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Original Research Paper

General Medicine

EFFECT OF EMPAGLIFLOZIN ON SERIOUS ADVERSE RENAL OUTCOMES IN CHRONIC HEART FAILURE

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KEYWORDS :

INTRODUCTION

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

In large-scale, randomized, placebo-controlled trials, the risk of hospitalization for heart failure was 30 to 35% lower among patients who received SGLT2 inhibitors compared to those who received placebo; this benefit was most striking in patients who had a left ventricular ejection fraction of 30% or less before treatment. In addition, the risk of progression of renal disease (including the occurrence of renal death or the need for dialysis or renal transplantation) was 35 to 50% lower compared to patients who received SGLT2 inhibitors than among those who received placebo. [2]

These observations are consistent with the hypothesis that SGLT2 inhibitors may slow the progression of cardiac and renal disease, regardless of cause and independent of the presence or absence of diabetes. [2]

Empagliflozin, a selective sodium–glucose cotransporter 2 inhibitor, reduces hyperglycaemia in patients with type 2 diabetes by reducing the renal reabsorption of glucose, thereby increasing urinary glucose excretion. [3] The use of empagliflozin has been associated with a lowering of glycated haemoglobin levels in patients with type 2 diabetes, including those with stage 2 or 3a chronic kidney disease, and with reductions in weight and blood pressure, without increases in heart rate.[4-11] Empagliflozin has been shown to reduce intraglomerular pressure and improve hyperfiltration in patients with type 1 diabetes,[12,13] and it has been suggested that these effects may translate into improved renal outcomes.[14]

Empagliflozin on Cardiovascular and Renal Outcomes in Patients with Heart Failure by Baseline Diabetes Status: The EMPEROR-Reduced Trial

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. The study group prespecified a comparison of the effect of empagliflozin in patients with and without diabetes.[1]

Out of 3730 patients enrolled, 1856 (50%) had diabetes, 1268 (34%) had prediabetes (haemoglobin A1c [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 greater in patients with diabetes but were similar between patients with prediabetes and normoglycemia. [1]

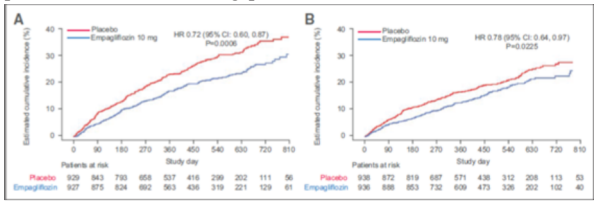

Figure 1. Effect of empagliflozin on the primary end point of EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction).

Time to first event of either cardiovascular death or heart failure hospitalization in (A) patients with diabetes and (B) patients without diabetes. HR indicates hazard ratio.

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

Empagliflozin lowered 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, P-interaction=0.57). Also, patients with and without diabetes 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. The effects of the drug did not differ in patients with prediabetes or normoglycemia among these end points. When analysed 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 as well as was not associated with increased risk of hypoglycemia.[1]

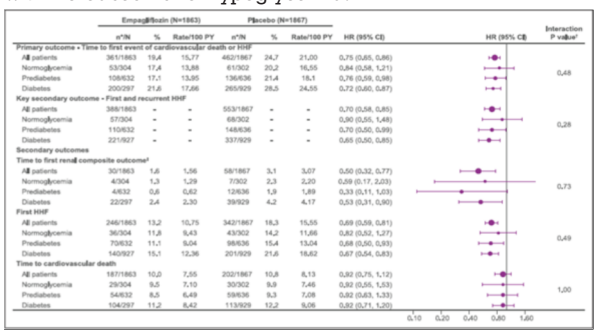

Figure 2: Treatment Effect Of Empagliflozin Vs Placebo On Primary And Secondary Outcomes In Patients With Normoglycemia, Prediabetes, And Diabetes.

Recurrent event analyses are based on a joint frailty model accounting for competing risk of cardiovascular death. *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 end point: time to first event of chronic dialysis or renal transplant or sustained reduction of ≥40% estimated glomerular filtration rate (eGFR; Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]cr); or for patients with eGFR (CKD-EPI)cr ≥30 mL/min/1.73 m^2 at baseline: sustained eGFR <15 mL/min/1.73 m^2; for patients with eGFR (CKD-EPI)cr <30 mL/min/1.73 m^2 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 2 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. HHF indicates hospitalization for heart failure.

Empagliflozin Improves Renal And Cardiovascular Outcomes In Heart Failure Irrespective Of Systolic Blood Pressure

The goal of the study was to evaluate the interplay of SBP and the effects of empagliflozin in EMPEROR-Reduced. The study explored the influence of SBP on the effects of empagliflozin on cardiovascular death or HF hospitalization (primary outcome), as well as on total HF hospitalizations, rate of decline in estimated glomerular filtration rate, renal outcomes, and empagliflozin's effects and significance on SBP.[15]

Corrected for placebo, a small early increase was observed in SBP at <110 mm Hg, no change at 110-130 mm Hg, and a slight reduction at >130 mm Hg. These between-group differences were of borderline significance (*P* for interaction trend = 0.05-0.10) after 4 and 12 weeks but were not significant later. SBP at baseline did not influence the effect of empagliflozin to reduce the risk of HF events or renal endpoints. The patients on empagliflozin with SBP <110 mm Hg did not have an increased rate of symptomatic hypotension.[15]

Empagliflozin attenuated the slope of eGFR decline similarly in all SBP categories (*P* for interaction trend = 0.68) (Figure 3A). As the eGFR slope could be influenced by the early eGFR changes on empagliflozin but not on placebo, the eGFR change was evaluated from baseline to the off-treatment values at 23 to 45 days after discontinuation of randomized treatments. There were no differences in the treatment effect of empagliflozin in the SBP groups on the eGFR change from baseline to off-treatment (*P* for interaction trend = 0.63). The effect of SBP on the ability of empagliflozin to reduce the risk of the renal composite was slightly greater in patients with SBP <110 mm Hg, but the *P* for interaction trend was borderline significant (*P* = 0.088) (Figure 3B), and this analysis is based on sparse events.[15]

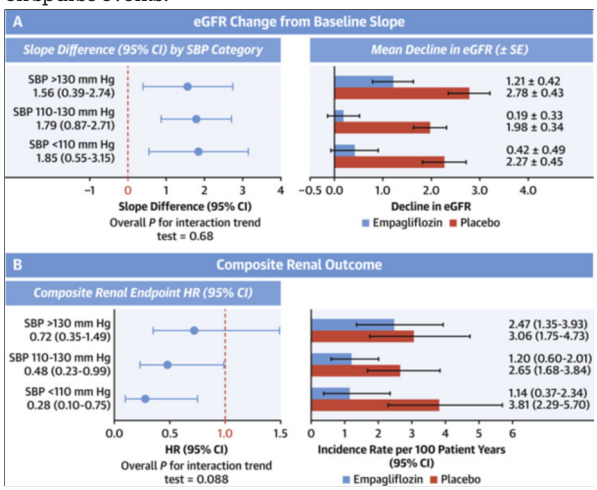

Figure 3. eGFR Change From Baseline According to Baseline SBP

Effect of empagliflozin compared with placebo on slope of change in estimated glomerular filtration rate (eGFR) (adjusted mean differences, mL/min/1.73 m^2/year) **(left)** and mean eGFR declines **(right) (A)** and the effect of empagliflozin compared with placebo on the risk of the composite renal outcomes (chronic dialysis, renal transplant, 40% sustained decrease in eGFR or a sustained eGFR <15 mL/min/1.73 m^2 [if baseline eGFR ≥30 mL/min/1.73 m^2] or <10 mL/min/1.73 m^2 [if baseline eGFR <30 mL/min/1.73 m2]) **(left)** and incidence rates **(right) (B)**. eGFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration equation.

Hence, it was confirmed that patients with heart failure with reduced ejection fraction and low SBP (i.e., <110 mm Hg) had the highest risk of heart failure outcomes. Empagliflozin reduced the risk of heart failure and renal outcomes independently of baseline SBP. Patients in the low SBP group tolerated empagliflozin treatment well as well as experienced no decline in SBP and no increased rates of symptomatic hypotension (Central Illustration).[15]

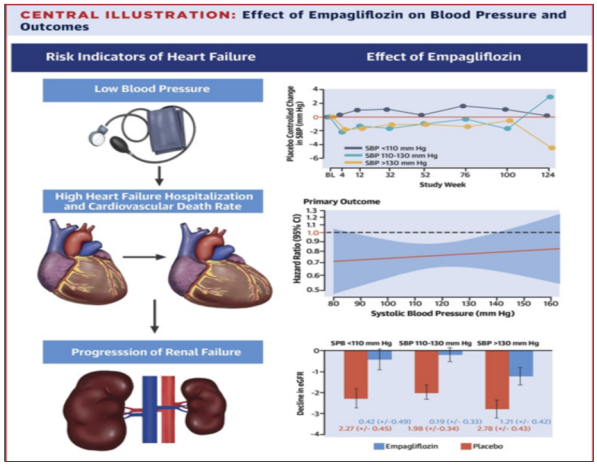

Figure 4: Central Illustration. Effect of Empagliflozin on Blood Pressure and Outcomes

Placebo-corrected effect of empagliflozin on systolic blood pressure (SBP) according to baseline SBP **(top)**, effect of empagliflozin on the primary outcome over the spectrum of baseline SBP **(middle)**, and effect of empagliflozin and placebo on decline of estimated glomerular filtration rate according to baseline SBP **(bottom)**.

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

In the EMPA-REG OUTCOME trial, empagliflozin, a sodium–glucose cotransporter 2 inhibitor, reduced the risk of major adverse cardiovascular events in patients with type 2 diabetes at high risk for cardiovascular events. So, the study group wanted to determine the long-term renal effects of empagliflozin, an analysis that was a prespecified component of the secondary microvascular outcome of that trial.

The patients with type 2 diabetes and an estimated glomerular filtration rate of at least 30 ml per minute per 1.73 m^2 of body-surface area were randomly assigned to receive either empagliflozin (at a dose of 10 mg or 25 mg) or placebo once daily. Prespecified renal outcomes consisted of incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) and incident albuminuria.[16]

Incident or worsening nephropathy reported in 525 of 4124 patients (12.7%) in the empagliflozin group and in 388 of 2061 (18.8%) in the placebo group (hazard ratio in the empagliflozin group, 0.61; 95% confidence interval, 0.53 to 0.70; P<0.001) as shown in figure 5. Doubling of the serum creatinine level reported in 70 of 4645 patients (1.5%) in the empagliflozin group and in 60 of 2323 (2.6%) in the placebo group, a significant relative risk reduction of 44%. Renal-replacement therapy was started in 13 of 4687 patients (0.3%) in the empagliflozin group and in 14 of 2333 patients (0.6%) in the placebo group, representing a 55% lower relative risk in the empagliflozin group. There was no significant between-group difference in the rate of incident albuminuria. The adverse-event profile of empagliflozin in patients with impaired kidney function at baseline was similar to that seen in the overall trial population.[16]

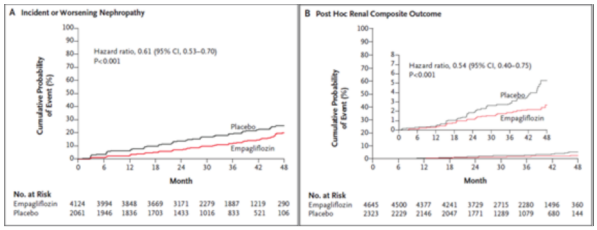

Figure 5: Kaplan–Meier Analysis of Two Key Renal Outcomes.

Shown are estimates of the probability of a first occurrence of a prespecified renal composite outcome of incident or worsening nephropathy (Panel A) and of a post hoc renal composite outcome (a doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease) (Panel B) among patients who received at least one dose of either empagliflozin or placebo. The inset in Panel B shows the data on an expanded y axis. Hazard ratios are based on Cox regression analyses. Because of the declining numbers of patients at risk, Kaplan–Meier curves have been truncated at 48 months.

All the analyses shown were performed with the use of Cox regression in patients who received at least one dose of either empagliflozin or placebo. All the analyses were prespecified except for the composite outcome of a doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease. The abbreviation eGFR denotes estimated glomerular filtration rate.

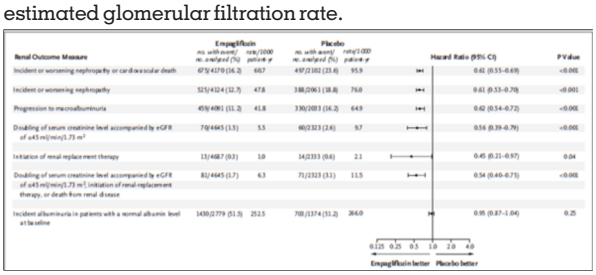

Figure 6. Risk Comparison For Seven Renal Outcomes.

In conclusion, in patients with type 2 diabetes who were at high risk for cardiovascular events, the use of empagliflozin was associated with slower progression of kidney disease than was placebo when added to standard care. Also, Empagliflozin was associated with a significantly lower risk of clinically relevant renal events.[16]

Summary:

In type 2 diabetes patients at high risk for cardiovascular events, those who received empagliflozin in addition to standard care had a significantly lower risk of microvascular outcome events than did those receiving placebo, a difference that was driven by a lower risk of progression of kidney disease (as defined by incident or worsening nephropathy). Patients in the empagliflozin group also had a significantly lower risk of progression to macroalbuminuria or clinically relevant renal outcomes, such as a doubling of the serum creatinine level and initiation of renal replacement.

Diabetes increased the risk of hospitalizations for heart failure by >50% and it nearly doubled the rate of decline in eGFR as well as the risk of a major renal event. In the placebo-controlled EMPEROR-Reduced, 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 greater in patients with diabetes but were similar between patients with prediabetes and normoglycemia. These favourable heart failure and renal effects of empagliflozin were consistent in patients with or without diabetes and across the spectrum of A1C. On the other hand, Empagliflozin did not lower glycohemoglobin in patients without diabetes and was not associated with increased risk of hypoglycemia.

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