoglycemic patients. 7.2% of the patients were found to have previously undiagnosed diabetes at baseline. Within each group, the baseline characteristics of the placebo and empagliflozin groups were well balanced, **Table 1 and Supplemental Table I**. The median duration of follow-up of 16 months was similar in the three groups.

The cumulative incidence curves for the primary outcome and the two key secondary outcomes by diabetes status are shown in **Figure 1-3. Figure 4** shows the cumulative incidence curves for the renal composite by diabetes status, whereas **Figure 5** shows treatment effect of empagliflozin vs. placebo on outcomes by glycemic status.

Primary Outcome and Total Hospitalizations for Heart Failure

When placebo event rates were considered, the incidence of the primary composite outcome of cardiovascular death or hospitalization for heart failure was about 40% higher in diabetic patients than in nondiabetic patients (24.6 vs 17.6 per 100 patient-years of follow-up, P<0.001; **Figure 1 and Table 2**), but there was no difference in risk between patients with prediabetes and no glycemic disorder (18.1 vs 16.6 per 100 patient-years of follow-up, P=0.63; **Figure 5**).

The effect of empagliflozin on the primary outcome variable was not influenced by the presence or absence of diabetes (P-interaction=0.57). In patients with diabetes, the primary outcome occurred in 200 of 927 (21.6%) in the empagliflozin group and 265 of 929 (28.5%) in the placebo group (hazard ratio 0.72 [95% CI 0.60–0.87]), **Table 2**. Among patients without diabetes, the primary outcome occurred in 161 of 936 (17.2%) in the empagliflozin group and 197 of 938 (21%) in the placebo group (hazard ratio 0.78 [95% CI 0.64-0.97]). Cumulative incidence plots according to treatment are shown for patients with and without diabetes in **Figures 1A and 1B**. The hazard ratios for the effect of empagliflozin on the risk of cardiovascular death or heart failure hospitalization in patients with prediabetes and in those with normoglycemia were 0.76 (95% CI 0.59–0.98) and 0.84 (95% CI 0.58–1.21), respectively (P-trend=0.48); the estimate in patients with normoglycemia was imprecise because it was based on only 114 events **(Figure 5)**. However, when considered as a continuous variable, HbA1c did not influence the effect of empagliflozin on the primary outcome when the relationship was evaluated assuming linearity (P-interaction=0.40), **Figure 2**.

A similar pattern of response was observed for total (first and recurrent) hospitalizations for heart failure. When the placebo event rates were considered, there were 337 hospitalizations for heart failure in the 1856 patients with diabetes, but only 216 in the 1874 patients without

diabetes, indicating an about 50-60% higher rate in diabetic patients. However, the rate of heart failure hospitalization in the patients with prediabetes was similar to those with normoglycemia, **Figure 5**. Empagliflozin reduced the risk of a first or recurrent heart failure hospitalization to a similar degree in both diabetic and nondiabetic patients (hazard ratio 0.65 [95% CI 0.50–0.85] and 0.76 (95% CI 0.57–1.01), respectively, **Table 2** and **Figure 3**. Among the patients without diabetes, the hazard ratios for the effect of empagliflozin on total hospitalizations for heart failure in patients with prediabetes and normoglycemia were 0.70 (95% CI 0.50–0.99) and 0.90 (95% CI 0.55–1.48), respectively; the latter estimate was imprecise because it was based on only 125 events (**Figure 5**).

Renal Outcomes

When only the placebo groups were considered, the rate of decline in eGFR in patients with diabetes was nearly twice that in patients without diabetes (–2.9 vs –1.7 mL/min/1.73 m^2 per year, P=0.02; **Table 2, Supplemental Figure I**), but there was no difference in the rate of decline in eGFR between patients with prediabetes and normoglycemia (–1.7 vs –1.8 mL/min/1.73 m^2 per year, respectively) (**Supplemental Figure I**). Furthermore, when the study medication was withdrawn to assess the effects of double-blind treatment unconfounded by the presence of an SGLT2 inhibitor, in those allocated to placebo, eGFR declined over a median of 16 months by 3.0 mL/min/1.73 m^2 in patients with prediabetes (n=194) and by 3.5 mL/min/1.73 m^2 in those with normoglycemia and by 5.4 mL/min/1.73 m^2 in patients with diabetes. The incidence of the composite renal outcome was 4.2, 1.9 and 2.2 events per 100 patient-years of follow-up in the patients with diabetes, prediabetes and normoglycemia, respectively (**Figure 5**). For the latter two analyses, the decline in renal function and the incidence of adverse renal

outcomes in the placebo group were greater in patients with diabetes, but were similar in patients with prediabetes and normoglycemia.

In light of the more rapid decline in glomerular function in diabetic patients, the magnitude of the effect of empagliflozin to slow the rate of decline in eGFR was somewhat greater in patients with diabetes than without diabetes (+2.2 vs +1.3 mL/min/1.73 m^2), however, the treatment-by-diabetes interaction was not significant (P=0.15). Furthermore, when the study medication was withdrawn to assess the unconfounded effects of double-blind treatment, empagliflozin, as compared with placebo, slowed the decline in eGFR by 4.8 mL/min/1.73 m^2 in patients with diabetes, by 1.3 mL/min/1.73 m^2 in patients with prediabetes, and by 3.1 mL/min/1.73 m^2 in patients with normoglycemia (P-trend=0.17), indicating no influence of baseline HbA1c on the ability of empagliflozin to mitigate the progressive decline in renal function during double-blind treatment.

Consistent with the lack of effect modification by baseline HbA1c on eGFR decline, glycemic status also did not modify the benefits of empagliflozin on clinically important renal events. Empagliflozin reduced the risk of the composite renal endpoint by 47% (hazard ratio 0.53 [95% CI 0.31–0.90] in patients with diabetes and by 58% in patients without diabetes (hazard ratio 0.42 [95% CI 0.19–0.97]), with no significant treatment-by-diabetes interaction (p=0.65), **Table 2 and Figure 4**. The hazard ratios of the risk reduction in prediabetes and in patients with no glycemic disorder were 0.33 [95% CI 0.11–1.03] and 0.59 [95% CI 0.17–2.03] in patients with no glycemic disorder; the latter estimate was based on only 11 events (**Figure 5**).

Other Efficacy Measures, Vital Signs and Laboratory Tests

The effects of empagliflozin on first hospitalization for heart failure and cardiovascular mortality according to glycemic status are shown in **Figure 5 and Supplemental Figure II**. The

magnitude of the treatment effects in patients with or without diabetes was similar for these endpoints as well as for the change in KCCQ clinical summary score at 52 weeks in an on-treatment analysis (**Supplemental Figure III and Table 2**).

The effects of empagliflozin on body weight, hemoglobin, systolic blood pressure and N-terminal-proBNP according to glycemic status are shown in **Supplemental Figures IV, V, VI and VII**. The magnitude of the treatment effects in patients with or without diabetes was similar. Empagliflozin lowered HbA1c at 52 weeks only in patients with diabetes, but not in patients with prediabetes or normoglycemia; the treatment-by diabetes interaction was significant (P-trend=0.033), **Figure 6 and Supplemental Figure VIII.**

Adverse Events

The study medication was stopped due to adverse events in 147 patients (15.7%) in the empagliflozin group and 152 (16.2%) in the placebo group among patients without diabetes and in 175 (18.9%) in the empagliflozin group and 176 (19.0%) in the placebo group among patients with diabetes, **Table 3**. For adverse events other than genital tract infections, there were no meaningful increases in the empagliflozin group, and the pattern of between-group differences was not influenced by the presence or absence of diabetes. Although confirmed hypoglycemia occurred more frequently in diabetic than nondiabetic patients, no imbalance between treatment groups was seen. There were no episodes of severe hypoglycemia requiring assistance in patients without diabetes.

Discussion

Disorders of glycemic control are exceptionally common in patients with chronic heart failure,[9,10] perhaps because heart failure itself represents a state of insulin resistance,[11,12] which is

partially driven by the severity of the hemodynamic abnormality.[13] Over 80% of our patients had either diabetes or prediabetes, a prevalence very similar to that in previous reports on patients with heart failure and a reduced ejection fraction.[9,10] However, in the current trial, compared with patients with heart failure and normoglycemia, only patients with diabetes showed a marked increase in the risk of heart failure and renal events in the absence of treatment with an SGLT2 inhibitor. Diabetes increased the risk of hospitalizations for heart failure by > 50%, and it nearly doubled both the rate of decline in eGFR as well as the risk of a major renal event. In contrast, the rate of evolution and progression of heart failure and kidney disease did not differ in patients among patients with prediabetes as compared with those with normoglycemia. Our observation regarding the risk of heart failure events is consistent with earlier reports that (when compared to those with normoglycemia) nondiabetic dysglycemia (i.e. prediabetes) is associated with little or only a modest increase in the risk of cardiovascular death and heart failure hospitalization in patients with heart failure and a reduced ejection fraction.[9,10] Furthermore, our finding regarding the risk of renal disease progression is consistent with the lack of an increased risk of nephropathy in patients with prediabetes who do not have heart failure.[14,15] Taken collectively, these observations highlight the importance of distinguishing between diabetes and prediabetes in the prediction of end-organ injury, even in patients with heart failure and a reduced ejection fraction.

Empagliflozin reduced the risk of the primary outcome variables as well as total hospitalizations for heart failure by 25-30%, and additionally, treatment with the drug slowed the rate of decline in eGFR during double-blind therapy and reduced the risk of serious adverse events by 50%. Importantly, the benefits were seen in patients with or without diabetes, and the magnitude of these favorable effects were not influenced by the baseline level of HbA1c.

Interestingly, the effect of empagliflozin on heart failure and renal outcomes was such that treatment with the drug effectively negated the deleterious effect of diabetes on the risk of heart failure and renal events. For the primary outcome of cardiovascular death or hospitalization for heart failure, the event rate per 100 patient-years of follow-up among patients with diabetes was reduced from 24.6 in the placebo group to 17.7 in the empagliflozin group, a risk similar to that seen in patients with normoglycemia who received placebo (i.e., 16.5). For total hospitalizations for heart failure, the event rate per 100 patient-years among those with diabetes was reduced from 27.2 in the placebo group to 18.0 in the empagliflozin group, a risk similar to that seen in patients with normoglycemia who received placebo (i.e., 16.9). Finally, for the composite renal endpoint, the event rate per 100 patient-years of follow-up among patients with diabetes was reduced from 4.2 to 2.3 by empagliflozin; the latter risk was similar to that seen in patents with normoglycemia who were treated with placebo (i.e., 2.2).

Beyond lowering excess risk associated with diabetes, treatment with empagliflozin also reduced the risk of heart failure and renal events in patients with prediabetes and normoglycemia. The magnitude of the benefit in nondiabetic patients was similar to those with diabetes, and the heart failure and renal benefits of empagliflozin were consistent across a broad range of baseline values for HbA1c. Consistent with its known mechanism of action to lower blood glucose only in the setting of hyperglycemia, empagliflozin only reduced HbA1c in patients with diabetes and not in patients with prediabetes or normoglycemia. These findings strongly underscore the conclusion that the benefits of empagliflozin on the heart and the kidneys are not related to the level of dysglycemia or to changes in glycated hemoglobin. The precise mechanism of action of SGLT2 inhibitors to lower the risk of heart failure events remains to be defined, but given our findings, the pathophysiologic abnormalities that are ameliorated by

empagliflozin are not dependent on or are likely to be meaningfully influenced by abnormalities in blood glucose.[4] It is therefore noteworthy that various biomarkers of the effect of empagliflozin in heart failure (i.e., changes in body weight, natriuretic peptides and hemoglobin) were influenced to a similar degree in patients with or without diabetes.

There were no meaningful imbalances in the tolerability or safety events between the empagliflozin and placebo group among heart failure patients with and without diabetes. Adverse effects that are typical of other heart failure medications (e.g., such as hyperkalemia and hypotension) were observed similarly in the placebo and empagliflozin groups. No reports of diabetic ketoacidosis or severe hypoglycemic episode occurred with empagliflozin in patients with pre-diabetes or normoglycemia. This shows the favorable benefit-risk profile of empagliflozin and provides reassurance to clinicians in initiating SGLT2 inhibitors in patients with heart failure who do not have diabetes.

Our findings should be considered in light of both strengths and limitations of the current trial. Each of our major endpoints were prespecified, and the analysis of the effect of empagliflozin in patients with and without diabetes was designated as our most important subgroup analysis. The patients with no diabetes comprised a substantial proportion of our population (i.e., 50%), and we were also able to study the effect of empagliflozin in a considerable number of patients with prediabetes. Since insulin resistance is exceptionally common in heart failure and a reduced ejection fraction, we expected that the proportion of patients with normoglycemia would be comparatively small, leading to estimates of a treatment effect in patients with normoglycemia that were necessarily less precise. However, when comparing the magnitude of the treatment effect across the three glycemia subgroups, there was a remarkably consistency of the benefit of empagliflozin with no evidence for heterogeneity.

In conclusion, in this secondary analysis of the EMPEROR-Reduced trial, empagliflozin significantly reduced the risk of cardiovascular death or heart failure hospitalizations, decreased total hospitalizations for heart failure, slowed the decline in renal function, prevented serious renal events and improved measures of health status to a similar degree in patients with and without diabetes. Our findings reinforce those recently reported in a similar trial with dapagliflozin in heart failure with a reduced ejection fraction, but we extend those findings to include benefits on the evolution of renal disease as well as defined benefits in patients with prediabetes and no glycemic disorder. The combined results of the two trials reinforce a new role for SGLT2 inhibitors in patients with heart failure and a reduced ejection fraction, independent of diabetes or the baseline level of glycated hemoglobin.

Acknowledgments

The authors were fully responsible for all content and editorial decisions, were involved at all stages of development, and have approved the final version. We thank Tomoko Iwata for statistical support, and Ivana Ritter for the compilation and management of safety-related aspects in this manuscript. Graphical assistance, supported financially by Boehringer Ingelheim, was provided by Jonathon Gibbs of Elevate Scientific Solutions.

Sources of Funding

The EMPEROR-Reduced trial was funded by the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance.

Disclosures

- **Stefan D. Anker** reports grants and personal fees from Vifor Int. and Abbott Vascular, and personal fees from Astra-Zeneca, Bayer, Brahms, Boehringer Ingelheim, Cardiac Dimensions, Novartis, Occlutech, Servier, and Vifor Int.
- **Javed Butler** reports consulting fees from BI, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, Sequana Medical, V-Wave Ltd., and Vifor.
- **Gerasimos Filippatos** reports Committee Member contributions in trials sponsored by Medtronic, Vifor, Servier, Novartis, and Boehringer Ingelheim
- **Muhammad Shahzeb Khan**: No relevant disclosures.
- **Nikolas Marx:** is funded by the German Research Foundation SFB TRR 219 (projects M-03 and M-05); reports giving lectures for and receiving honoraria from Amgen, Boehringer Ingelheim, Sanofi-Aventis, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Lilly, Novo Nordisk; receiving unrestricted research grants from Boehringer Ingelheim; serving as an advisor for Amgen, Bayer, Boehringer Ingelheim, Sanofi-Aventis, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Novo Nordisk; serving in trial leadership for Boehringer Ingelheim and Novo Nordisk; and declining all personal compensation from pharmaceutical and device companies.

- **Carolyn S.P. Lam** reports research grants from Bayer, Boston Scientific, Roche Diagnostic, Medtronic, Vifor Pharma, and AstraZeneca; consulting fees from Merck, Bayer, Boston Scientific, Roche Diagnostic, Vifor Pharma, AstraZeneca, Novartis, Amgen, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, Novo Nordisk, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, Cytokinetics, WebMD Global LLC, Radcliffe Group Ltd, and Corpus; and serves as co-founder & non-executive director of eKo.ai.
- **Sven Schnaidt, Anne Pernille Ofstad, Martina Brueckmann, Waheed Jamal** are employees of Boehringer Ingelheim.
- **Edimar Bocchi** 1.Consulting Fee: Servier, Astra-Zeneca; 2. Subsidized Travel/Hotel/Registration Fees: Servier, Baldacc; 3. Membership in Steering Committee: Servier, Novartis; 4. 'Contracted Research': Jansen, Bayer/Merck, Astra-Zeneca, Boehringer Ingelheim; 5.Honoraria: Servier, Novartis, Astra-Zeneca
- **Piotr Ponikowski** reports personal fees from Boehringer Ingelheim, Astra Zeneca, Servier, BMS, Amgen, Novartis, Merck, Pfizer, Berlin Chemie, and grants and personal fees from Vifor Pharma.
- **Sergio Perrone** reports serves on the advisory boards and receives personal fees from Laboratorios Ferrer, Abbott- St Jude, Novartis and Laboratorios Bago.
- **James Januzzi** reports grant support, consulting income and participation in clinical endpoint committees/data safety monitoring boards from Janssen, participation in clinical endpoint committees/data safety monitoring boards from Boehringer Ingelheim, grant support from Novartis, Innolife, Applied Therapeutics, Siemens Diagnostics and consultancy fees from Novartis, Roche Diagnostics and Abbott Diagnostics.
- **Subodh Verma** holds a Tier 1 Canada Research Chair in Cardiovascular Surgery; and reports receiving research grants and/or speaking honoraria from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, EOCI Pharmacomm Ltd, HLS Therapeutics, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, Sun Pharmaceuticals, PhaseBio and the Toronto Knowledge Translation Working Group. He is a member of the scientific excellence committee of the EMPEROR-Reduced trial and served as a national lead investigator of the DAPA-HF and EMPEROR-Reduced trials. He is the

President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization .

- **Michael Böhm** reports fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Servier, Medtronic, ReCor, Vifor, Novartis and Abbott. MB is supported by the Deutsche Forschungsgemeinschaft (DFG, TTR 219, S-01).
- **João Pedro Ferreira** is a consultant for Boehringer Ingelheim.
- **Stuart J. Pocock** is a consultant for Boehringer Ingelheim.
- **Faiez Zannad** has recently received steering committee or advisory board fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cardior, CVRx, Janssen, Livanova, Merck, Mundipharma, Novartis, Novo Nordisk, and Vifor Fresenius.
- **Milton Packer** reports personal fees from Boehringer Ingelheim, during the conduct of the study; personal fees from Abbvie, Akcea, Amarin, AstraZeneca, Amgen, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Johnson & Johnson, Lilly, Novartis, Pfizer, Relypsa, Sanofi, Synthetic Biologics, Theravance, NovoNordisk, outside the submitted work.

Supplemental Materials

Supplemental Table I

Baseline characteristics of patients with prediabetes vs those with normoglycemia

Supplemental Figure I

Effects of empagliflozin on eGFR and mean slope of change in eGFR by glycemic status

Supplemental Figures II and III

Effects of empagliflozin on
- the components of the primary outcome by diabetes status
- KCCQ clinical summary score,

Supplemental Figures IV, V, VI, VII and VIII

Effects of empagliflozin on
- body weight,
- hemoglobin,
- systolic blood pressure and
- N-terminal-proBNP
- HbA1c by diabetes status

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Table 1: Baseline characteristics by diabetes status

	No diabetes (n=1874)		Diabetes (n=1856)	
	Empagliflozin (n=936)	Placebo (n=938)	Empagliflozin (n=927)	Placebo (n=929)
Age — yr	67.6±11.6	66.3±12.0	66.8±10.0	66.6±10.3
Female sex — no. (%)	227 (24.3)	238 (25.4)	210 (22.7)	218 (23.5)
Race — no. (%)				
White	679 (72.5)	665 (70.9)	646 (69.7)	639 (68.8)
Black	66 (7.1)	71 (7.6)	57 (6.1)	63 (6.8)
Asian	154 (16.5)	160 (17.1)	183 (19.7)	175 (18.8)
Other or Missing	37 (4.0)	42 (4.5)	41 (4.4)	52 (5.6)
Region — no. (%)				
North America	105 (11.2)	98 (10.4)	107 (11.5)	115 (12.4)
Latin America	330 (35.3)	331 (35.3)	311 (33.5)	314 (33.8)
Europe	344 (36.8)	349 (37.2)	332 (35.8)	328 (35.3)
Asia	125 (13.4)	124 (13.2)	123 (13.3)	121 (13.0)
Other	32 (3.4)	36 (3.8)	54 (5.8)	51 (5.5)
NYHA functional classification — no. (%)				
II	742 (79.3)	733 (78.1)	657 (70.9)	668 (71.9)
III	190 (20.3)	202 (21.5)	265 (28.6)	253 (27.2)
IV	4 (0.4)	3 (0.3)	5 (0.5)	8 (0.9)
Body mass index (kg/m^2)	27.2±5.3	27.0±5.2	28.8±5.5	28.6±5.4
Heart rate — beats/min	69.7±11.6	70.9±12.1	72.3±11.6	72.2±11.3
Systolic blood pressure — mm Hg	122.0±15.9	119.9±14.9	123.2±15.9	122.9±15.6
HbA1c (%)	5.8±0.4	5.7±0.4	7.4±1.6	7.4±1.6
Left ventricular ejection fraction — %	27.9±6.0	27.2±6.0	27.6±6.0	27.2±6.1
Median NT-proBNP (IQR) — pg/mL	1882 (1071, 3251)	1908 (1164, 3529)	1894 (1093, 3572)	1937 (1151, 3501)
Principal cause of heart failure — no. (%)				
Ischemic	429 (45.8)	433 (46.2)	554 (59.8)	513 (55.2)
Nonischemic	507 (54.2)	505 (53.8)	373 (40.2)	416 (44.8)
Medical history — no. (%)				
Hospitalization for heart failure in last 12 months	261 (27.9)	260 (27.7)	316 (34.1)	314 (33.8)
Atrial fibrillation*	354 (37.8)	382 (40.7)	310 (33.4)	323 (34.8)
Hypertension	619 (66.1)	620 (66.1)	730 (78.7)	729 (78.5)
Estimated GFR				
Mean— mL/min/1.73 m^2	62.7±21.1	63.0±21.0	61.0±22.3	61.4±22.1
Rate of <60 mL/min/1.73 m^2 — no./total no. (%)	434 (46.4)	426 (45.4)	459 (49.5)	480 (51.7)
Device therapy — no. (%)				
Implantable cardioverter-defibrillator†	320 (34.2)	294 (31.3)	258 (27.8)	299 (32.2)
Cardiac resynchronization therapy‡	117 (12.5)	105 (11.2)	103 (11.1)	117 (12.6)
Heart failure medication — no. (%)				
ACE inhibitor	451 (48.2)	425 (45.3)	416 (44.9)	411 (44.2)
ARB§	213 (22.8)	227 (24.2)	238 (25.7)	230 (24.8)
ARNi	178 (19.0)	193 (20.6)	162 (17.5)	194 (20.9)
Diuretic‖	779 (83.2)	809 (86.2)	831(89.6)	829 (89.2)
Mineralocorticoid Receptor Antagonist	667 (71.3)	694 (74.0)	639 (68.9)	661 (71.2)
Beta blocker	890 (95.1)	885 (94.3)	875 (94.4)	883 (95.0)
Glucose lowering therapy – no. (%)				
Any glucose lowering therapy	4 (0.4)	7 (0.7)	683 (73.7)	687 (74.0)
Biguanide	4 (0.4)	7 (0.7)	444 (47.9)	418 (45.0)
Insulin	0	0	224 (24.2)	248 (26.7)
Sulfonylurea	0	0	211 (22.8)	191 (20.6)
DPP4-inhibitors	0	0	132 (14.2)	120 (12.9)
GLP1 receptor analogues	0	0	13 (1.4)	6 (0.6)

Data given as mean±standard deviation unless otherwise stated

* atrial fibrillation reported in any ECG before treatment intake or history of atrial fibrillation reported as medical history

† Implantable cardioverter defibrillator with or without cardiac resynchronization therapy.

‡ Cardiac resynchronization therapy with or without a defibrillator

§Excluding valsartan when taken with sacubitril because sacubitril/valsartan is shown as ARNI

‖ diuretics other than mineralocorticoid receptor antagonists

NYHA=New York Heart Association; ARB=Angiotensin Receptor Blocker; ACE=Angiotensin Converting enzyme; ARNI=Angiotensin receptor neprilysin inhibition; GFR= glomerular filtration rate; NT-pro BNP=N-terminal prohormone B-type natriuretic peptide

Table 2: Primary and secondary outcomes in the EMPEROR-Reduced trial by diabetes status

	Empagliflozin (n=1863)		Placebo (n=1867)			
	n*/N (%)	Incidence rate per 100 patient years	n*/N (%)	Incidence rate per 100 patient years	HR (95% CI)/slope difference (95% CI)	p-value for interaction
Primary outcome						
Time to first event of CV death or HHF						
All patients	361/1863 (19.4)	15.77	462/1867 (24.7)	21.00	0.75 (0.65, 0.86)	
No diabetes	161/936 (17.2)	13.93	197/938 (21.0)	17.59	0.78 (0.64, 0.97)	0.57
Diabetes	200/927 (21.6)	17.66	265/929 (28.5)	24.55	0.72 (0.60, 0.87)	
Key secondary outcomes						
First and recurrent HHF						
All patients	388/1863	-	553/1867	-	0.70 (0.58, 0.85)	
No diabetes	167/936	-	216/938	-	0.76 (0.57, 1.01)	0.44
Diabetes	221/927		337/929		0.65 (0.50, 0.85)	
Mean slope of change in eGFR – ml/min/1.73 m^2/year†						
All patients	-0.55	-	-2.28	-	1.73 (1.10, 2.37)	
No diabetes	-0.45	-	-1.72	-	1.27 (0.38, 2.16)	0.15
Diabetes	-0.64	-	-2.85	-	2.21 (1.31, 3.10)	
Secondary outcomes						
Time to first renal composite outcome‡						
All patients	30 / 1863 (1.6)	1.56	58/1867 (3.1)	3.07	0.50 (0.32, 0.77)	
No diabetes	8/936 (0.9)	0.83	19/938 (2.0)	1.99	0.42 (0.19, 0.97)	0.65
Diabetes	22/927 (2.4)	2.29	39/929 (4.2)	4.17	0.53 (0.31, 0.90)	
Time to first HHF						
All patients	246 / 1863 (13.2)	10.75	342/1867 (18.3)	15.55	0.69 (0.59, 0.81)	
No diabetes	106/936 (11.3)	9.17	141/938 (15.0)	12.59	0.72 (0.56, 0.93)	0.66
Diabetes	140/927 (15.1)	12.36	201/929 (21.6)	18.62	0.67 (0.54, 0.83)	
Time to CV death						
All patients	187/1863 (10.0)	7.55	202/1867 (10.8)	8.13	0.92 (0.75, 1.12)	
No diabetes	83/936 (8.9)	6.69	89/938 (9.5)	7.20	0.92 (0.68, 1.24)	0.98
Diabetes	104/927 (11.2)	8.42	113/929 (12.2)	9.06	0.92 (0.71, 1.20)	
Change in KCCQ clinical summary score‖ **at 52 w (On-treatment)**	Adjusted mean (SE) empagliflozin group	Change from baseline Empagliflozin group	Adjusted Mean (SE) placebo group	Change from baseline Placebo group	Difference in change (95% CI)	
All patients	77.51 (0.44)	5.83 (0.44)	75.77 (0.44)	4.09 (0.45)	1.75 (0.5, 3.0)	
No diabetes	77.87 (0.62)	5.43 (0.62)	76.77 (0.63)	4.33 (0.63)	1.10 (-0.64, 2.85)	0.30
Diabetes	76.59 (0.63)	6.58 (0.63)	74.19 (0.64)	4.17 (0.64)	2.41 (0.64, 4.17)	

Recurrent event analyses are based on a joint frailty model accounting for competing risk of CV death or all-cause mortality respectively.
* 'n' corresponds to number of events in recurrent event analyses and number of patients with event for time to first event analysis.
† eGFR slope is analyzed based on the treated set considering measurements until end of treatment
‡ Composite renal endpoint: Time to first event of chronic dialysis or renal transplant or sustained§ reduction of ≥40% eGFR (CKD-EPI)cr or
- (for patients with eGFR (CKD-EPI)cr ≥30 mL/min/1.73 m2 at baseline): sustained eGFR <15 mL/min/1.73m^2§
- (for patients with eGFR (CKD-EPI)cr <30 mL/min/1.73 m2 at baseline): sustained eGFR < 10 mL/min/1.73 m^2§
§An eGFR (CDK-EPI)cr reduction is considered sustained, if it is determined by two or more consecutive postbaseline central laboratory measurements separated by at least 30 days (first to last of the consecutive eGFR values). If there is no additional measurement >= 30 days after the eGFR reduction is observed and the patient dies within 60 days of this measurement, then the eGFR reduction is also considered sustained
‖ HF symptoms (Total Symptom Score) and physical limitations (Physical limitation score)
CV=Cardiovascular; HHF=Hospitalization for heart failure; KCCQ=Kansas City Cardiomyopathy Questionnaire;

Table 3: Adverse events of interest by diabetes status

	Empagliflozin (n=1863)		Placebo (n=1863)	
	n/N (%)	Incidence rate per 100 patient years	n/N (%)	Incidence rate per 100 patient years
Patients with SAE				
No diabetes	375/936 (40.1)	42.6	439/937 (46.9)	52.8
Diabetes	397/927 (42.8)	45.1	457/926 (49.4)	57.6
Patients with AE leading to discontinuation				
No diabetes	147/936 (15.7)	13.0	152/937 (16.2)	13.5
Diabetes	175/927 (18.9)	15.6	176/926 (19.0)	15.8
Hypotension				
No diabetes	85/936 (9.1)	7.93	91/937 (9.7)	8.61
Diabetes	91/927 (9.8)	8.51	72/926 (7.8)	6.78
Volume depletion				
No diabetes	94/936 (10.0)	8.84	100/937 (10.7)	9.54
Diabetes	103/927 (11.1)	9.68	84/926 (9.1)	7.99
Acute renal failure				
No diabetes	77/936 (8.2)	7.07	94/937 (10.0)	8.74
Diabetes	98/927 (10.6)	9.20	98/926 (10.6)	9.29
Confirmed* hypoglycemic event				
Normoglycemic	1/304 (0.3)	0.27	1/302 (0.3)	0.26
Pre-diabetes	6/632 (0.9)	0.79	5/635 (0.8)	0.67
Diabetes	20/927 (2.2)	1.79	22/926 (2.4)	2.00
Severe† hypoglycemic event				
Normoglycemic	0/304	-	0/302	-
Pre-diabetes	0/632	-	0/635	-
Diabetes	6/927 (0.6)	0.53	7/926 (0.8)	0.63
Diabetic ketoacidosis				
Normoglycemic	0/304	-	0/302	-
Pre-diabetes	0/632	-	0/635	-
Diabetes	0/927	-	0/926	-
Lower limb amputation				
No diabetes	1/936 (0.1)	0.08	1/937 (0.1)	0.08
Diabetes	12/927 (1.3)	0.94	9/926 (1.0)	0.70
Fractures				
No diabetes	25/936 (2.7)	2.23	16/937 (1.7)	1.42
Diabetes	20/927 (2.2)	1.79	26/926 (2.8)	2.36
Hyperkaelamia events‡				
No diabetes	48/936 (5.1)	4.37	53/937 (5.7)	4.87
Diabetes	61/927 (6.6)	5.67	74/926 (8.0)	7.01
Genital infections				
No diabetes	13/936 (1.4)	1.15	8/937 (0.9)	0.71
Diabetes	18/927 (1.9)	1.62	4/926 (0.4)	0.36
Urinary tract infection				
No diabetes	39/936 (4.2)	3.52	34/937 (3.6)	3.06
Diabetes	52/927 (5.6)	4.74	49/926 (5.3)	4.47

* defined as hypoglycemic AEs with a plasma glucose value of ≤70 mg/dL or that required assistance
†defined as a hypoglycemic episode requiring assistance
‡ defined by MedDRA PTs "hyperkalaemia" and "blood potassium increased"
AE= Adverse event, SAE=Serious Adverse events;
Shown are adverse events up to 7 days following discontinuation of study medication, but lower limb amputations are shown for the total period. Search for specified adverse events of interest was based on the predefined list of preferred terms.

Figure Legends

Figure 1. Effect of empagliflozin on the primary endpoint of EMPEROR-Reduced, i.e. time to first event of either CV death or HF hospitalization, in patients with (A) and without diabetes (B)

Figure 2. A) Effect of empagliflozin on the primary outcome of EMPEROR-Reduced by baseline HbA1c as continuous variable* B) Distribution of HbA1c at baseline in the range between 5% and 12% *This figure shows the linear association between HbA1c and log hazard ratio for the primary endpoint. The nonsignificant interaction test (p=0.40] indicates that the slope is not significantly different from zero. However, the display makes assumptions about linearity that are difficult to validate, and the slope is strongly influenced by a relatively small number of patients with extreme values.

Figure 3. Effect of Empagliflozin on first and recurrent hospitalizations for heart failure in patients with (A) and without (B) diabetes

Figure 4. Effect of empagliflozin on renal composite endpoint in patients with (A) and without (B) diabetes

Composite renal endpoint is defined as chronic dialysis, renal transplant, sustained reduction of ≥40% eGFR or sustained eGFR <15 ml/min/1.73 m^2 for patients with eGFR ≥30 ml/min/1.73 m^2 at baseline (<10 ml/min/1.73 m^2 for patients with eGFR <30 ml/min/1.73 m^2 at baseline). Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days. In accordance with usual practice, cumulative incidence plots were truncated when the number of patients being followed in individual subgroups became extremely sparse.

Figure 5: Treatment effect of empagliflozin vs. placebo on primary and secondary outcomes in patients with normoglycemia, prediabetes and diabetes.

Recurrent event analyses are based on a joint frailty model accounting for competing risk of CV death respectively.

* 'n' corresponds to number of events in recurrent event analyses and number of patients with event for time to first event analysis.

†interaction p-values from trend test assuming ordered categories. The trend test reflects an assumed ordering of the subgroups from normoglycemia to prediabetes to diabetes testing a linear trend across subgroups.

‡ Composite renal endpoint: Time to first event of chronic dialysis or renal transplant or sustained§ reduction of ≥40% eGFR (CKD-EPI)cr or

- (for patients with eGFR (CKD-EPI)cr ≥30 mL/min/1.73 m2 at baseline): sustained eGFR <15 mL/min/1.73m2§

- (for patients with eGFR (CKD-EPI)cr <30 mL/min/1.73 m2 at baseline): sustained eGFR < 10 mL/min/1.73 m2§

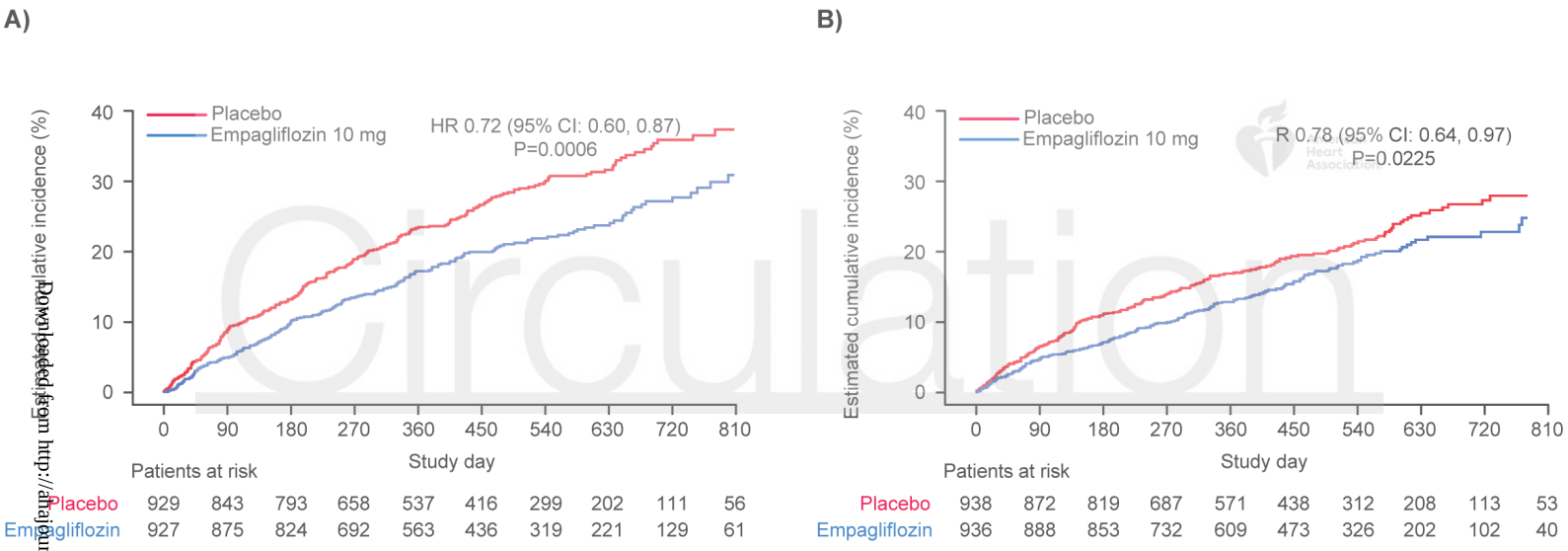
§An eGFR (CDK-EPI)cr reduction is considered sustained, if it is determined by two or more consecutive postbaseline central laboratory measurements separated by at least 30 days (first to last of the consecutive eGFR values). If there is no additional measurement >= 30 days after the eGFR reduction is observed and the patient dies within 60 days of this measurement, then the eGFR reduction is also considered sustained.

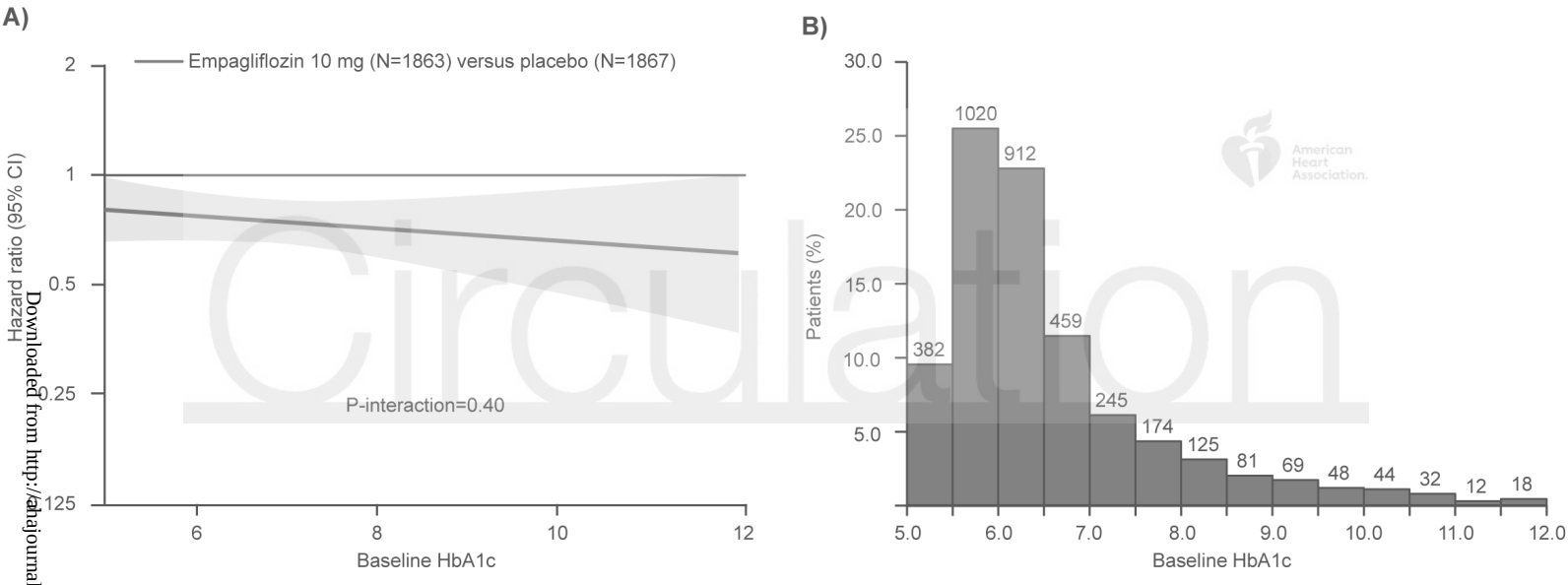
CV=Cardiovascular; HHF=Hospitalization for heart failure

Figure 6. Changes of HbA1c from baseline by glycemic status

A) Diabetes, B) Prediabetes, C) Normoglycemia

HbA1c, hemoglobin A1c





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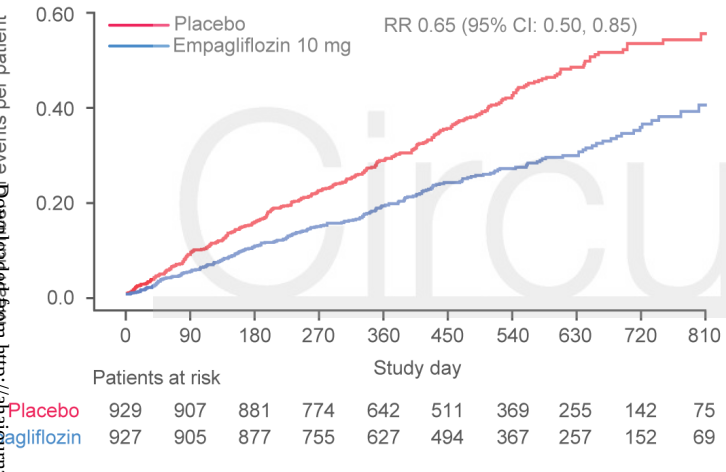

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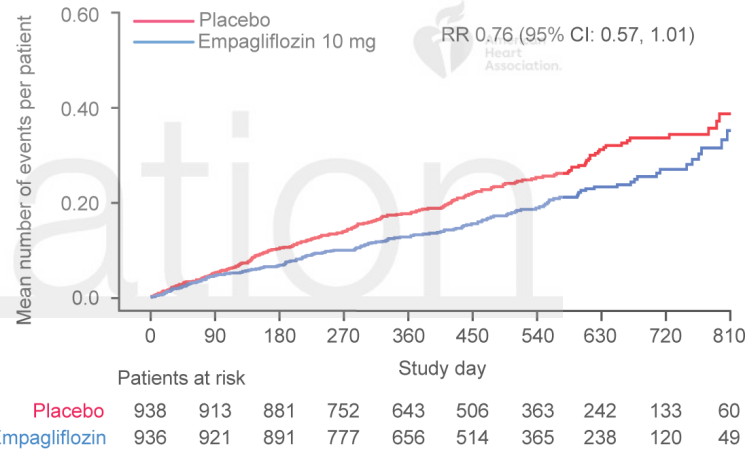

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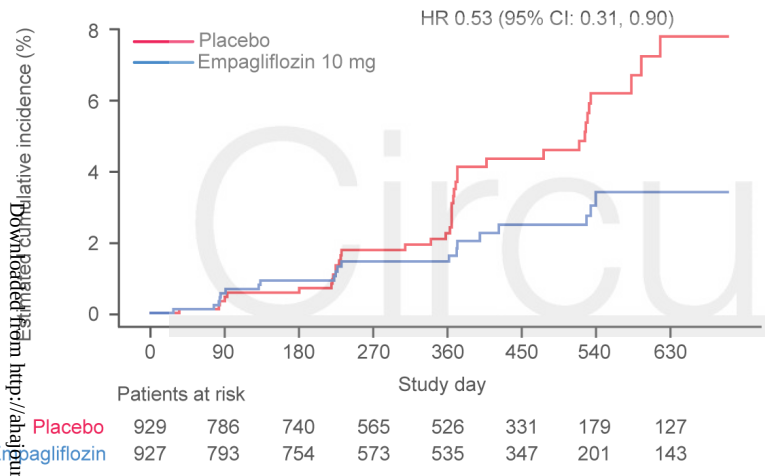

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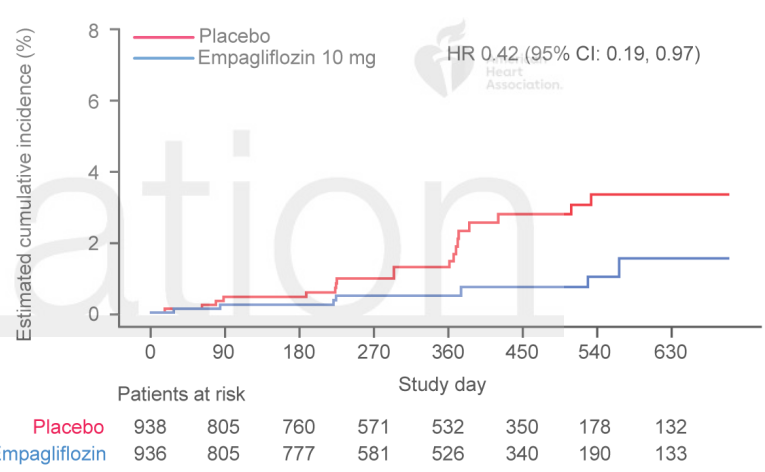
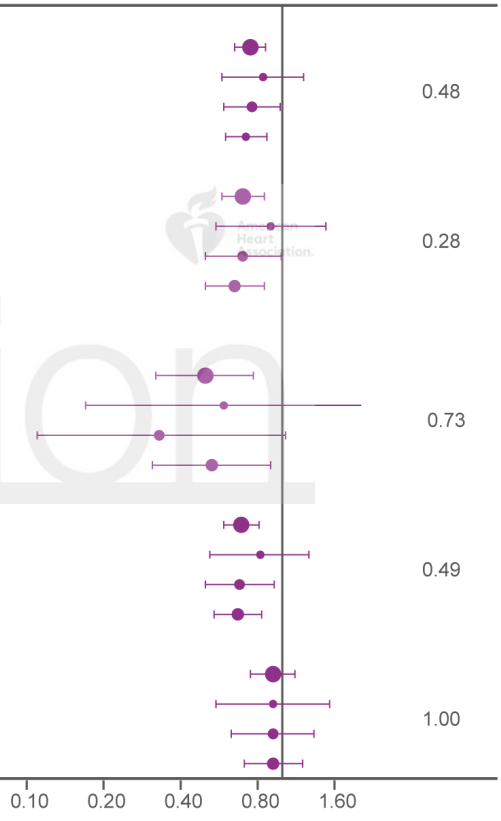


	Empagliflozin (N=1863)			Placebo (N=1867)			HR (95% CI)/ RR (95% CI)	Interaction P-value†
	n*/N	%	Rate/100 PY	n^/N	%	Rate/100 PY		
Primary outcome - Time to first event of CV death or HHF								
All patients	361/1863	19.4	15.77	462/1867	24.7	21.00	0.75 (0.65, 0.86)	
Normoglycemia	53/304	17.4	13.88	61/302	20.2	16.55	0.84 (0.58, 1.21)	0.48
Pre-diabetes	108/632	17.1	13.95	136/636	21.4	18.1	0.76 (0.59, 0.98)	
Diabetes	200/297	21.6	17.66	265/929	28.5	24.55	0.72 (0.60, 0.87)	
Key secondary outcome - First and recurrent HHF								
All patients	388/1863	-	-	553/1867	-	-	0.70 (0.58, 0.85)	
Normoglycemia	57/304	-	-	68/302	-	-	0.90 (0.55, 1.48)	0.28
Pre-diabetes	110/632	-	-	148/636	-	-	0.70 (0.50, 0.99)	
Diabetes	221/927	-	-	337/929	-	-	0.65 (0.50, 0.85)	
Secondary outcomes								
Time to first renal composite outcome‡								
All patients	30/1863	1.6	1.56	58/1867	3.1	3.07	0.50 (0.32, 0.77)	
Normoglycemia	4/304	1.3	1.29	7/302	2.3	2.20	0.59 (0.17, 2.03)	0.73
Pre-diabetes	4/632	0.6	0.62	12/636	1.9	1.89	0.33 (0.11, 1.03)	
Diabetes	22/297	2.4	2.30	39/929	4.2	4.17	0.53 (0.31, 0.90)	
First HHF								
All patients	246/1863	13.2	10.75	342/1867	18.3	15.55	0.69 (0.59, 0.81)	
Normoglycemia	36/304	11.8	9.43	43/302	14.2	11.66	0.82 (0.52, 1.27)	0.49
Pre-diabetes	70/632	11.1	9.04	98/636	15.4	13.04	0.68 (0.50, 0.93)	
Diabetes	140/927	15.1	12.36	201/929	21.6	18.62	0.67 (0.54, 0.83)	
Time to CV death								
All patients	187/1863	10.0	7.55	202/1867	10.8	8.13	0.92 (0.75, 1.12)	
Normoglycemia	29/304	9.5	7.10	30/302	9.9	7.46	0.92 (0.55, 1.53)	1.00
Pre-diabetes	54/632	8.5	6.49	59/636	9.3	7.08	0.92 (0.63, 1.33)	
Diabetes	104/297	11.2	8.42	113/929	12.2	9.06	0.92 (0.71, 1.20)	



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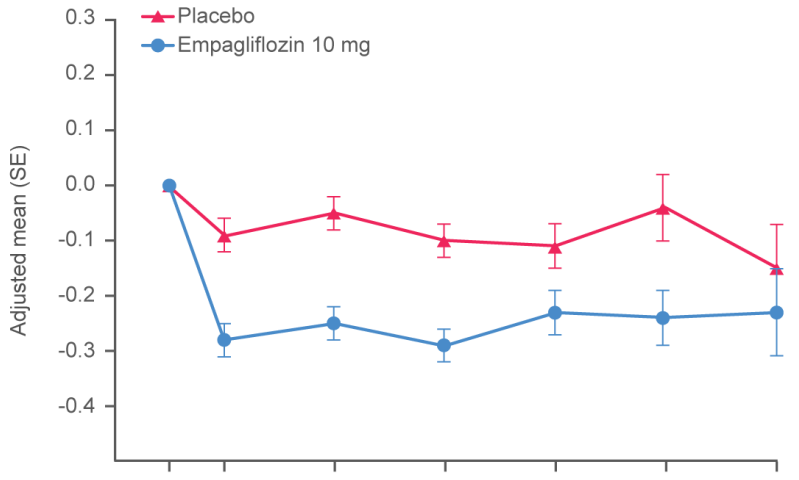
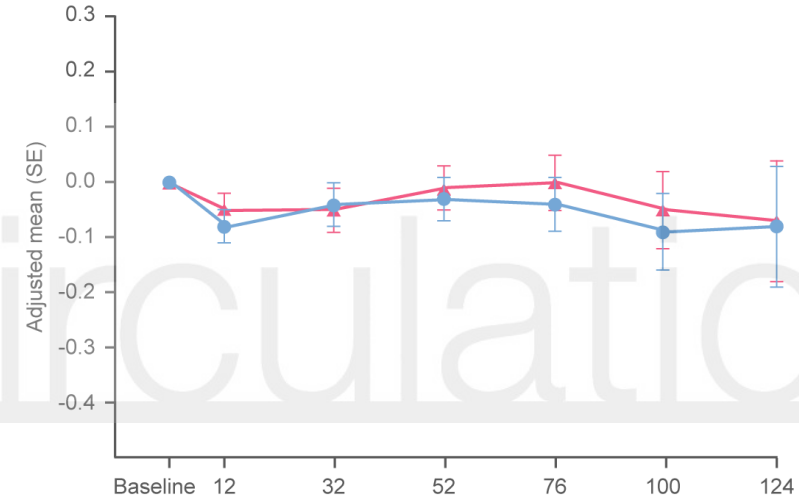


N with data at visit

Placebo	873	848	753	594	391	180	47
Empagliflozin	883	871	799	602	396	200	49

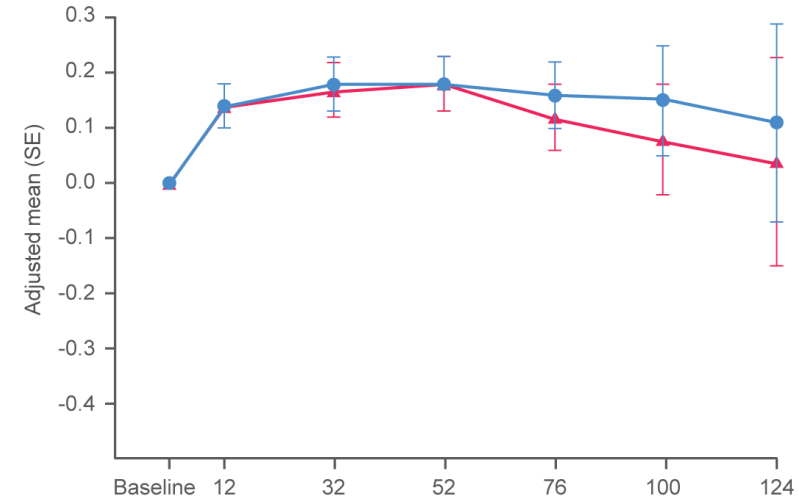
B)



N with data at visit

Placebo	597	586	533	389	265	121	29
Empagliflozin	612	599	550	421	259	123	28

C)



N with data at visit

Placebo	293	290	268	215	137	55	10
Empagliflozin	286	279	257	199	140	59	11