Circulation: Heart Failure

ORIGINAL ARTICLE

Empagliflozin Improves Kidney Outcomes in Patients With or Without Heart Failure

Insights From the EMPA-REG OUTCOME Trial

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BACKGROUND: In EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) empagliflozin significantly reduced the risk of cardiovascular and kidney outcomes in patients with type 2 diabetes mellitus and established cardiovascular disease. Post hoc, we evaluated empagliflozin on kidney outcomes in patients with or without heart failure (HF).

METHODS AND RESULTS: Individuals were randomized to empagliflozin 10 mg, 25 mg, or placebo. Prespecified analyses by baseline HF status included risk of incident or worsening nephropathy and estimated glomerular filtration rate slope analyses. Cox proportional hazards models assessed consistency of treatment effect across subgroups. Safety evaluations included kidney-related adverse events. At baseline, 244 (10.5%) and 462 (9.9%) patients had HF in the placebo and empagliflozin groups, respectively. Overall, the incidence of kidney outcome events was numerically higher in patients with than without HF. In the HF group, empagliflozin reduced risk of incident or worsening nephropathy or cardiovascular death by 43% (hazard ratio, 0.57 [95% CI, 0.42–0.77]) and progression to macroalbuminuria by 50% (hazard ratio, 0.50 [0.33–0.75]). After an initial transient decrease, estimated glomerular filtration rate stabilized over time with empagliflozin but gradually declined with placebo. Kidney effects in patients with HF were consistent with those in the overall study population (all *P* values for interaction >0.05). Across groups, the incidence rate of kidney-related adverse events/100 patient-years was higher in patients with than without HF; however, overall rates were comparable between groups.

CONCLUSIONS: These findings from EMPA-REG OUTCOME support the hypothesis that empagliflozin could reduce the risk of clinically relevant kidney events and may slow progression of chronic kidney disease in individuals with type 2 diabetes mellitus regardless of HF status.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01131676.

Key Words: cardiovascular diseases ■ chronic kidney disease ■ diabetes mellitus, type 2 ■ heart failure ■ sodium-glucose transporter 2

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WHAT IS NEW?

- Chronic kidney disease is a common condition and predicts a worse prognosis in patients with heart failure (HF), especially in those with type 2 diabetes mellitus.
- Patients with type 2 diabetes mellitus and HF are at higher risk of adverse kidney outcomes compared with patients without HF.
- In a subgroup analysis of the EMPA-REG OUTCOME study (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), the SGLT2 (sodium-glucose cotransporter 2) inhibitor empagliflozin reduced the risk of clinically relevant kidney events and slowed progression of chronic kidney failure in patients with and without HF at baseline. These effects were consistent with those reported for the overall study population.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Empagliflozin may have the potential to slow progressive kidney function loss in patients with type 2 diabetes mellitus and concomitant HF.
- Several randomized clinical trials are now underway that will investigate further the potential role of SGLT2 inhibitors as a treatment specifically for HF.
- These trials are enrolling HF patients with or without type 2 diabetes mellitus, and those with an estimated glomerular filtration rate as low as 20 mL/min per 1.73 m^2.

Heart failure (HF) is a major global problem, affecting ≈26 million people worldwide in 2014.[1] In developed countries, HF prevalence is ≈1% to 2% of the adult population, increasing to ≥10% in people aged >70 years.[2] Hospitalization for HF accounts for over 1 million admissions per year in both Europe and the United States.[1] Type 2 diabetes mellitus (T2DM) is common in people with HF with numerous studies showing a prevalence of up to 50%.[3] T2DM is associated with a 2- to 5-fold increased risk of developing HF[2,3] as well as a worse prognosis in those with concomitant presence of both as opposed to either one alone.[4] The presence of T2DM is also associated with a higher rate of, and worse outcomes with, hospitalization for HF.[5] A commonly linked comorbidity with HF and T2DM is chronic kidney disease (CKD), which affects over 10% of the population in many countries. Approximately 40% of people with HF have concomitant impairment of kidney function (defined as an estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m^2).[6] Similar to T2DM and HF associations, the presence of CKD is common in either or both conditions and has an overlapping, underlying common pathophysiology, and frequently worsens prognosis.

Empagliflozin is a selective SGLT2 (sodium-glucose cotransporter 2) inhibitor indicated for the treatment of T2DM. In the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), empagliflozin, when given in addition to standard of care and compared with placebo, significantly reduced the risk of cardiovascular death by 38%,[7] improved clinically relevant kidney outcomes,[8] and slowed the progression of kidney function decline,[8] in patients with T2DM and established cardiovascular disease. The beneficial cardiovascular effects of empagliflozin included a reduction in the risk for hospitalization for HF and cardiovascular death, with consistent effects seen in patients with or without HF at baseline.[9]

CKD and HF have common interrelated underlying pathophysiology (eg, inflammation, comorbidity burden, hemodynamic changes, and neurohormonal activation), and the progression of CKD and its associated adverse outcomes in people with T2DM may differ in people with or without HF. Importantly, the glucose-lowering drug empagliflozin induces secondary diuresis and natriuresis, with consequent hemodynamic influences on the kidney, at the arteriolar level. These mechanisms could be important for the long-term progression of both CKD and HF; however, their implications are still poorly understood. Here, we report analyses from the EMPA-REG OUTCOME trial investigating post hoc the impact of empagliflozin on prespecified kidney outcomes in patients with or without HF at baseline.

METHODS

Data Sharing

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfill their role and obligations as authors under the ICMJE criteria. Furthermore, clinical study documents (eg, study report, study protocol, and statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary article in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/transparency_policy.html.

Before providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants. Clinical study reports and related clinical documents can be requested via this link: https://trials.boehringer-ingelheim.com/trial_results/clinical_submission_documents.html.

All such requests will be governed by a Document Sharing Agreement. Bona fide, qualified scientific, and medical researchers may request access to de-identified, analyzable participant clinical study data with corresponding

documentation describing the structure and content of the data sets. On approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request. Researchers should use https://clinicalstudydatarequest.com to request access to study data.

Trial Design and Procedures

The design of the EMPA-REG OUTCOME trial has been described previously.[4,7,9] Briefly, patients with T2DM (with glycated hemoglobin [HbA1c] 7.0%–9.0% for drug-naïve patients and 7.0%–10.0% for those on stable glucose-lowering therapy) and established cardiovascular disease were eligible to participate. Individuals were required to have a body mass index (BMI) of ≤45 kg/m^2 and eGFR >30 mL/min per 1.73 m^2 at screening (as calculated using the modification of diet in renal disease formula). Patients were randomized 1:1:1 to once daily empagliflozin 10 mg, 25 mg, or placebo, in addition to standard of care.

The trial was planned to continue until at least 691 patients experienced a composite primary outcome event (defined as first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). Cardiovascular outcome events and deaths were prospectively adjudicated by Clinical Events Committees.[7] Patients were asked to attend the clinic at prespecified times during the study including a follow-up visit 30 days following the end of the treatment period. Patients who prematurely discontinued their study medication were asked to attend all visits as originally planned.[10]

For laboratory values, serum creatinine and urinary albumin-to-creatinine ratio in spot urine samples obtained during regular study visits were determined in central laboratories using standardized procedures. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and was approved by local authorities. An independent ethics committee or institutional review board approved the clinical protocol at each participating center. Patients provided written informed consent before study entry.

Heart Failure

Patients with HF were allowed to participate without any restriction about ejection fraction or New York Heart Association functional class symptoms. HF was neither required nor excluded for participation. Investigator-reported HF status at study baseline was identified by searching for preferred terms in the Standardized Medical Dictionary for Drug Regulatory Activities Query "cardiac failure" (comprising acute pulmonary edema; cardiac failure; cardiac failure, acute; cardiac failure, chronic; cardiac failure, congestive; cardiogenic shock; cardiopulmonary failure; left ventricular failure; pulmonary edema; and right ventricular failure).[9] Cardiac imaging was not performed or required for the definition of HF.

Kidney Outcomes

Results of the primary outcomes and secondary outcomes from the EMPA-REG OUTCOME trial have been previously reported in the overall population.[8] Prespecified kidney outcomes included incident or worsening nephropathy, defined as a composite of progression to macroalbuminuria (urine albumin-to-creatinine ratio, >300 mg/g); a doubling of serum creatinine level accompanied by an eGFR value of ≤45 mL/min per 1.73 m^2 (modification of diet in renal disease); initiation of renal replacement therapy; or death from renal disease.[8] Other prespecified outcomes included a composite of incident or worsening nephropathy or death from cardiovascular causes and the individual components of incident or worsening nephropathy. A previous post hoc analysis also examined the composite of doubling of serum creatinine, initiation of renal replacement therapy, or death from renal disease.[8] The post hoc analyses presented herein focused on the outcomes mentioned above in the specific patient subgroups with or without investigator-reported HF at baseline. We also assessed a composite of sustained (ie, ≥2 consecutive measurements that were ≥4 weeks apart) eGFR decline of ≥40%, initiation of renal replacement therapy, or renal death.

Changes in eGFR values were assessed over time, alongside a prespecified eGFR slope analysis for 3 prespecified study periods (treatment-initiation effects from baseline to week 4; chronic maintenance treatment effects from week 4 to last value on treatment; and post-treatment effects from last value on treatment to follow-up).[11]

Furthermore, progression to sustained improvement or deterioration of albuminuria category, in terms of progression to sustained normoalbuminuria or microalbuminuria in patients with macroalbuminuria at baseline (as a measure of improvement in kidney function) and progression to sustained macroalbuminuria in patients with normoalbuminuria or microalbuminuria at baseline (as a measure of deterioration) were also assessed.[12]

Safety was assessed based on adverse events (AEs) reported in subgroups by HF status. Throughout this analysis, AE data were based on investigator reports without any formal adjudication.

Statistical Analysis

For efficacy outcomes, we used a modified intent-to-treat approach to perform analyses in patients treated with ≥1 dose of study drug (treated set) and compared the placebo and pooled empagliflozin (10 and 25 mg) groups. The modification of diet in renal disease formula was used to calculate eGFR at baseline and for all eGFR-based analyses (including slopes). For kidney outcomes, Kaplan-Meier estimates and a Cox proportional hazards model was used to investigate the consistency of the treatment effect between the subgroup of patients with versus without HF at baseline. The Cox model included treatment, age, sex, baseline BMI category, baseline HbA1c category, baseline eGFR, geographic region, prior HF, and treatment-by-prior-heart-failure interaction.

A mixed model, repeated measures analysis was used to evaluate changes from baseline in eGFR over time and included patients who had a baseline and postbaseline eGFR measurement, using all available data, including values obtained on treatment, post-treatment, and after intake of rescue medication. The model included baseline eGFR and baseline HbA1c as linear covariates and geographic region, baseline BMI category, the last week a patient could have had an eGFR measurement, treatment, visit, HF at baseline, treatment by visit interaction, visit by HF at baseline

interaction, treatment by HF at baseline interaction, treatment by visit by HF at baseline interaction, baseline HbA1c by visit interaction, and baseline eGFR by visit interaction as fixed effects. Because measurements of the variable of interest collected from the same patient at different time points are correlated, these data constitute the repeated measures in the mixed model, repeated measures model. Calculation of eGFR slopes within the 3 prespecified study periods was performed by applying a separate random coefficient model for each period allowing for random intercept random slope per patient.[11] The model included baseline HbA1c as a linear covariate, and geographic region, baseline BMI category, heart-failure-at-baseline-by-treatment interaction, and time-by-heart-failure-at-baseline-by-treatment as fixed classification effects. Patients were required to provide at least 2 measurements per study period to be included in the respective analysis, that is, baseline and week 4 measurements for the acute period, and last value on treatment and follow-up measurements for the post-treatment period. Analysis of the treatment-initiation period assumed that any patients lost to follow-up or otherwise excluded were missing completely at random. Analyses for the chronic maintenance and post-treatment periods assumed that any patients lost to follow-up or otherwise excluded before this specific study period were also missing completely at random. In addition, analyses of the chronic maintenance treatment period required that missing data occurring after the start of the chronic phase followed a missing at random mechanism—this includes missing data because of (1) lost to follow-up and (2) artificial censoring when patients discontinued study medication. The missing at random assumption allows the probability of missing data to depend on the observed covariates and the observed values for eGFR but not on the values of eGFR that were not observed.[11]

AEs were assessed descriptively and presented separately for the empagliflozin 10 and 25 mg groups. Exposure-adjusted incidence rates were calculated and included events until 7 days after the last receipt of the study drug. All analyses were performed using SAS version 9.4.

RESULTS

In total, 97.0% of patients completed the study, with 25.4% of patients prematurely discontinuing study medication, and final vital status available for 99.2% of patients.[7]

Baseline Characteristics

At baseline, 244 (10.5%) and 462 (9.9%) individuals in the placebo and empagliflozin group, respectively, had investigator-reported HF. Baseline characteristics for patients with or without HF have been previously published in detail[9]; selected key characteristics are shown in Table 1. Baseline characteristics were generally balanced between the empagliflozin and placebo groups, although some differences were noted between patients with versus without HF. Thus, patients with HF were slightly older, had a higher BMI, and a greater percentage of patients had a history of myocardial infarction or atrial fibrillation, and an eGFR <60 mL/min per 1.73 m^2. As expected, more patients with HF were receiving β-blockers, diuretics, and mineralocorticoid receptor antagonists before randomization (Table 1).

Kidney Outcomes

Patients with HF were at overall greater risk of CKD progression versus those without HF. Thus, the incidence rate of kidney outcome events was numerically higher in patients with concomitant HF (Figure 1). Empagliflozin significantly reduced the risk of clinically relevant kidney outcome events as compared with placebo in both patients with and without HF (all *P* values for interaction >0.05; Figure 1; Figure I in the Data Supplement), and this observation was consistent with findings in the overall population.[8] Similar findings were also seen when all-cause mortality was added in the composite outcome (Figure III in the Data Supplement).

Kidney Function

Figure 2 depicts changes in eGFR over the course of the study. The overall number and percentage of patients included in this analysis were N=6967 and 99.2% of the total population, respectively. Patients with HF had an overall lower baseline eGFR compared with those without HF. Despite this difference in kidney function at baseline, a consistent pattern in eGFR change over time was apparent independent of HF status, which was characterized by an acute decline in eGFR at week 4, followed by a period of stable kidney function during long-term follow-up. This observation was consistent with findings in the overall population.[8]

Adjusted mean eGFR slopes during the 3 prespecified study periods are shown in Figure II in the Data Supplement. During the first 4 weeks of treatment, the weekly mean adjusted eGFR decrease was numerically larger in the empagliflozin compared with the placebo groups (for both subgroups with or without HF; Figure IIA in the Data Supplement). Thereafter, the annual adjusted change in mean eGFR during the chronic maintenance treatment period was stable in both empagliflozin subgroups but declined in the placebo subgroups (Figure IIA in the Data Supplement). During the post-treatment follow-up, the weekly adjusted mean eGFR increased and returned towards mean baseline eGFR levels in the empagliflozin subgroups, whereas there was little change seen in eGFR levels in the placebo groups (Figure IIA in the Data Supplement). As indicated by *P* values for interaction (all >0.05), the pattern of eGFR changes was consistent in the subgroups of patients

Table 1. Baseline Characteristics of Patients With and Without HF at Baseline

	Patients With HF* at Baseline		Patients Without HF* at Baseline	
	Placebo (N=244)	Empagliflozin (N=462)	Placebo (N=2089)	Empagliflozin (N=4225)
Age, mean (SD), y	64.5 (8.9)	64.5 (8.8)	63.1 (8.8)	63.0 (8.5)
Male, n (%)	175 (71.7)	320 (69.3)	1505 (72.0)	3016 (71.4)
eGFR, mean (SD), mL/min per 1.73 m^2	69.3 (20.7)	68.4 (20.2)	74.3 (21.0)	74.8 (21.6)
eGFR, n (%)				
≥90, mL/min per 1.73 m^2	37 (15.2)	73 (15.8)	451 (21.6)	977 (23.1)
60–<90, mL/min per 1.73 m^2	118 (48.4)	215 (46.5)	1120 (53.6)	2208 (52.3)
<60, mL/min per 1.73 m^2	89 (36.5)	174 (37.7)	518 (24.8)	1038 (24.6)
Urine albumin-to-creatinine ratio, n (%)				
<30 mg/g	140 (57.4)	272 (58.9)	1242 (59.5)	2517 (59.6)
30–300 mg/g	72 (29.5)	130 (28.1)	603 (28.9)	1208 (28.6)
>300 mg/g	31 (12.7)	59 (12.8)	229 (11.0)	450 (10.7)
Body mass index, mean (SD), kg/m^2	32.3 (5.4)	31.9 (5.6)	30.5 (5.2)	30.5 (5.2)
Cardiovascular risk factor, n (%)	243 (99.6)	461 (99.8)	2064 (98.8)	4196 (99.3)
Coronary artery disease	209 (85.7)	385 (83.3)	1554 (74.4)	3160 (74.8)
Multivessel coronary artery disease	122 (50.0)	226 (48.9)	978 (46.8)	1953 (46.2)
History of myocardial infarction	164 (67.2)	292 (63.2)	919 (44.0)	1898 (44.9)
Coronary artery bypass graft	70 (28.7)	119 (25.8)	493 (23.6)	1056 (25.0)
History of stroke†	57 (23.4)	108 (23.4)	496 (23.7)	976 (23.1)
Peripheral artery disease	50 (20.5)	100 (21.6)	429 (20.5)	882 (20.9)
Atrial fibrillation	43 (17.6)	76 (16.5)	99 (4.7)	171 (4.0)
Single vessel coronary artery disease†	26 (10.7)	45 (9.7)	212 (10.1)	453 (10.7)
HbA1c, mean (SD), %	8.01 (0.82)	8.11 (0.87)	8.09 (0.85)	8.06 (0.85)
Antihypertensive therapy, n (%)	242 (99.2)	456 (98.7)	1979 (94.7)	3990 (94.4)
ACE inhibitors/angiotensin receptor blockers	206 (84.4)	406 (87.9)	1662 (79.6)	3392 (80.3)
β-blockers	199 (81.6)	360 (77.9)	1299 (62.2)	2696 (63.8)
Diuretics	172 (70.5)	334 (72.3)	816 (39.1)	1713 (40.5)
Loop diuretics	110 (45.1)	224 (48.5)	254 (12.2)	501 (11.9)
Calcium channel blockers	70 (28.7)	111 (24.0)	718 (34.4)	1418 (33.6)
Mineralocorticoid receptor antagonists	53 (21.7)	116 (25.1)	83 (4.0)	189 (4.5)
Renin inhibitors	1 (0.4)	3 (0.6)	18 (0.9)	24 (0.6)
Other	20 (8.2)	33 (7.1)	171 (8.2)	350 (8.3)
Systolic BP, mean (SD), mm Hg	134.9 (19.2)	133.6 (16.9)	135.9 (17.0)	135.4 (16.9)
Diastolic BP, mean (SD), mm Hg	76.4 (10.6)	76.6 (10.2)	76.9 (10.1)	76.6 (9.7)

Data in patients treated with at least one dose of study drug. eGFR: empagliflozin n=4223 for patients without HF at baseline. UACR: placebo n=243 and empagliflozin n=461 for patients with HF at baseline; placebo n=2074 and empagliflozin n=4175 for patients without HF at baseline. ACE indicates angiotensin-converting enzyme; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HF, heart failure; MedDRA, Medical Dictionary for Regulatory Activities; and UACR, urine albumin-to-creatinine ratio.

*Based on narrow Standardized MedDRA Query (SMQ) cardiac failure, which comprised these preferred terms: acute pulmonary edema; cardiac failure; cardiac failure, acute; cardiac failure, chronic; cardiac failure, congestive; cardiogenic shock; cardiopulmonary failure; left ventricular failure; pulmonary edema; and right ventricular failure.

†Information was not available for 1 patient.

with or without HF, and the findings were consistent with those reported in the overall population.[11]

Albuminuria

Figure 3 shows changes in albuminuria over the course of the study. Fewer patients in the empagliflozin versus placebo groups had a deterioration in albuminuria category, defined as progression to sustained macroalbuminuria in patients with normoalbuminuria or microalbuminuria at baseline. This outcome was consistent across the subgroups of patients with or without HF (*P* value for interaction, *P*=0.7957), and the findings were consistent with those reported in the overall population.[12]

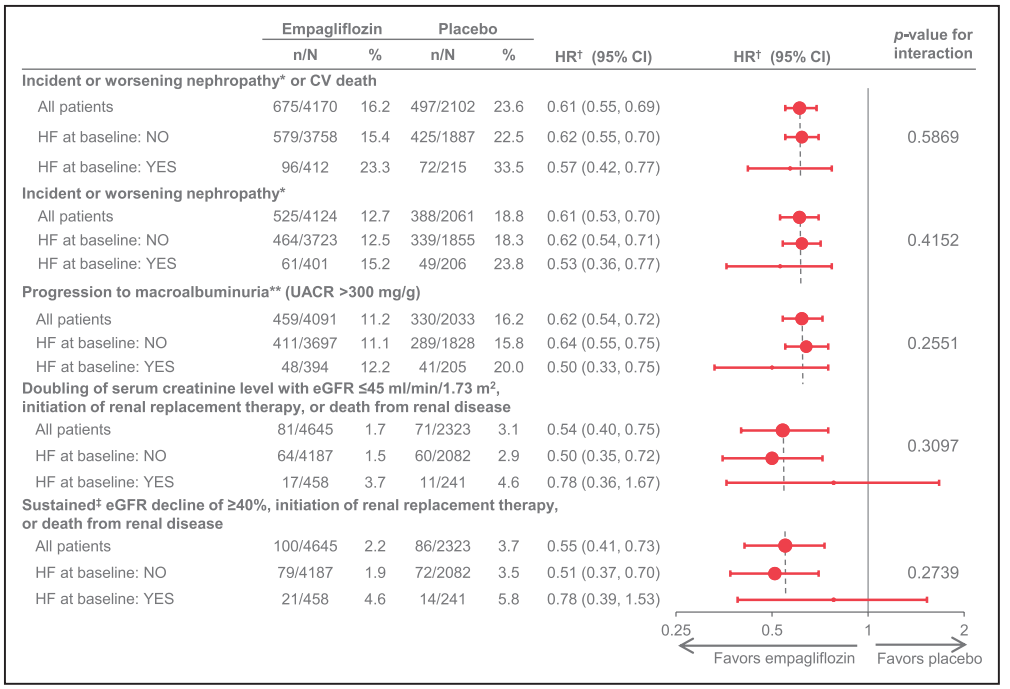

Figure 1. Effects of empagliflozin on kidney outcomes in patients with or without heart failure (HF) at baseline.
CV indicates cardiovascular; and HR, hazards ratio. *Progression to macroalbuminuria (urinary albumin-to-creatinine ratio [UACR] >300 mg/g); a doubling of the serum creatinine level, accompanied by an estimated glomerular filtration rate (eGFR) of ≤45 mL/min per 1.73 m^2; the initiation of renal replacement therapy; or death from renal disease. **Time to macroalbuminuria was assessed only in patients without macroalbuminuria at baseline. †Based on Cox regression analysis in patients who received at least one dose of study drug. ‡Sustained requires 2 consecutive measurements fulfilling the condition that are at least 4 wk apart. eGFR calculated according to Modification of Diet in Renal Disease formula.

Safety

AEs for the overall trial population,[7] as well as in patient subgroups based on HF status,[9] have been previously reported. Overall, percentages of patients with AEs, serious AEs, and AEs leading to discontinuation were similar in the empagliflozin and placebo groups. There again, genital infections were more common in patients receiving empagliflozin versus placebo.[7]

Compared with patients without HF at baseline, a higher proportion of patients with HF at baseline had severe AEs, AEs leading to discontinuation, and serious AEs (including fatal AEs) across both treatment groups.

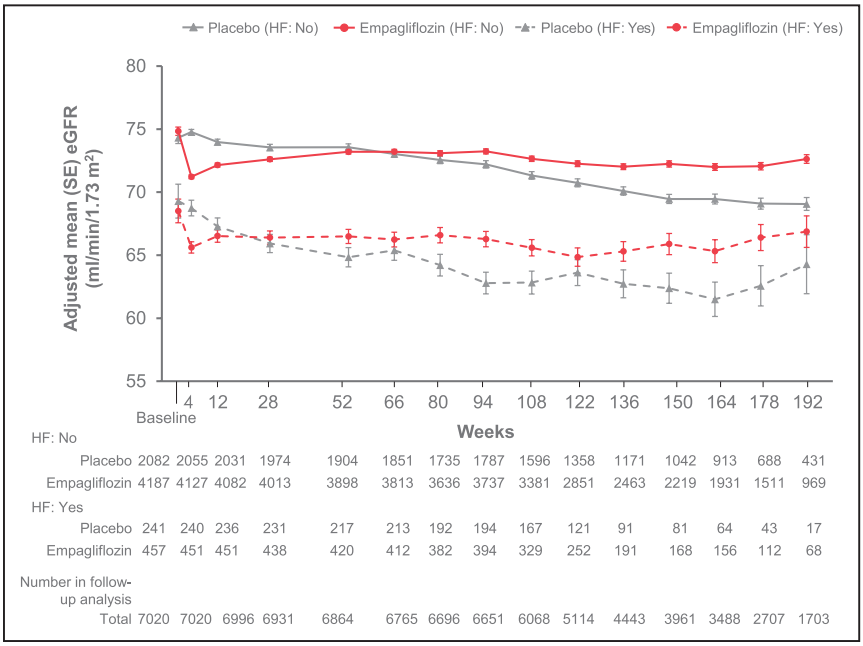

Figure 2. Estimated glomerular filtration rate (eGFR) over time.
N at baseline=6967 (99.2% of total population): patients with at least a baseline and one postbaseline measurement of eGFR. Mixed model, repeated measures analysis in patients who received at least one dose of study drug. HF indicates heart failure.

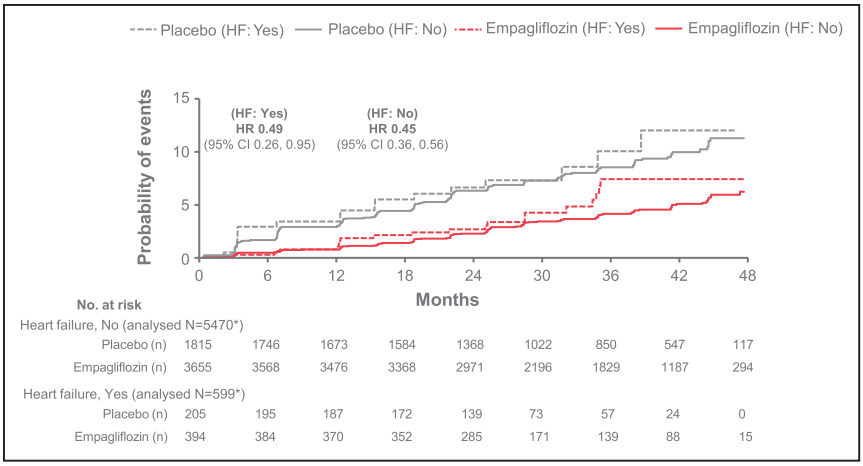

Figure 3. Progression to sustained macroalbuminuria in patients with normoalbuminuria or microalbuminuria at baseline.
HF indicates heart failure; and HR, hazard ratio. *Number of patients with normoalbuminuria or microalbuminuria at baseline who were assessable for this end point.

In the current analysis, we further assessed clinically relevant kidney-related AEs. Overall, the rate of kidney-related AEs per 100 patient-years was higher in patients with than without HF, including events reported as acute kidney failure, acute kidney injury, edema, hyperkalemia, volume depletion, and hypotension (Table 2) across both treatment groups. Notably, however, incidence rates were generally balanced between the empagliflozin and placebo groups, respectively. Moreover, events consistent with edema in the overall population were numerically lower in the empagliflozin groups versus the placebo group, (Table 2) and this observation was independent of HF status.

DISCUSSION

In this post hoc analysis from the EMPA-REG OUTCOME trial, patients with T2DM and concomitant HF were at a greater risk of progressive CKD, eventually leading to adverse kidney outcomes, as compared with patients without HF. Although this clinical observation could have been expected based on previous reports of an increased CKD risk in patients with HF, especially if they also have concomitant diabetes mellitus, our report adds significant new insights into the clinical potential of empagliflozin to improve kidney outcomes in this particular vulnerable patient population. Thus, novel analyses based on HF status of study participants revealed that empagliflozin was associated with a significant reduction in risk across various kidney outcomes, including hard kidney outcomes, such as end-stage kidney disease or renal death as well as the additional risk of premature cardiovascular mortality. Notably, the HF status of patients per se did not alter the beneficial kidney effects observed with empagliflozin, and findings in the HF subgroups were overall consistent with those reported in the overall trial population.

Low GFR is often a concern when initiating novel treatments in patients with HF, in particular, if drugs may be prone to worsening short- and long-term kidney function and, therefore, regular assessment of kidney function is recommended in patients with HF. As expected, patients with HF in EMPA-REG OUTCOME had a lower baseline eGFR compared with patients without HF. However, comprehensive eGFR slopes analyses revealed that the pattern of eGFR changes during treatment of up to 178 weeks was similar for both HF subgroups, namely a transient decrease in eGFR with empagliflozin shortly after treatment initiation followed by stabilization during long-term follow-up, while eGFR levels gradually declined in the placebo groups. The pattern of eGFR changes during treatment initiation and long-term follow-up is in line with results published earlier for the overall EMPA-REG population.[11] These findings serve as a strong indicator that the proposed hemodynamic effect of empagliflozin, that is, a modulation of the glomerular afferent arteriole tone and concomitant reduction in the glomerular hypertension secondary to diabetes mellitus,[13,14] is present whether patients have concomitant HF or not. Moreover, the rapid reversal of eGFR after drug cessation in both HF subgroups further indicates that the renal hemodynamic effect of empagliflozin appeared to be swiftly reversible even after long-term treatment. We think these observations are clinically relevant, as they could support physicians in appropriately interpreting short-term changes in kidney function after starting or stopping empagliflozin, respectively: (1) we did not observe an excess of the initial eGFR dip in patients with HF as compared to those without HF (despite lower eGFR values at treatment initiation of the former) and (2) the rapid recovery of eGFR after drug cessation was not impaired in patients with HF. Most importantly, however, our results suggest that empagliflozin may have the potential to slow progressive kidney function loss in patients with T2DM and concomitant HF.

Albuminuria is another established kidney marker in clinical routine and commonly assessed to stage and monitor kidney damage. Although some drugs indicated for the treatment of patients with HF have also

Table 2. Kidney-Related Adverse Events of Interest in Patients With or Without HF at Baseline

	Placebo (N=2333)		Empagliflozin 10 mg (N=2345)		Empagliflozin 25 mg (N=2342)	
	n/N (%)	Rate*	n/N (%)	Rate*	n/N (%)	Rate*
Acute kidney failure†						
All patients	155/2333 (6.6)	2.77	121/2345 (5.2)	2.07	125/2342 (5.3)	2.12
With HF at baseline	21/244 (8.6)	4.12	22/240 (9.2)	4.26	18/222 (8.1)	3.52
Without HF at baseline	134/2089 (6.4)	2.63	99/2105 (4.7)	1.86	107/2120 (5.0)	1.99
Acute kidney injury						
All patients	37/2333 (1.6)	0.64	26/2345 (1.1)	0.43	19/2342 (0.8)	0.31
With HF at baseline	6/244 (2.5)	1.14	7/240 (2.9)	1.28	3/222 (1.4)	0.57
Without HF at baseline	31/2089 (1.5)	0.59	19/2105 (0.9)	0.35	16/2120 (0.8)	0.29
Edema						
All patients	216/2333 (9.3)	3.95	106/2345 (4.5)	1.81	106/2342 (4.5)	1.80
With HF at baseline	30/244 (12.3)	6.17	9/240 (3.8)	1.66	9/222 (4.1)	1.73
Without HF at baseline	186/2089 (8.9)	3.73	97/2105 (4.6)	1.82	97/2120 (4.6)	1.81
Hyperkalemia						
All patients	65/2333 (2.8)	1.14	30/2345 (1.3)	0.50	39/2342 (1.7)	0.65
With HF at baseline	8/244 (3.3)	1.53	5/240 (2.1)	0.91	7/222 (3.2)	1.34
Without HF at baseline	57/2089 (2.7)	1.10	25/2105 (1.2)	0.46	32/2120 (1.5)	0.58
Volume depletion						
All patients	115/2333 (4.9)	2.04	115/2345 (4.9)	1.97	124/2342 (5.3)	2.11
With HF at baseline	17/244 (7.0)	3.31	22/240 (9.2)	4.19	17/222 (7.7)	3.33
Without HF at baseline	98/2089 (4.7)	1.91	93/2105 (4.4)	1.75	107/2120 (5.0)	2.00
Hypotension						
All patients	58/2333 (2.5)	1.02	57/2345 (2.4)	0.96	62/2342 (2.6)	1.04
With HF at baseline	9/244 (3.7)	1.72	9/240 (3.8)	1.65	12/222 (5.4)	2.33
Without HF at baseline	49/2089 (2.3)	0.95	48/2105 (2.3)	0.89	50/2120 (2.4)	0.92
Dehydration						
All patients	16/2333 (0.7)	0.28	18/2345 (0.8)	0.30	18/2342 (0.8)	0.30
With HF at baseline	1/244 (0.4)	0.19	3/240 (1.3)	0.54	1/222 (0.5)	0.19
Without HF at baseline	15/2089 (0.7)	0.29	15/2105 (0.7)	0.28	17/2120 (0.8)	0.31

HF indicates heart failure; and MedDRA, Medical Dictionary for Drug Regulatory Activities.

*Rate per 100 patient-years (all events occurred within 7 d after the last receipt of the study drug).

†Decreased renal function, a regulatory term defined by the narrow SMQ 20000003 (acute renal failure), which includes 18 preferred terms (acute prerenal failure, anuria, azotemia, hemodialysis, nephropathy toxic, oliguria, peritoneal dialysis, renal failure, renal failure neonatal, renal impairment neonatal, neonatal anuria, hemofiltration, dialysis, renal impairment, continuous hemodiafiltration, acute kidney injury, acute phosphate nephropathy, and prerenal failure). Hyperkalemia was identified via a search of adverse events by using 2 MedDRA preferred terms (hyperkalemia and increased blood potassium). Edema, an adverse event of special interest, was assessed through a search of adverse events defined using 6 MedDRA preferred terms (fluid overload, fluid retention, generalized edema, edema, edema peripheral, and peripheral swelling).

been shown to reduce levels of albuminuria, such as renin-angiotensin system inhibitors or mineralocorticoid receptor antagonists, others have been associated with an increase in albuminuria after treatment initiation, such as angiotensin receptor-neprilysin inhibitors.[15] Because albuminuria is an established marker of increased kidney risk, including in patients with concomitant HF, treatments that lower rather than increase albuminuria levels may have a plausible pathophysiological basis to improve long-term kidney prognosis. Our analyses showed that fewer patients in the empagliflozin-treated groups showed deterioration in albuminuria, in terms of progression to sustained macroalbuminuria in patients who had normoalbuminuria or microalbuminuria at baseline. This outcome was consistent across the subgroups of patients with or without HF, and similar findings have been reported in the overall patient population.[12] The rapid effect of empagliflozin on reducing albuminuria may at least, in part, be explained by the potential of this drug to lower intraglomerular pressure, as previously reported in individuals with T1DM. The consistent albuminuria-lowering effect of empagliflozin in patients with and without HF in EMPA-REG OUTCOME may further sup-

port a hypothesis that increased rather than decreased intraglomerular pressure (distinct from filtration pressure across the glomerular filtration barrier) may be an important pathophysiological component for progressive kidney function loss in patients with T2DM and concomitant HF. Future mechanistic studies to further decipher the renal hemodynamic and intraglomerular adaptations with SGLT2 inhibitors in patients with HF are, therefore, warranted.

Additional mechanisms beyond renal hemodynamics and reductions in intraglomerular pressure have been proposed to explain the kidney protective effects of empagliflozin in EMPA-REG OUTCOME.[16–18] Of these, the effect of empagliflozin on diuresis (osmotic diuresis and natriuresis) could reflect a mechanism with particular importance for patients with HF and associated fluid overload.[17] Increases in 24-hour urine volume of around 300 mL/d have been observed with empagliflozin after the first day of treatment but daily urine output returns to baseline within a few days.[19] Furthermore, SGLT2 inhibition produces an acute but modest natriuresis-related plasma volume contraction, which usually stabilizes within a few weeks, potentially helping to alleviate volume overload and reduce cardiac preload.[16–18] Notably, a recent study showed that osmotic diuresis induced by SGLT2 inhibition has a distinctly different diuretic mechanism than that of other diuretic classes (eg, loop diuretics or thiazides).[20] By using a mathematical model derived from a clinical study in healthy individuals, the authors showed that SGLT2 inhibition resulted in greater electrolyte-free water clearance and, ultimately, in greater fluid clearance from the interstitial fluid space than from the circulation. The model predicted that an SGLT2 inhibitor reduces interstitial fluid volume by 3× as much as it reduces blood volume (480 versus 150 mL, respectively). In comparison, the predicted reduction in interstitial fluid volume with the loop diuretic bumetanide was only 66% of blood volume reduction (510 versus 780 mL, respectively).[20] It may thus be plausible that both plasma, as well as interstitial volume reduction, could contribute to a reduction in the risk of hospitalization for HF, which was observed in EMPA-REG OUTCOME.[9] Furthermore, kidney organ decongestion and, in particular, reduction in kidney venous stasis may positively influence intraglomerular hemodynamics and may, at least in part, restore filtration physiology. In addition, the decrease in myocardial stretch, potentially mediated by contraction of plasma and cardiac interstitial volume, may have reduced cardiac arrhythmogenesis, which has also been proposed as a mechanism for the reduction in cardiovascular mortality seen in the trial.[17]

With regard to renal safety, no notable differences of the effect of empagliflozin were observed between HF subgroups in relation to kidney outcomes, nor with any AEs, serious AEs, and AEs leading to discontinuation of the therapy.[9] Of note, the incidence of acute kidney-related AEs (both injury and failure) was higher in patients with versus without HF at baseline, regardless of treatment.

A prespecified eGFR slopes analysis has been reported in the overall population of EMPA-REG OUTCOME.[8] The findings of the previous slopes analyses support the hypothesis that a hemodynamic effect of empagliflozin would lead to a decrease in intraglomerular pressure, an effect that, during long-term therapy, could result in preservation of kidney function.[11] As stated above, in the current slopes analysis the pattern of changes over 178 weeks with empagliflozin or placebo was similar for both HF subgroups, consistent with findings in the overall population, and suggesting that the effects of empagliflozin in kidney function over time are not affected by baseline HF status.

Several systemic and renal physiological effects, some already mentioned, may be contributing to the kidney-protective effects of empagliflozin observed in the current study. These include the alleviation of renal workload, in particular through via increased distal sodium delivery to the macula densa, activation of tubuloglomerular feedback and decreased hyperfiltration.[17] In addition, empagliflozin may result in a potential improvement in renal oxygenation, resulting from a shift towards more favorable renal fuel energetics.[21,22]

The current study has limitations. The subgroup of patients with HF in this post hoc analysis was modest (and comprises only ≈10% of the overall study population). In addition, the diagnosis of HF at baseline was based on investigator reports according to the narrow Standardized Medical Dictionary for Drug Regulatory Activities Query, in the absence of objective measures of biomarkers or cardiac function. Thus, it was also not possible to further assess the impact of reduced or preserved ejection fraction on kidney outcomes with empagliflozin.

Several randomized clinical trials are now underway to further investigate the potential role of SGLT2 inhibitors as a treatment specifically for HF, and these trials are enrolling HF patients with or without T2DM. These include EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) (URL: https://www.clinicaltrials.gov. Unique identifier: NCT03057977), EMPEROR-Preserved (URL: https://www.clinicaltrials.gov. Unique identifier: NCT03057951), Dapa-HF (URL: https://www.clinicaltrials.gov. Unique identifier: NCT03036124), DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) (URL: https://www.clinicaltrials.gov. Unique identifier: NCT03619213), and SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) (URL: https://www.clinicaltrials.gov. Unique identifier: NCT03521934).

In conclusion, the EMPA-REG OUTCOME trial previously reported that empagliflozin significantly reduced the risk of clinically relevant kidney outcomes[8] and slowed progression of CKD.[23] Novel insights from this post hoc analysis add to this evidence by showing that these beneficial kidney effects of empagliflozin are also seen in the particular high-risk population of patients with concomitant HF. This suggests that reduction in intraglomerular pressure may have the potential to benefit long-term kidney outcomes in HF populations, and further clinical research addressing this hypothesis is currently underway.

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