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# Empagliflozin in Heart Failure With Predicted Preserved Versus Reduced Ejection Fraction: Data From the EMPA-REG OUTCOME Trial

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## ABSTRACT

**Background:** In the EMPA-REG OUTCOME trial, ejection fraction (EF) data were not collected. In the subpopulation with heart failure (HF), we applied a new predictive model for EF to determine the effects of empagliflozin in HF with predicted reduced (HF<sub>r</sub>EF) vs preserved (HF<sub>p</sub>EF) EF vs no HF.

**Methods and Results:** We applied a validated EF predictive model based on patient baseline characteristics and treatments to categorize patients with HF as being likely to have HF with mid-range EF (HF<sub>mr</sub>EF)/HF<sub>r</sub>EF (EF <50%) or HF<sub>p</sub>EF (EF ≥50%). Cox regression was used to assess the effect of empagliflozin vs placebo on cardiovascular death/HF hospitalization (HHF), cardiovascular and all-cause mortality, and HHF in patients with predicted HF<sub>p</sub>EF, HF<sub>mr</sub>EF/HF<sub>r</sub>EF and no HF. Of 7001 EMPA-REG OUTCOME patients with data available for this analysis, 6314 (90%) had no history of HF. Of the 687 with history of HF, 479 (69.7%) were predicted to have HF<sub>mr</sub>EF/HF<sub>r</sub>EF and 208 (30.3%) to have HF<sub>p</sub>EF. Empagliflozin's treatment effect was consistent in predicted HF<sub>p</sub>EF, HF<sub>mr</sub>EF/HF<sub>r</sub>EF and no-HF for each outcome (HR [95% CI] for the primary outcome 0.60 [0.31–1.17], 0.79 [0.51–1.23], and 0.63 [0.50–0.78], respectively; *P* interaction = 0.62).

**Conclusions:** In EMPA-REG OUTCOME, one-third of the patients with HF had predicted HF<sub>p</sub>EF. The benefits of empagliflozin on HF and mortality outcomes were consistent in nonHF, predicted HF<sub>p</sub>EF and HF<sub>mr</sub>EF/HF<sub>r</sub>EF. (*J Cardiac Fail* 2021;27:888–895)

**Key Words:** Heart failure with preserved ejection fraction, heart failure with mid-range ejection fraction, heart failure with mildly reduced ejection fraction, heart failure with reduced ejection fraction, EMPA-REG OUTCOME, empagliflozin, type 2 diabetes mellitus.

Heart failure (HF) and type 2 diabetes mellitus (T2DM) are both highly prevalent and often coexist. Concomitant HF and T2DM are associated with a more adverse prognosis than each individually.<sup>1</sup>

The EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus

Patients) trial was the first randomized controlled trial to show the efficacy of an antihyperglycemic agent, the sodium-glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin, on HF outcomes in patients with T2DM.<sup>2</sup> This effect was consistent regardless of the HF status at the baseline.<sup>3</sup> Similar findings have been observed for other

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See page 894 for disclosure information.

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SGLT2is in subsequent trials,<sup>4,5</sup> which has led to current guidelines recommending the use of SGLT2is for the prevention of HF in patients with T2DM<sup>6</sup> and to trials testing the hypothesis of SGLT2is as potential treatment in populations with HF.

The EMPEROR-Reduced (Empagliflozin Outcome Trial In Patients With Chronic Heart Failure With Reduced Ejection Fraction) and the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trials have recently shown that empagliflozin and dapagliflozin, respectively, reduce the risk of cardiovascular (CV) mortality or hospitalization due to HF in patients with HF and with reduced ejection fraction (HFrEF; EF  $\leq$ 40%) with and without T2DM.<sup>7-9</sup>

HF with preserved EF (HFpEF) remains a major unmet medical need, with mortality/morbidity rates as high as those in HFrEF.<sup>10</sup> Sacubitril/valsartan has only recently received expanded indication in the United States to treat HF with EF below normal, including HF with mid-range EF (HFmrEF) and part of the HFpEF EF spectrum.

Previous analyses of the EMPA-REG OUTCOME trial confirmed the efficacy of empagliflozin in patients with T2DM with and without a reported history of HF at randomization.<sup>5</sup> Whether this effect depended on ejection fraction (EF) is unknown because EF was not captured at randomization or during follow-up.

Therefore, in the HF subpopulation of the EMPA-REG OUTCOME trial, we applied a new EF predictive model<sup>11</sup> to gain insight into how empagliflozin's benefits may apply to patients with T2DM and with predicted HFpEF vs predicted HFrEF vs no HF.

## Methods

### Study Design

The design and primary results of the EMPA-REG OUTCOME trial have been reported previously.<sup>2</sup> Briefly, patients with T2DM, established CV disease and an estimated glomerular filtration rate  $\geq$ 30 mL/min/1.73m<sup>2</sup> were randomized 1:1:1 to empagliflozin 10 or 25 mg or placebo on top of standard of care. HF was neither required nor excluded as a selection criterion and was defined based on the presence of a condition or a diagnosis fulfilling a narrow standardized MedDRA query (Medical Dictionary for Regulatory Activities Standardized MedDRA Queries [SMQ]) "cardiac failure" (Supplementary Table 1). In the current analysis, the empagliflozin arm included patients receiving 10 mg or 25 mg of empagliflozin.

### EF Predictive Model

An EF predictive model previously derived from the Swedish HF Registry (SwedeHF) and validated in the CHECK-HF registry was applied to the EMPA-REG OUTCOME HF subpopulation to identify those patients more likely to have HFpEF (EF  $\geq$ 50%) vs HFmrEF or HFrEF (EF <50%). The model was derived and validated based on

the following predictors: age, sex, important clinical characteristics (mean arterial pressure, heart rate, body mass index, estimated glomerular filtration rate), comorbidities (history of ischemic heart disease, atrial fibrillation, chronic obstructive pulmonary disease, diabetes, hypertension, anemia, history of malignancies, valvular disease), and use of HF treatments, including renin-angiotensin-aldosterone system inhibitors, beta-blockers, diuretics, digoxin, and device therapy (implantable cardioverter defibrillator or cardiac resynchronization therapy).<sup>11</sup> A predicted probability threshold of 0.23 was used to maximize sensitivity and specificity of the model, allowing us to reach an overall accuracy of 68.2%, a sensitivity (accurate HFpEF prediction) of 66.9% and a specificity (accurate HFrEF + HFmrEF prediction) of 68.6%.<sup>11</sup>

### Statistical Analysis

Baseline characteristics in patients with predicted HFpEF, predicted HFmrEF/HFrEF and no HF were summarized as mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables and as percentages for categorical variables, respectively.

Outcomes were the same as in EMPA-REG OUTCOME, that is, a composite of CV death or HF hospitalization as primary; all-cause mortality, CV death and HF hospitalization were secondary outcomes. Cox proportional hazard models, including the study treatment, predicted HF subtype/no HF, hygu and an interaction term treatment\* predicted HF subtype/no HF were fitted in the overall study population to estimate whether the efficacy of empagliflozin differed in predicted HFpEF vs predicted HFmrEF/HFrEF vs no HF. The same Cox proportional hazard models were performed to calculate the hazard ratios (HR) with 95% confidence intervals (CI) for the predicted HF subtypes (predicted HFmrEF/HFrEF or predicted HFpEF) vs the reference group of no HF at baseline for each study outcome (ie, role of HF and HF type rather than empagliflozin vs placebo). All models were adjusted for age, sex, baseline body mass index, HbA1c, estimated glomerular filtration rate, and geographical region, as in the main EMPA-REG OUTCOME analysis.<sup>2</sup> The proportional hazards assumption was checked on the overall patient population by visual inspection of log(-log(survival function)) against the log of time by treatment group. Time to event data were visualized using cumulative incidence functions. Censoring was performed at the last day they were known to be free of the outcomes in those patients who did not report any endpoint of interest.

A modified intention-to-treat approach was adopted in the current analysis, that is, patients were considered to be in the treatment group to which they were randomized as long as they received at least 1 dose of the study drug.

All statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

## Results

Between September 2010 and April 2013, 7028 patients were randomized. Of these, 8 were excluded based on the modified intention-to-treat approach and 19 due to missing baseline characteristics data needed to predict the HF subtype; therefore, 7001 patients were included in the current analysis. Of these, 6314 (90%) patients had no history of HF at baseline. Of 687 patients with investigator-reported HF at baseline, 208 (30%) had predicted HFpEF, and 479 (70%) had predicted HFmrEF/HFrEF. The median follow-up was 3.1 years.<sup>2</sup>

### Baseline Characteristics

Baseline patient characteristics according to treatment and HF status and predicted HF subtype are reported in Table 1. Consistent with the characteristics of the registry cohort in which the EF predictive model was derived, patients with predicted HFpEF were more likely to be

female, older and have higher body mass indexes. They were also more likely to have atrial fibrillation, anemia, chronic obstructive pulmonary disease, valvular disease, or malignant cancer and more likely to be receiving diuretics compared to patients with predicted HFmrEF/HFrEF. Conversely, patients with predicted HFmrEF/HFrEF were more likely to report history of ischemic heart disease and use of HF treatments, such as renin-angiotensin-aldosterone-system inhibitors and beta-blockers. Baseline characteristics were comparable in the empagliflozin and the placebo groups.

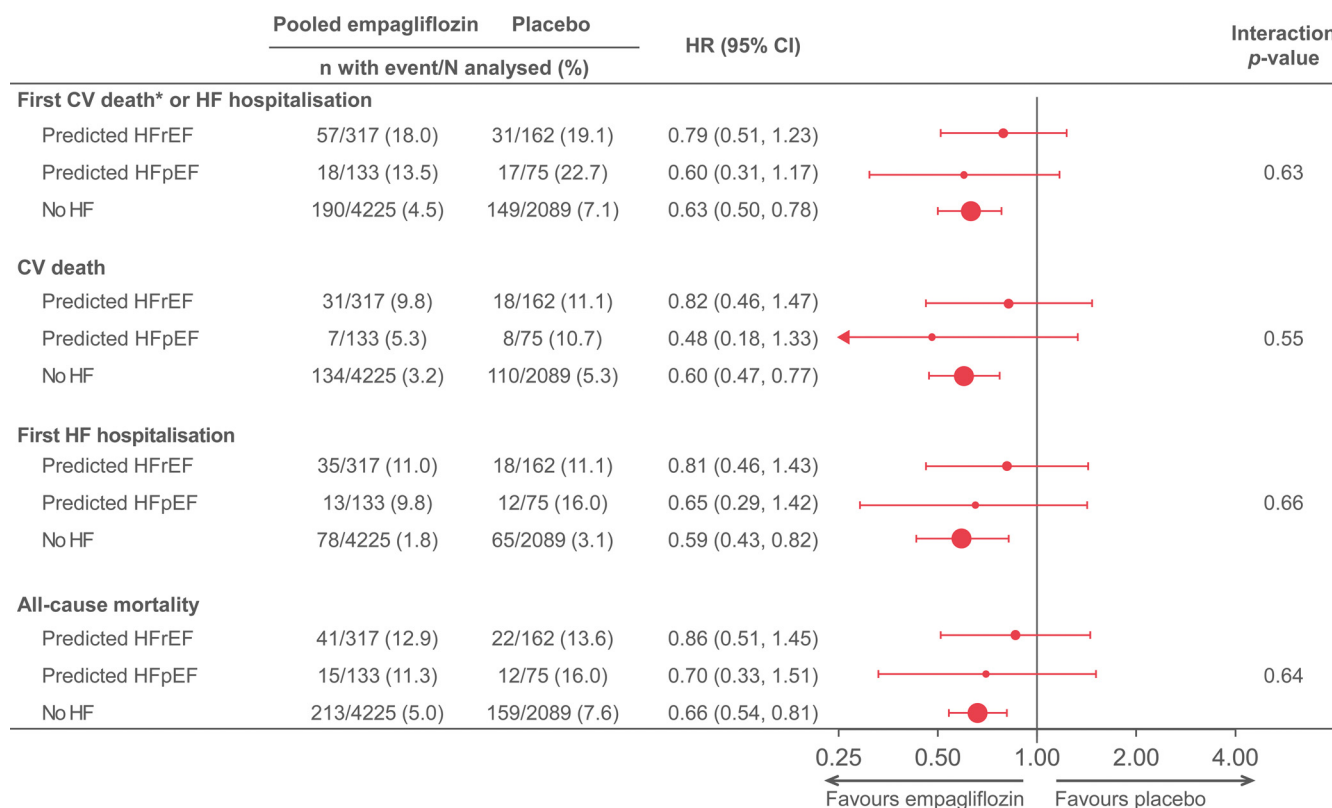
### Outcome Analysis

*Composite of CV Death or Hospitalization due to HF.* Regardless of the treatment allocation, the adjusted risk of CV death or hospitalization due to HF was similarly higher in those with predicted HFpEF and predicted HFmrEF/HFrEF vs those with no HF (Supplementary Fig. 1).

**Table 1.** Baseline Characteristics Stratified According to Heart Failure Status and Predicted Subtype Plus Treatment Group

	No HF at baseline n = 6314		Predicted HFrEF/HFmrEF n = 479		Predicted HFpEF n = 208	
	Placebo	Empagliflozin	Placebo	Empagliflozin	Placebo	Empagliflozin
Number	2089	4225	162	317	75	133
Age (years, mean (SD))	63.1 (8.8)	63.0 (8.5)	64.1 (8.8)	64.0 (8.5)	65.4 (9.1)	65.8 (9.6)
Sex (n female (%))	584 (28.0)	1209 (28.6)	22 (13.6)	54 (17.0)	47 (62.7)	84 (63.2)
Race (n (%))						
White	1478 (70.8)	3027 (71.6)	134 (82.7)	252 (79.5)	59 (78.7)	112 (84.2)
Asian	486 (23.3)	954 (22.6)	16 (9.9)	41 (12.9)	9 (12.0)	11 (8.3)
Black/African-American	103 (4.9)	204 (4.8)	11 (6.8)	23 (7.3)	6 (8.0)	10 (7.5)
Other	21 (1.0)	40 (1.0)	1 (0.6)	1 (0.3)	1 (1.3)	0 (0)
Region (n (%))						
Europe	834 (39.9)	1689 (40.0)	80 (49.4)	148 (46.7)	38 (50.7)	78 (58.6)
North America (plus Australia and New Zealand)	404 (19.3)	820 (19.4)	36 (22.2)	83 (26.2)	22 (29.3)	29 (21.8)
Latin America	329 (15.7)	680 (16.1)	26 (16.0)	28 (8.8)	5 (6.7)	12 (9.0)
Asia	430 (20.6)	849 (20.1)	12 (7.4)	39 (12.3)	8 (10.7)	9 (6.8)
Africa	92 (4.4)	187 (4.4)	8 (4.9)	19 (6.0)	2 (2.7)	5 (3.8)
Clinical measures						
SBP (mmHg, mean (SD))	135.9 (17.0)	135.4 (16.9)	134.0 (19.1)	131.7 (16.9)	135.6 (19.3)	137.5 (15.9)
DBP (mmHg, mean (SD))	76.9 (10.1)	76.6 (9.7)	75.8 (10.0)	76.0 (10.0)	77.3 (11.7)	77.7 (10.6)
Heart rate (bpm, median [IQR])	67.0 [60.2–75.3]	67.3 [60.2–75.3]	69.2 [61.3–76.7]	69.0 [62.0–77.3]	67.0 [60.0–77.3]	67.0 [62.0–76.0]
HbA1c (%; mean (SD))	8.1 (0.9)	8.1 (0.9)	7.9 (0.8)	8.1 (0.9)	8.1 (0.8)	8.0 (0.9)
BMI (kg/m <sup>2</sup> , mean (SD))	30.5 (5.2)	30.5 (5.2)	31.5 (5.3)	31.5 (5.6)	33.9 (5.3)	32.9 (5.4)
eGFR (mL/min/1.73m <sup>2</sup> , median [IQR])	73.4 [60.1–87.4]	73.5 [60.3–88.5]	67.8 [55.3–80.7]	65.2 [51.9–81.5]	68.9 [51.0–83.3]	67.4 [56.5–81.5]
Medical history (n (%))						
Atrial fibrillation	99 (4.7)	171 (4.0)	21 (13.0)	49 (15.5)	21 (28.0)	24 (18.0)
Anemia	414 (19.8)	875 (20.7)	26 (16.0)	53 (16.7)	25 (33.3)	45 (33.8)
COPD	100 (4.8)	209 (4.9)	19 (11.7)	24 (7.6)	14 (18.7)	24 (18.0)
Hypertension	1918 (91.8)	3829 (90.6)	154 (95.1)	292 (92.4)	74 (98.7)	132 (99.0)
Ischemic heart disease	1597 (76.4)	3244 (76.8)	152 (93.8)	304 (91.5)	64 (85.3)	104 (78.2)
Valvular disease	66 (3.2)	117 (2.8)	10 (6.2)	22 (6.9)	11 (14.7)	20 (15.0)
Malignant cancer	77 (3.7)	150 (3.6)	10 (6.2)	16 (5.0)	9 (12.0)	8 (6.0)
Devices (CRT or ICD)	6 (0.3)	13 (0.3)	8 (4.9)	12 (3.8)	0 (0)	0 (0)
Medication use (n (%))						
RAS inhibitors	1662 (79.6)	3392 (80.3)	155 (95.7)	296 (93.4)	46 (61.3)	98 (73.7)
Beta-blockers	1299 (62.2)	2696 (63.8)	144 (88.9)	276 (87.1)	50 (66.7)	74 (55.6)
MRA	83 (4.0)	189 (4.5)	40 (24.7)	94 (29.7)	10 (13.3)	17 (12.8)
Digoxin	39 (1.9)	71 (1.7)	23 (14.2)	45 (14.2)	9 (12.0)	11 (8.3)
Diuretics	816 (39.1)	1713 (40.5)	108 (66.7)	224 (70.7)	58 (77.3)	100 (75.2)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; IQR, interquartile range; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; RAS inhibitor, renin-angiotensin-system inhibitor; SBP, systolic blood pressure; SD, standard deviation.



**Fig. 1.** Efficacy of empagliflozin by HF status and predicted HF subtype. Prediction model variables: age, sex, mean arterial pressure, heart rate, body mass index, eGFR, ischemic heart disease, anemia, atrial fibrillation, chronic obstructive pulmonary disease, hypertension, valvular disease, malignancies, device therapy, use of renin-angiotensin system-inhibitors, beta-blockers, mineralocorticoid receptor antagonists, digoxin, or diuretics. Applied prediction model has a sensitivity (accurate prediction of HF<sub>p</sub>EF) of 66.9% and specificity (accurate prediction of HF<sub>r</sub>EF) of 68.6%.

\*Excluding fatal stroke; 19 subjects excluded with missing BL values.

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HF<sub>p</sub>EF, HF preserved ejection fraction (predicted LVEF  $\geq$ 50%); HF<sub>r</sub>EF, HF reduced ejection fraction (predicted LVEF <50%); LVEF, left ventricular ejection fraction.

In the overall population, empagliflozin reduced the risk of CV death or hospitalization due to HF by 35% compared with placebo (HR: 0.65; 95% CI: 0.54–0.78). No statistically significant interaction was observed between predicted HF subtypes/no HF and treatment effect ( $P$  value for the interaction = 0.63). Individual HRs (95% CIs) were 0.63 (0.50–0.78) for no HF, 0.60 (0.31–1.17) for predicted HF<sub>p</sub>EF, and 0.79 (0.51–1.23) for predicted HF<sub>r</sub>EF (Fig. 1) (Fig. 2).

## Secondary Outcomes

Patients with predicted HF<sub>p</sub>EF and predicted HF<sub>r</sub>EF/HFrEF had similarly increased adjusted risk of outcomes compared with those without histories of HF at baseline, regardless of the treatment arm (Supplementary Fig. 1).

In the overall EMPA-REG OUTCOME cohort, which included 7001 patients with available data for the current analysis, empagliflozin significantly reduced the risk of CV death by 38% (HR: 0.62; 95% CI: 0.50–0.78), of HF hospitalization by 36% (HR: 0.64; 95% CI: 0.49–0.84), and of all-cause death by 31% (HR: 0.69; 95% CI: 0.57–0.82).

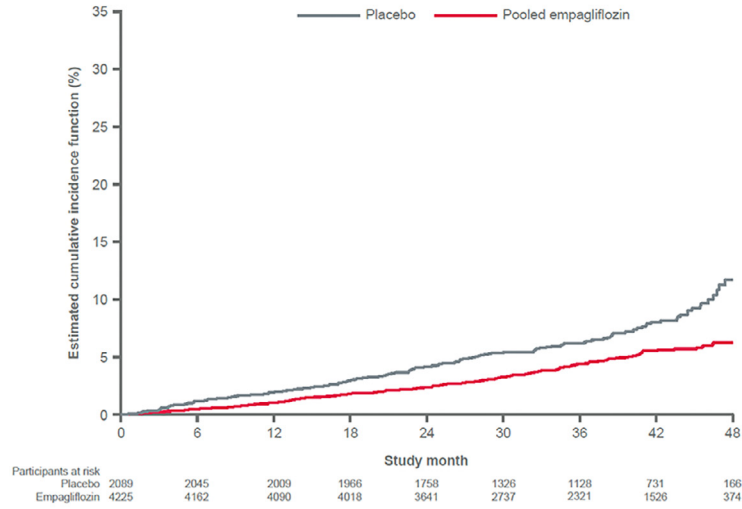
Individual HRs (95% CIs) for empagliflozin vs placebo in no HF, in predicted HF<sub>p</sub>EF and in predicted HF<sub>r</sub>EF/HFrEF were, respectively, 0.60 (0.47–0.77), 0.48 (0.18–1.33) and 0.82 (0.46–1.47) for CV death; 0.59 (0.43–0.82), 0.65 (0.29–1.42) and 0.81 (0.46–1.43) for first HF hospitalization; 0.66 (0.54–0.81), 0.70 (0.33–1.51) and 0.86 (0.51–1.45) for all-cause death.

There was no statistically significant interaction between treatment effect and predicted HF subtypes/no HF for each of the secondary outcomes explored ( $P$  value for the interaction = 0.55 for CV death; 0.66 for HF hospitalization and 0.64 for all-cause death).

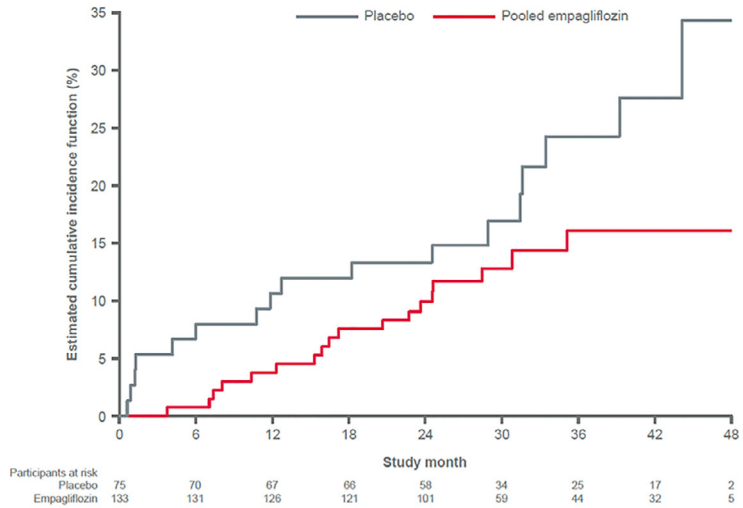
## Discussion

In the EMPA-REG OUTCOME trial, EF data were not collected, so we applied a novel EF predictive model to the population with HF in this trial to predict HF<sub>p</sub>EF and HF<sub>r</sub>EF/HFrEF, and then we compared the empagliflozin treatment effect in patients with predicted HF<sub>p</sub>EF vs predicted HF<sub>r</sub>EF/HFrEF vs no HF. We observed that empagliflozin was effective in reducing the risk of CV death/HF hospitalization, of all-cause death and of CV death and HF

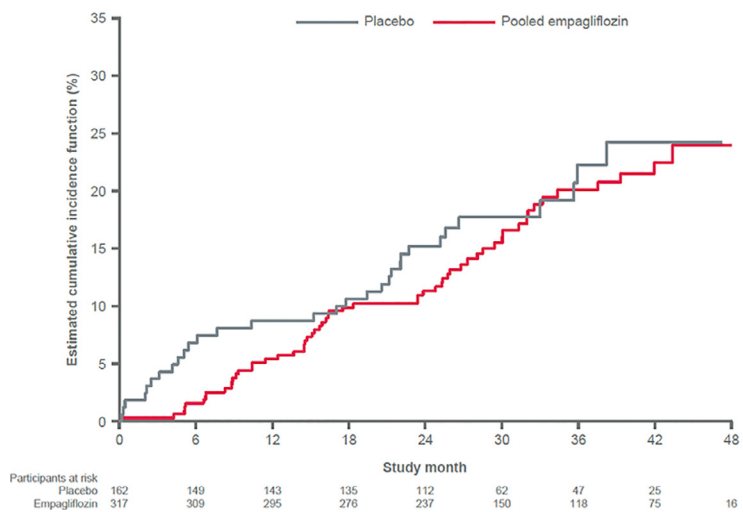
### No HF



### Predicted HFpEF



### Predicted HFmrEF/HFrEF



**Fig. 2.** Kaplan-Meier curves for the outcome of cardiovascular death or hospitalization because of heart failure. HF, heart failure; HFpEF, HF with preserved ejection fraction (predicted LVEF  $\geq 50\%$ ); HFmrEF, HF with mid-range ejection fraction; HFrEF, HF with reduced ejection fraction (predicted LVEF  $< 50\%$ ); LVEF, left ventricular ejection fraction.

hospitalization individually, in patients with T2DM and HF, regardless of predicted EF.

Our analysis and previous analyses of the EMPA-REG OUTCOME trial showed similar benefit in terms of CV death/HF hospitalization risk reduction with empagliflozin in patients with T2DM with and without history of HF at the baseline.<sup>3</sup> In contrast, in the CANVAS (Canagliflozin Cardiovascular Assessment Study) program and the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58) trials, the SGLT2is canagliflozin and dapagliflozin, respectively, were more effective in reducing CV death/HF hospitalization in patients with HF.<sup>4,5</sup> Differences in study populations, such as different proportions of primary vs secondary prevention of CV disease, might contribute to the explanation of these results.

Of the large SGLT2i outcome trials, only the DECLARE-TIMI 58 collected EF in patients with history of HF at the baseline, and reported greater treatment effect on CV death/HF hospitalization and all-cause death in HF<sub>r</sub>EF (defined as EF <45%) vs nonHF<sub>r</sub>EF/no HF, casting some doubt on the potential of SGLT2is in HF<sub>p</sub>EF.<sup>5</sup> However, dapagliflozin reduced risk of HF hospitalization in patients with and without HF<sub>r</sub>EF.<sup>5</sup> The efficacy of dapagliflozin in HF<sub>r</sub>EF patients (defined as EF ≤40%) with and without T2DM was assessed in the DAPA-HF trial, where dapagliflozin reduced CV and all-cause mortality and risk of HF hospitalization regardless of T2DM.<sup>8</sup> Whether dapagliflozin is effective also in patients with HF<sub>p</sub>EF with and without T2DM is currently unknown but is under investigation in the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) trial (NCT03619213).

In our analysis of the EMPA-REG OUTCOME trial, where an EF predictive model was applied to estimate EF, empagliflozin similarly improved outcomes in patients with T2DM and with predicted HF<sub>p</sub>EF, predicted HF<sub>m</sub>rEF/HF<sub>r</sub>EF and no HF. Our results in predicted HF<sub>r</sub>EF are consistent, overall, with the EMPEROR-Reduced trial, where empagliflozin reduced the primary outcome, which was a composite of CV death or HF hospitalization, by 25% (by 28% in patients with diabetes), whereas we observed a 21% risk reduction in our EMPA-REG OUTCOME analysis.<sup>7</sup> Furthermore, consistent with the EMPEROR-Reduced, we also observed reduced risk of HF hospitalization with empagliflozin.<sup>7</sup> Notably, the reduction in risk of CV and all-cause death with empagliflozin observed in the EMPEROR-Reduced did not reach statistical significance, whereas in our analysis there was no interaction between empagliflozin treatment effect and predicted HF subtypes/no-HF and, therefore, the significant reduction in CV and all-cause mortality with empagliflozin in the overall EMPA-REG OUTCOME population can be assumed also in predicted HF<sub>r</sub>EF/HF<sub>m</sub>rEF and predicted HF<sub>p</sub>EF.<sup>7</sup> Furthermore, our results for mortality are consistent with the findings from a recent meta-analysis pooling DAPA-HF and EMPEROR-

Reduced trials, where SGLT2i (dapagliflozin or empagliflozin) were shown to significantly reduce the risk of all-cause death by 13% (14% risk reduction in our predicted HF<sub>m</sub>rEF/HF<sub>r</sub>EF analysis) and of CV death by 14% (18% risk reduction in our analysis).<sup>9</sup> The similarities between our post hoc analysis of the EMPA-REG OUTCOME and the EMPEROR-Reduced in terms of observed risk reduction with empagliflozin might further highlight the ability of our EF predictive model to discriminate correctly between HF<sub>r</sub>EF/HF<sub>m</sub>rEF and HF<sub>p</sub>EF in patients with HF.

Our findings might further extend the evidence of and support for the hypothesis that empagliflozin is beneficial also in patients with HF<sub>p</sub>EF or HF<sub>m</sub>rEF, which is currently being tested in the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trial.<sup>12</sup> Previous subgroup and post hoc analyses of HF randomized controlled trials have shown that patients with HF<sub>m</sub>rEF but not HF<sub>p</sub>EF appear to respond to the same treatments as those with HF<sub>r</sub>EF.<sup>13–16</sup> The positive findings from SOLOIST-WHF (Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure) trial, where sotagliflozin showed efficacy in patients with T2DM recently hospitalized for worsening HF regardless of EF,<sup>17</sup> together with our analysis, might suggest a benefit of empagliflozin in EF of 40%–49%. Metabolic and hemodynamic mechanisms, such as a natriuretic effect, reduced inflammation of the adipose tissue surrounding heart and vessels, altered fuel substrates, and/or reduced progression of chronic kidney disease, are, among others, key mechanisms that might explain an effect of SGLT2i on outcomes in HF<sub>p</sub>EF. Also, SGLT2is improve diastolic function by leading to a regression in cardiac hypertrophy, a reduction in interstitial fibrosis and the enhancement of the eNOS/NO/PcGMP/PKG/titin pathway that mitigates cardiomyocyte stiffness.<sup>12,18–21</sup> Our analysis, albeit with predicted rather than measured EF, suggests empagliflozin's efficacy in HF<sub>p</sub>EF. Similar to SOLOIST-WHF, we observed lower HRs with SGLT2i for CV death/HF hospitalization in predicted HF<sub>p</sub>EF vs predicted HF<sub>m</sub>rEF/HF<sub>r</sub>EF, although with no interaction between treatment effect and predicted EF.<sup>17</sup> However, it must be acknowledged that in our analysis and in the SOLOIST-WHF as well, the sample size and the number of events in the subgroup with HF<sub>p</sub>EF (ie, EF ≥50%) were very limited, leading to wide and overlapping confidence intervals.<sup>17</sup> Additionally, the SOLOIST-WHF enrolled an HF population in the acute/subacute phase to receive a dual SGLT1/2 inhibitor, whereas the EMPA-REG OUTCOME, as well as the EMPEROR trials, the DAPA-HF and DELIVER, investigate SGLT2i in stable patients, with EMPA-REG OUTCOME being a T2DM rather than an HF trial.<sup>17</sup> However, our data, together with the findings from the SOLOIST-WHF, provide a further rationale for the ongoing EMPEROR-Preserved and DELIVER trials (NCT03619213) testing SGLT2is in patients with HF<sub>p</sub>EF.<sup>12</sup>

## Limitations

This study has some limitations linked with the trial design and the use of a predictive model to estimate EF in HF patients. First, the EMPA-REG OUTCOME trial was not designed specifically to investigate patients with HF. Therefore, the sample size of the HF subpopulation was limited, and the stratification based on EF further limited the power of the analysis, with few events per treatment groups in particular in predicted HFpEF (~10–15), leading to wide and overlapping confidence intervals. Second, we used a predictive model to identify the HF subtype and, therefore, the chance of misclassification must be taken into account. Further, the EF predictive model was derived and validated in HF registry cohorts. Although it had a good discriminative performance, the distribution of some of the predictors included in the model, such as use of treatments, might differ in an HF registry vs a nonHF trial setting.

Third, we defined the HF subtypes based on the predicted EF at the baseline. Therefore, further misclassification of the HF subtype might be due to changes in EF over the time. Finally, multiple outcomes and testing, as well as the post hoc design of this analysis, might increase the risk that some of the results were observed by chance.

## Conclusions

In this post hoc analysis of the EMPA-REG OUTCOME trial where EF was estimated by the use of a novel predictive model in patients with HF, the SGLT2i empagliflozin similarly reduced the risk of hospitalization for HF or CV death, CV and all-cause mortality, as well as risk of HF hospitalization, in patients with T2DM with predicted HFpEF and with predicted HFmrEF/HFrEF, as well as in those without histories of HF. Our findings support a rationale for assessing the benefit of empagliflozin across the range of EF in patients with HF.

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## Data disclosure

The sponsor of the EMPA-REG OUTCOME Trial (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents, and patient level clinical study data. Researchers are invited to submit inquiries via the following website: <https://trials.boehringer-ingelheim.com>.

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## Supplementary materials

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