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Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial

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Aims We previously reported that in the EMPA-REG OUTCOME® trial, empagliflozin added to standard of care reduced the risk of 3-point major adverse cardiovascular events, cardiovascular and all-cause death, and hospitalization for heart failure in patients with type 2 diabetes and high cardiovascular risk. We have now further investigated heart failure outcomes in all patients and in subgroups, including patients with or without baseline heart failure.

Methods and results Patients were randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo. Seven thousand and twenty patients were treated; 706 (10.1%) had heart failure at baseline. Heart failure hospitalization or cardiovascular death occurred in a significantly lower percentage of patients treated with empagliflozin [265/4687 patients (5.7%)] than with placebo [198/2333 patients (8.5%)] [hazard ratio, HR: 0.66 (95% confidence interval: 0.55–0.79); $P < 0.001$], corresponding to a number needed to treat to prevent one heart failure hospitalization or cardiovascular death of 35 over 3 years. Consistent effects of empagliflozin were observed across subgroups defined by baseline characteristics, including patients with vs. without heart failure, and across categories of medications to treat diabetes and/or heart failure. Empagliflozin improved other heart failure outcomes, including hospitalization for or death from heart failure [2.8 vs. 4.5%; HR: 0.61 (0.47–0.79); $P < 0.001$] and was associated with a reduction in all-cause hospitalization [36.8 vs. 39.6%; HR: 0.89 (0.82–0.96); $P = 0.003$]. Serious adverse events and adverse events leading to discontinuation were reported by a higher proportion of patients with vs. without heart failure at baseline in both treatment groups, but were no more common with empagliflozin than with placebo.

Conclusion In patients with type 2 diabetes and high cardiovascular risk, empagliflozin reduced heart failure hospitalization and cardiovascular death, with a consistent benefit in patients with and without baseline heart failure.

Keywords Cardiovascular disease • Hospitalization • Mortality

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Introduction

Heart failure is highly prevalent in patients with diabetes,[1,2] occurring in more than one in five patients with diabetes aged over 65 years.[1] Patients with both diabetes and heart failure have a poor prognosis, with a median survival of approximately 4 years.[3] Glucose-lowering treatment options for patients with type 2 diabetes and heart failure are limited. In a meta-analysis, no benefit on heart failure hospitalization or death was demonstrated with more intensive vs. less intensive glucose control.[4] Furthermore, specific glucose-lowering medications have not been shown to improve heart failure outcomes and some may actually have deleterious effects.[5–8]

Empagliflozin is a potent and selective inhibitor of the sodium glucose cotransporter 2 (SGLT2) used in the treatment of type 2 diabetes. By inhibiting SGLT2, empagliflozin reduces renal glucose reabsorption and increases urinary glucose excretion.[9] In addition to reducing hyperglycaemia, empagliflozin is associated with osmotic diuresis, reductions in weight and blood pressure without increases in heart rate,[10–17] and has favourable effects on markers of arterial stiffness and vascular resistance,[18] albuminuria,[17] and serum uric acid.[10–16]

In the EMPA-REG OUTCOME® trial, treatment with empagliflozin added to standard of care reduced the primary composite outcome of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (3-point major adverse cardiovascular events), cardiovascular death, hospitalization for heart failure, and overall mortality compared with placebo in patients with type 2 diabetes and high cardiovascular risk.[19] Here we report further analyses of the EMPA-REG OUTCOME® trial with respect to heart failure outcomes in the overall patient population and in subgroups, including patients with investigator-reported heart failure at baseline, and the effect of empagliflozin on hospitalization due to any cause.

Methods

Study design

The design of the EMPA-REG OUTCOME® trial (NCT01131676) has been described.[19,20] Briefly, the study population comprised patients with type 2 diabetes (with glycated haemoglobin 7.0–9.0% for drug-naïve patients and 7.0–10.0% for those on stable glucose-lowering therapy), established cardiovascular disease, and estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2. Patients with investigator-reported heart failure at baseline were allowed to participate without any restriction regarding ejection fraction or New York Heart Association (NYHA) class. Participants were randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily as addition to standard of care. Throughout the trial (or after week 12 for glucose-lowering medication), investigators were encouraged to treat cardiovascular risk factors to achieve optimal standard of care according to local guidelines. The trial continued until at least 691 patients experienced an adjudicated event included in the primary outcome: first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (3-point major adverse cardiovascular events). Patients who prematurely discontinued study medication continued to be followed for ascertainment of cardiovascular outcomes and vital status.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines and was approved by local authorities. An independent ethics committee or institutional review board approved the clinical protocol at every participating centre. All the patients provided written informed consent before study entry.

Safety was assessed based on adverse events that occurred during treatment or $\leq$7 days after the last intake of study medication, coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) version 18.0. Oedema, an adverse event of special interest, was assessed through a search of adverse events defined using six MedDRA preferred terms (fluid overload, fluid retention, generalized oedema, oedema, oedema peripheral, peripheral swelling).

Outcomes

Definitions of the major clinical outcomes in the EMPA-REG OUTCOME® trial have been published.[19] All cardiovascular outcome events and deaths were prospectively adjudicated by two Clinical Events Committees (for cardiac and neurological events).[19] Outcomes assessed included hospitalization for heart failure, the composite outcome of heart failure hospitalization or cardiovascular death (excluding fatal stroke), recurrent heart failure hospitalization, investigator-reported heart failure, introduction of loop diuretics, death from heart failure, and all-cause hospitalization (defined as hospitalization due to any adverse event). Subgroup analyses were performed in subgroups defined by baseline characteristics, including the presence/absence of investigator-reported heart failure.

Hospitalization for heart failure was defined as an event requiring at least an admission to an in-patient unit or a 12 h stay in the emergency department as a result of clinical manifestations of new or worsening heart failure. These included dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, oedema, pulmonary basilar crackles, jugular venous distension, third heart sound or gallop rhythm, and radiological evidence of worsening heart failure. An additional criterion was the need for added or increased therapy that included (i) initiation or up-titration of diuretics, inotropes, or vasodilator therapy and/or (ii) initiation of mechanical or surgical therapy, such as mechanical circulatory support, heart transplantation, or ventricular pacing to improve cardiac function, and/or (iii) use of ultrafiltration, haemofiltration, or dialysis directed at the treatment of heart failure.

Investigator-reported heart failure was based on the narrow standardized MedDRA query (SMQ) 'cardiac failure' (defined in *Table 1*). This narrow SMQ was also used to define whether a patient had heart failure at baseline.

Statistical analysis

It was pre-specified that analyses would compare the pooled empagliflozin dose groups vs. placebo. Treatment group differences in the risk of an outcome were assessed using a Cox proportional hazards model with treatment, age, sex, baseline body mass index, baseline glycated haemoglobin, baseline eGFR, and region as factors. Subgroup analyses included additional effects for a subgroup factor and a treatment by subgroup factor interaction. Cumulative incidence function estimates were corrected for non-cardiovascular mortality as a competing risk.[21] Due to the declining numbers of patients at risk, cumulative incidence plots have been truncated at 48 months. Numbers needed to treat were computed from an estimate of the risk difference based on an exponential model with a linearized (constant) hazard over time.

The primary analyses were conducted following a modified intent-to-treat approach in patients treated with at least one dose of study drug. Each patient who did not have an event was censored on the last day they were known to be free of the outcome. Secondary

Table 1 Heart failure outcomes and all-cause hospitalization

Outcome	Placebo ($N = 2333$)		Empagliflozin ($N = 4687$)		HR (95% CI)	*P*-value
	n (%)	Rate/1000 patient-years	*n* (%)	Rate/1000 patient-years		
Heart failure hospitalization or cardiovascular death	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001
Hospitalization for or death from heart failure	104 (4.5)	15.8	129 (2.8)	9.6	0.61 (0.47–0.79)	<0.001
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Investigator-reported heart failure[a]	143 (6.1)	22.0	204 (4.4)	15.3	0.70 (0.56–0.87)	0.001
Investigator-reported serious heart failure[a,b]	136 (5.8)	20.9	192 (4.1)	14.4	0.69 (0.55–0.86)	0.001
All-cause hospitalization	925 (39.6)	183.3	1725 (36.8)	161.9	0.89 (0.82–0.96)	0.003

CI, confidence interval; HR, hazard ratio; MedDRA, Medical Dictionary for Regulatory Activities.
[a]Based on narrow standardized MedDRA query 'cardiac failure', which comprised these preferred terms: acute pulmonary oedema; cardiac failure; cardiac failure, acute; cardiac failure, chronic; cardiac failure, congestive; cardiogenic shock; cardiopulmonary failure; left ventricular failure; pulmonary oedema; right ventricular failure.
[b]Adverse events reported as serious adverse events by investigator. Patients treated with at least one dose of study drug.

analyses included comparisons of the individual doses (empagliflozin 10 mg or 25 mg) vs. placebo. Pre-specified sensitivity analyses were performed based on only those events that occurred during treatment or ≤30 days after a patient's last intake of study drug ('treated set plus 30 days'), and based on only those events that occurred during treatment or ≤30 days after a patient's last intake of study drug in patients who received ≥30 days of study medication (cumulative) ('on-treatment set').

All analyses were performed on a nominal level of $\alpha = 0.05$ two sided without adjustment for multiplicity. Statistical analyses were performed using SAS® version 9.4. All analyses were pre-specified except for: analyses in the subgroups of patients with and without heart failure at baseline of cardiovascular death, all-cause mortality, hospitalization for heart failure, and adverse events; analyses in the subgroups of patients by use of loop diuretics at baseline; introduction of loop diuretics; hospitalization for heart failure by use of mineralocorticoid receptor antagonists at baseline; recurrent events of heart failure hospitalization or cardiovascular death (composite); and all-cause hospitalization.

Results

Patients

A total of 7020 patients at 590 sites in 42 countries received at least one dose of study drug. The baseline characteristics of the study population, including medications used at baseline, have been described.[19] Mean (SD) age was 63.1 (8.6) years, mean (SD) body mass index was 30.6 (5.3) kg/m^2, 72% were male, 25.9% had eGFR <60 mL/min/1.73 m^2, 46.6% had a history of myocardial infarction, 10.1% had heart failure, and 5.5% had atrial fibrillation. At baseline, ~81% of patients were on angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, 65% on β-blockers, 43% on diuretics, and 6% on mineralocorticoid receptor antagonists.

Patient disposition in this trial has been described.[19] Overall, 97% of patients completed the study, with 25% of patients prematurely discontinuing study drug. In both treatment groups, the most common reason for premature discontinuation of study medication was adverse events.[19] The median duration of treatment was 2.6 years and the median observation time was 3.1 years. Final vital status was available for 99% of patients.

Heart failure outcomes and cardiovascular death in overall patient population

The composite outcome of heart failure hospitalization or cardiovascular death occurred in a significantly lower percentage of patients treated with empagliflozin [265/4687 patients (5.7%)] than placebo [198/2333 patients (8.5%)] [hazard ratio, HR: 0.66 (95% confidence interval, 95% CI: 0.55–0.79; $P < 0.001$)] (*Figure 1A* and *Table 1*).[19] The effect of empagliflozin on heart failure hospitalization or cardiovascular death was consistent between doses (see Supplementary material online, *Table S1* and *Figure S1*) and across subgroups defined by a variety of baseline characteristics including age, race, eGFR, and use of glucose-lowering (including insulin) and cardiovascular medications [including renin-angiotensin-aldosterone system blockers, β-blockers, diuretics (including loop diuretics), and statins] (*Figure 2*); subgroup analyses of 3-point major adverse cardiovascular events and cardiovascular death by use of loop diuretics at baseline are shown in Supplementary material online, *Figure S2*. The results of sensitivity analyses were consistent with the primary analyses (see Supplementary material online, *Figure S3*), and there were no differences in censoring between empagliflozin and placebo. The median (interquartile range) of time to censoring for heart failure hospitalization or cardiovascular death was 1167 (802–1297) days in the placebo group and 1167 (805–1307) days in the empagliflozin group. Empagliflozin also reduced the risk of the composite outcome of hospitalization for heart failure or death from heart failure (*Table 1*).

As previously reported, hospitalization for heart failure occurred in a significantly lower percentage of patients treated with empagliflozin [126/4687 patients (2.7%)] than with placebo [95/2333 patients (4.1%)] [HR: 0.65 (95% CI: 0.50–0.85); $P = 0.002$].[19] The effect of empagliflozin on this outcome was consistent across doses, sensitivity analyses, and subgroups defined by baseline characteristics (*Figure 2*; see Supplementary material online, *Table S1* and *Figure S3*). In the 126 patients with at least one heart failure hospitalization event in the empagliflozin group, 43 patients had 111 recurrent events (either heart failure readmission or cardiovascular death), while in the 95 patients with at least one heart failure

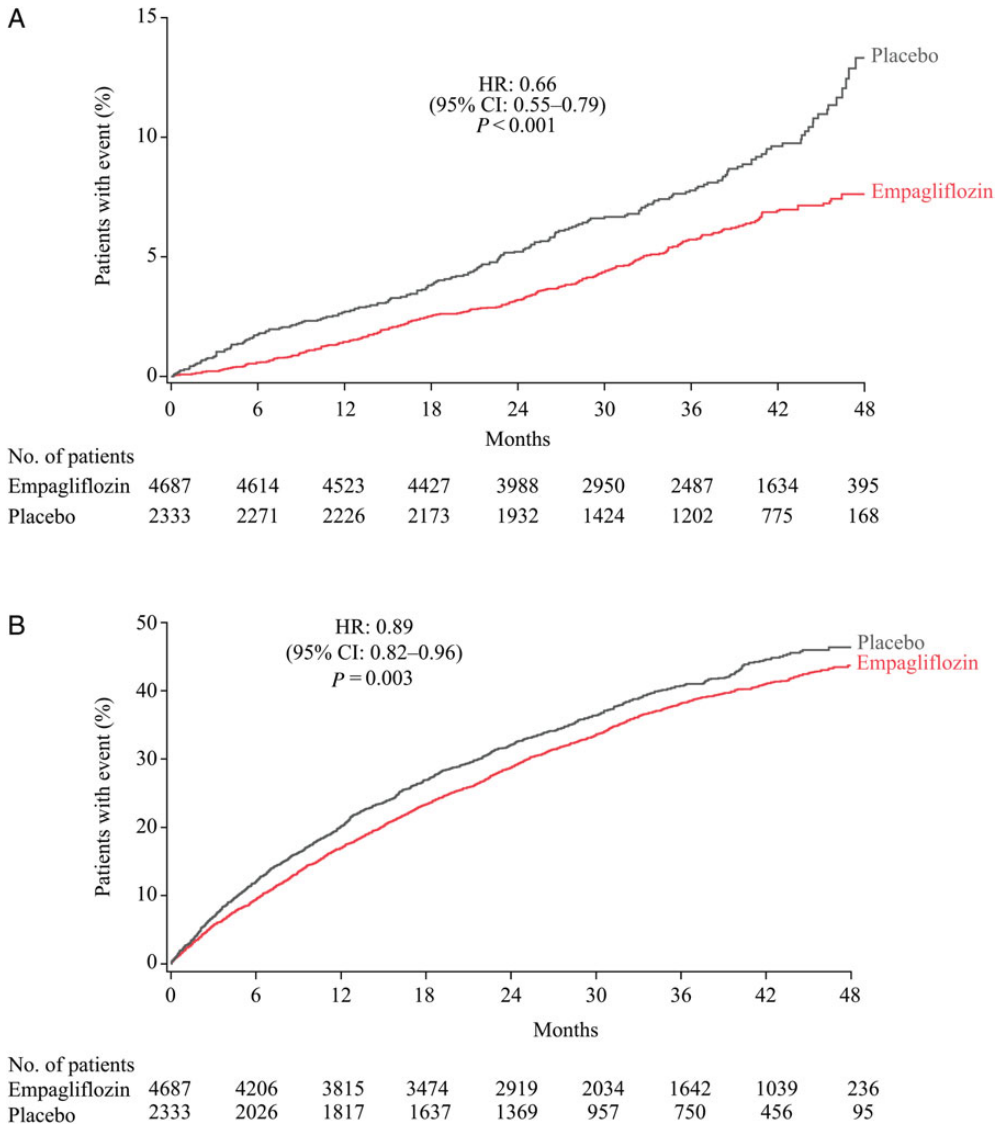

Figure 1 (*A*) Time to first hospitalization for heart failure or cardiovascular death. (*B*) Time to first all-cause hospitalization. Cumulative incidence function. Patients treated with at least one dose of study drug. HR, hazard ratio; CI, confidence interval.

hospitalization event in the placebo group, 43 patients had 115 recurrent events (see Supplementary material online, *Table S2*). Information on readmission for heart failure is shown in Supplementary material online, *Table S3*. Among patients who were hospitalized for heart failure during the study, a smaller proportion of patients treated with empagliflozin than with placebo died of cardiovascular causes [17 (13.5%) vs. 23 (24.2%)] (see Supplementary material online, *Table S2*).

Consistent with the adjudicated results, the proportions of patients with investigator-reported heart failure and with investigator-reported serious heart failure were significantly lower with empagliflozin than with placebo (*Table 1*). Loop diuretics were introduced in a significantly lower proportion of patients in the empagliflozin group than the placebo group [HR: 0.62 (95% CI: 0.53–0.73); $P < 0.001$] (see Supplementary material online, *Figures S4* and *S5*). Empagliflozin also reduced the risk of the composite outcomes of hospitalization for heart failure or introduction of loop diuretics [HR: 0.63 (95% CI: 0.54–0.73); $P < 0.001$] and heart failure hospitalization or cardiovascular death or introduction of loop diuretics [HR: 0.64 (95% CI: 0.56–0.73); $P < 0.001$] (see Supplementary material online, *Figures S4 and S5*). Furthermore, all-cause hospitalization occurred in a significantly lower percentage of patients treated with empagliflozin than with placebo (*Figure 1B*, *Table 1*; Supplementary material online, *Figure S6*).

As previously reported, empagliflozin was associated with a significant reduction in cardiovascular death compared with placebo, consistent across doses, sensitivity analyses, and patient subgroups defined by a variety of baseline characteristics.[19]

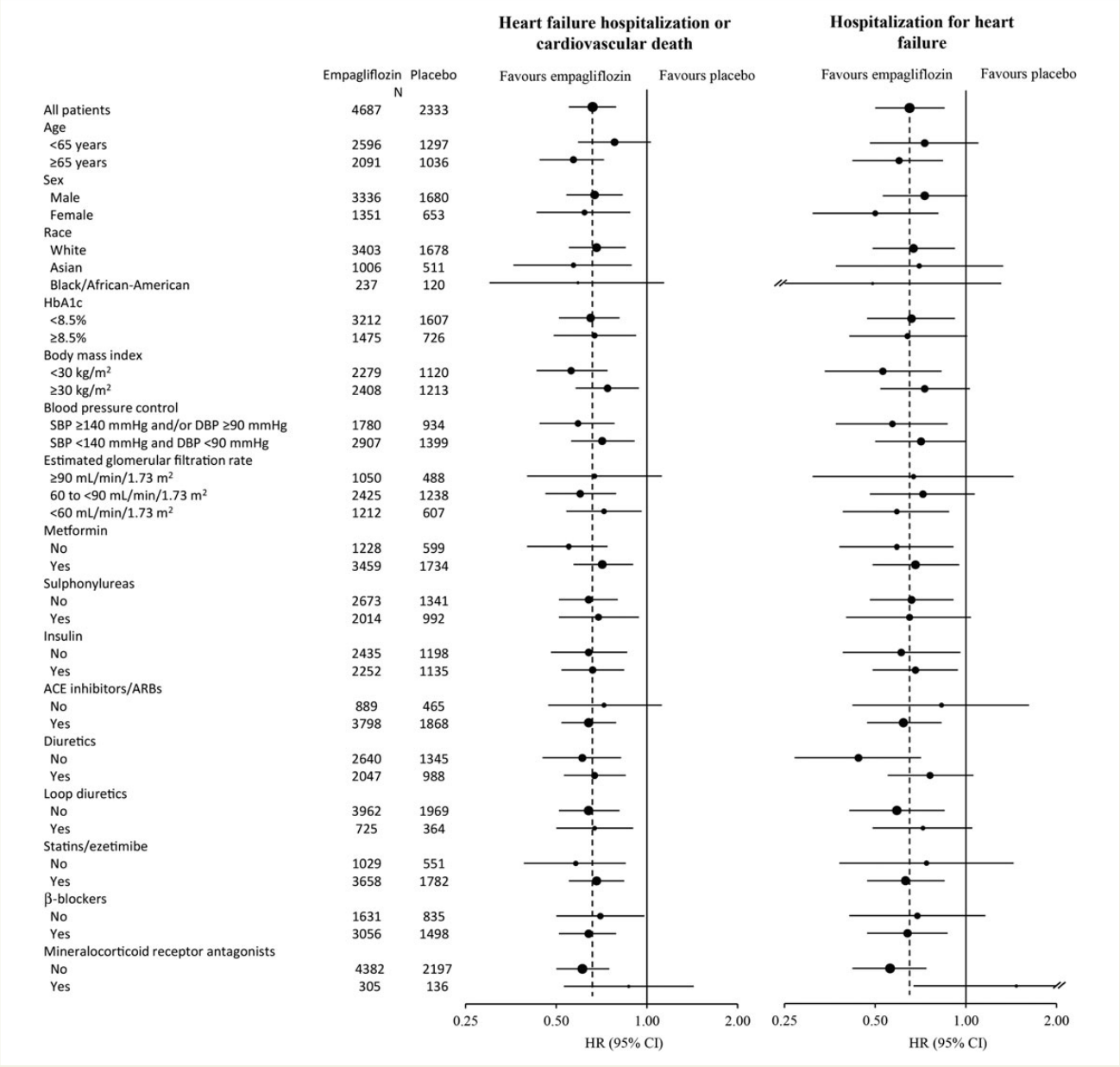

Figure 2 Subgroup analyses of heart failure hospitalization or cardiovascular death and hospitalization for heart failure by baseline characteristics. Patients treated with at least one dose of study drug. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; HR, hazard ratio; SBP, systolic blood pressure.

Outcomes in patients with vs. without heart failure at baseline

At baseline, 244 (10.5%) patients in the placebo group and 462 (9.9%) patients in the empagliflozin group had investigator-reported heart failure. Compared with patients without heart failure at baseline, patients with heart failure at baseline were slightly older, had a higher weight and body mass index, and a greater proportion had eGFR <60 mL/min/1.73 m^2, a history of myocardial infarction or atrial fibrillation, and were receiving insulin, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, diuretics, and mineralocorticoid receptor antagonists (see Supplementary material online, *Table S4*). Within the subgroups by presence/absence of heart failure at baseline, baseline characteristics were balanced between the empagliflozin and placebo groups. Systolic and diastolic blood pressure, weight, and haematocrit over the course of the study in patients with and without heart failure at baseline are shown in Supplementary material online, *Figure S7*.

Incidence rates for heart failure hospitalization or cardiovascular death, hospitalization for heart failure, cardiovascular death, and all-cause mortality were two- to six-fold higher in patients with heart failure at baseline compared with patients without heart failure at baseline (see Supplementary material online, *Table S5*). However, the reductions in the risk of these outcomes with

	Empagliflozin		Placebo		HR (95% CI)
	n with event/*n*	%	*n* with event/*n*	%	
Heart failure hospitalization or cardiovascular death					
All patients	265/4687	5.7	198/2333	8.5	0.66 (0.55–0.79)
Heart failure at baseline					
No	190/4225	4.5	149/2089	7.1	0.63 (0.51–0.78)
Yes	75/462	16.2	49/244	20.1	0.72 (0.50–1.04)
Hospitalization for heart failure					
All patients	126/4687	2.7	95/2333	4.1	0.65 (0.50–0.85)
Heart failure at baseline					
No	78/4225	1.8	65/2089	3.1	0.59 (0.43–0.82)
Yes	48/462	10.4	30/244	12.3	0.75 (0.48–1.19)
Cardiovascular death					
All patients	172/4687	3.7	137/2333	5.9	0.62 (0.49–0.77)
Heart failure at baseline					
No	134/4225	3.2	110/2089	5.3	0.60 (0.47–0.77)
Yes	38/462	8.2	27/244	11.1	0.71 (0.43–1.16)
All-cause mortality					
All patients	269/4687	5.7	194/2333	8.3	0.68 (0.57–0.82)
Heart failure at baseline					
No	213/4225	5.0	159/2089	7.6	0.66 (0.51–0.81)
Yes	56/462	12.1	35/244	14.3	0.79 (0.52–1.20)

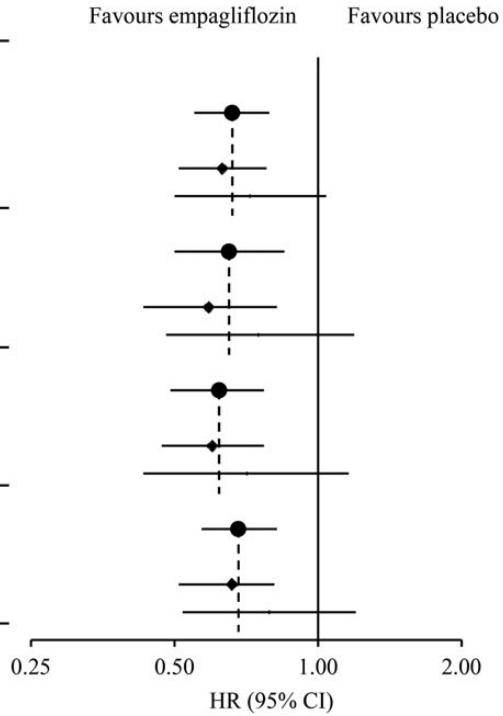

Figure 3 Outcomes in patients with and without heart failure at baseline. Cox regression analysis. Patients treated with at least one dose of study drug. CI, confidence interval; HR, hazard ratio.

empagliflozin were consistent in patients with and without heart failure at baseline (*Figure 3*). Categories of cardiovascular death in patients with and without heart failure at baseline are shown in Supplementary material online, *Table S6*.

Safety and tolerability

In the overall patient population, the percentages of patients with adverse events, serious adverse events, and adverse events leading to discontinuation were similar in the empagliflozin and placebo groups, but genital infections were more common in patients treated with empagliflozin than with placebo.[19] Adverse events consistent with oedema were reported in a higher proportion of patients treated with placebo [216/2333 (9.3%)] than with empagliflozin [212/4687 (4.5%)]. Adverse events consistent with volume depletion were observed in similar proportions of patients in the placebo [115/2333 (4.9%)] and empagliflozin [239/4687 (5.1%)] groups.

In patients with heart failure at baseline, the proportions of patients with severe adverse events, serious adverse events, and adverse events leading to discontinuation were higher compared with patients without heart failure at baseline in both treatment groups. However, lower proportions of patients treated with empagliflozin than with placebo had adverse events, serious adverse events, and adverse events leading to discontinuation (see Supplementary material online, *Table S7*).

Discussion

In the EMPA-REG OUTCOME® trial, the SGLT2 inhibitor empagliflozin, given in addition to standard of care, reduced the risk of the composite endpoint of hospitalization for heart failure or cardiovascular death, as well as its individual components, in patients with type 2 diabetes and established cardiovascular disease. Consistent reductions were observed across subgroups of patients defined by a variety of clinical characteristics, including the presence of heart failure at baseline and the use of medications commonly used in the treatment of patients with type 2 diabetes and/or heart failure, and between the two dose groups. In addition, empagliflozin reduced all-cause hospitalization, with both hospitalization for heart failure and hospitalization for other causes contributing to this reduction. The lower rate of introduction of loop diuretics in the empagliflozin group is consistent with a reduced incidence of hospitalization for heart failure. Importantly, prior to these findings, no glucose-lowering drug had been shown to improve heart failure outcomes in patients with type 2 diabetes. Indeed, the thiazolidinediones and the DPP-4 inhibitor saxagliptin have been associated with increased risk of heart failure hospitalization in patients with type 2 diabetes at high cardiovascular risk.[22]

Heart failure is a common comorbidity and a common cause of hospitalization in patients with type 2 diabetes, presenting a high medical need for effective therapies. Treatment of patients with type 2 diabetes and heart failure presents challenges for physicians due to a lack of evidence-based guidelines on the optimal management of such patients. Guidelines published by the European Society of Cardiology (ESC) in 2012[23] and by the ESC in collaboration with the European Association for the Study of Diabetes (EASD) in 2013[24] recognized the lack of adequate evidence on the safety and efficacy of drugs used to treat diabetes in patients with heart failure, as well as the need for further research into whether glucose-lowering therapies can reduce the progression of heart failure.

Preventing hospital admission and improving survival are key goals of the treatment of patients with heart failure.[23] Importantly, empagliflozin reduced hospitalization for heart failure, cardiovascular death, and all-cause mortality to the same extent in patients with heart failure at baseline, who had high use of medications used to treat heart failure, as in patients without heart failure at baseline. Thus, the overall effect of empagliflozin on these important outcomes was not predominantly driven by patients with heart failure at baseline. Of note, patients who survived a hospitalization for heart failure were at high risk of subsequent mortality. Similar observations were made in the SAVOR-TIMI 53 study, in which 26% of patients hospitalized for heart failure died.[7]

Our study has several limitations. The diagnosis of heart failure at baseline was based solely on the report of investigators according to the narrow SMQ, with no measures of cardiac function or biomarkers, such as brain natriuretic peptide, recorded. However, given the baseline characteristics of these patients, including the high use of drugs to treat heart failure and the high incidence of hospitalizations for heart failure and cardiovascular death, it is reasonable to assume that this was indeed largely a population of patients with pre-existing heart failure. The type of heart failure outcomes relative to ejection fraction could not be assessed based on the data available; thus, we cannot conclude on the applicability of these results with regard to reduced or preserved ejection fraction heart failure. In addition, the subgroup of patients with heart failure at baseline was relatively small and several of our analyses were conducted *post hoc*. The diagnosis of hospitalization for heart failure included the initiation or up-titration of oral or intravenous diuretic medication rather than the more stringent requirement of initiation of intravenous diuretic medication such as used in another study.[7] However, patients hospitalized with heart failure had a high risk of mortality, consistent with the diagnosis.

The effect of empagliflozin on heart failure hospitalization or cardiovascular death and on all-cause hospitalization was observed very early and was sustained throughout the trial. This suggests that the benefit was not driven by an effect on atherosclerosis. The mechanisms behind the effects of empagliflozin on heart failure and cardiovascular death are unknown. Potential contributors include osmotic diuresis, effects on plasma volume and sodium retention with modulation of the cardio-renal axis,[25,26] reductions in arterial stiffness and the rate pressure product, indicating diminished left ventricular afterload,[18] reductions in weight and blood pressure without increases in sympathetic nervous activity,[27] reductions in hyperglycaemia with concomitant reductions in insulin levels,[28] and reductions in uric acid.

In this trial, empagliflozin reduced the risk of hospitalization for heart failure or cardiovascular death by 34%, corresponding to a number needed to treat to prevent one heart failure hospitalization or cardiovascular death of 35 over 3 years. It remains unknown whether the benefits on outcomes reported herein apply to patient populations with other clinical characteristics.

In conclusion, in patients with type 2 diabetes and high cardiovascular risk, empagliflozin, given in addition to standard of care, reduced heart failure hospitalization and cardiovascular death,

with a consistent benefit observed in patients with and without heart failure at baseline.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

S.H. performed statistical analysis; S.H., A.S., O.E.J., H.J.W, and U.C.B. handled funding and supervision; B.Z. acquired the data; D.F., B.Z., C.W., J.M.L., S.H., A.S., O.E.J., H.J.W., U.C.B., and S.E.I. conceived and designed the research; D.F., S.E.I., and S.H. drafted the manuscript; and B.Z., C.W., J.M.L., S.H., A.S., O.E.J., H.J.W., and U.C.B. made critical revision of the manuscript for key intellectual content.

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Conflict of interest: D.F. has received personal fees from Boehringer Ingelheim, Novo Nordisk, AstraZeneca, Sanofi, and Merck & Co. B.Z. has received personal fees from Boehringer Ingelheim, Merck & Co, Novo Nordisk, Sanofi, Eli Lilly and Company, Takeda, AstraZeneca, and Janssen and has received grants from Boehringer Ingelheim, Merck & Co, and Novo Nordisk. C.W. has received a grant from Boehringer Ingelheim. J.M.L. has received personal fees from Boehringer Ingelheim, Merck & Co, Gilead Sciences, Janssen, and Novartis. S.H., A.S., O.E.J., H.J.W. and U.C.B. are employees of Boehringer Ingelheim. S.E.I. has received personal fees from Merck & Co, Janssen, Novo Nordisk, Sanofi, Regeron, Intarcia, Lexicon, Poxel, and Eli Lilly and Company; received personal fees and non-financial support from Boehringer Ingelheim; and received non-financial support from Takeda.

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