Empagliflozin and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Left Ventricular Hypertrophy: A Subanalysis of the EMPA-REG OUTCOME Trial

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Molecular and cellular changes in the diabetic heart lead to aberrant myocardial remodeling, characterized by left ventricular hypertrophy (LVH) and eventual diastolic and/or systolic dysfunction (1,2). Although the differential effects of antihypertensive therapy on cardiovascular outcomes in patients with type 2 diabetes and LVH have been studied, those of antihyperglycemic therapy have not (3). In this post hoc analysis of the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial, we report the effects of empagliflozin on cardiovascular outcomes in subjects with type 2 diabetes, established cardiovascular disease, and electrocardiogram (ECG) evidence of LVH.

EMPA-REG OUTCOME (NCT01131676, ClinicalTrials.gov) enrolled patients with type 2 diabetes, inadequate glycemic control, and established cardiovascular disease who had an estimated glomerular filtration rate (eGFR) $\geq$30 mL/min/1.73 m^2 at baseline. In total, 7,020 subjects were treated with empagliflozin 10 mg/day, empagliflozin 25 mg/day, or placebo in addition to standard of care (4). In subgroups with/without LVH at baseline (defined on ECG as RV5/V6 + SV1/V2 $>$3.5 mV or RaVL $\geq$1.3 mV plus $\geq$1 of the following: left atrial abnormality, left axis deviation, and ST- and/or T-wave changes consistent with LVH), we assessed the risks of cardiovascular death, all-cause mortality, and 3-point major adverse cardiovascular events (MACE) with pooled empagliflozin doses versus placebo. We excluded 134 participants without a baseline ECG, 7 who had a baseline ECG that was uninterpretable or did not have QT interval data, and 906 who took the study drug prior to ECG. Therefore, 5,973 participants had a usable baseline ECG (manually analyzed; 2,008 in the placebo group and 3,965 in the empagliflozin groups), of whom 140 had LVH (45 in the placebo group and 95 in the empagliflozin groups). We used a Cox proportional hazards model with factors for age, sex, region, treatment, BMI, HbA_{1c}, eGFR, LVH at baseline, and treatment-by-baseline-LVH interaction. Interaction *P* values, without adjustment for multiple testing, are presented.

Baseline characteristics were similar in patients with versus without LVH for age (mean $\pm$ SD 62.5 $\pm$ 8.4 vs. 63.2 $\pm$ 8.6 years), proportion of patients with a duration of diabetes of $>$10 years (57.9% vs. 56.9%), baseline HbA_{1c} (8.03% vs. 8.07%), BMI (29.0 kg/m^2 vs. 30.6 kg/m^2), male sex (74.3% vs. 71.7%), history of hypertension (93.6% vs. 91.4%), eGFR $<$60 (21.4% vs. 26.4%), myocardial infarction (54.3% vs. 45.7%), and history of heart failure (5.7% vs. 4.1%). Baseline cardiovascular medication use was also relatively equal between groups (92.9% vs. 95.0% for antihypertensive therapy [ACE inhibitors/angiotensin receptor blockers 80.7% vs. 80.6% and β-blockers 59.3% vs. 64.8%] and 75.0% vs. 81.0% for lipid-lowering therapy).

In the placebo group, the rate of cardiovascular death was 4 times greater in patients with LVH (78.9 vs. 19.1 per 1,000 patient-years), and rates of all-cause mortality and 3-point MACE were 3.5 times greater (Fig. 1). Empagliflozin reduced the risk of cardiovascular death versus placebo irrespective of LVH

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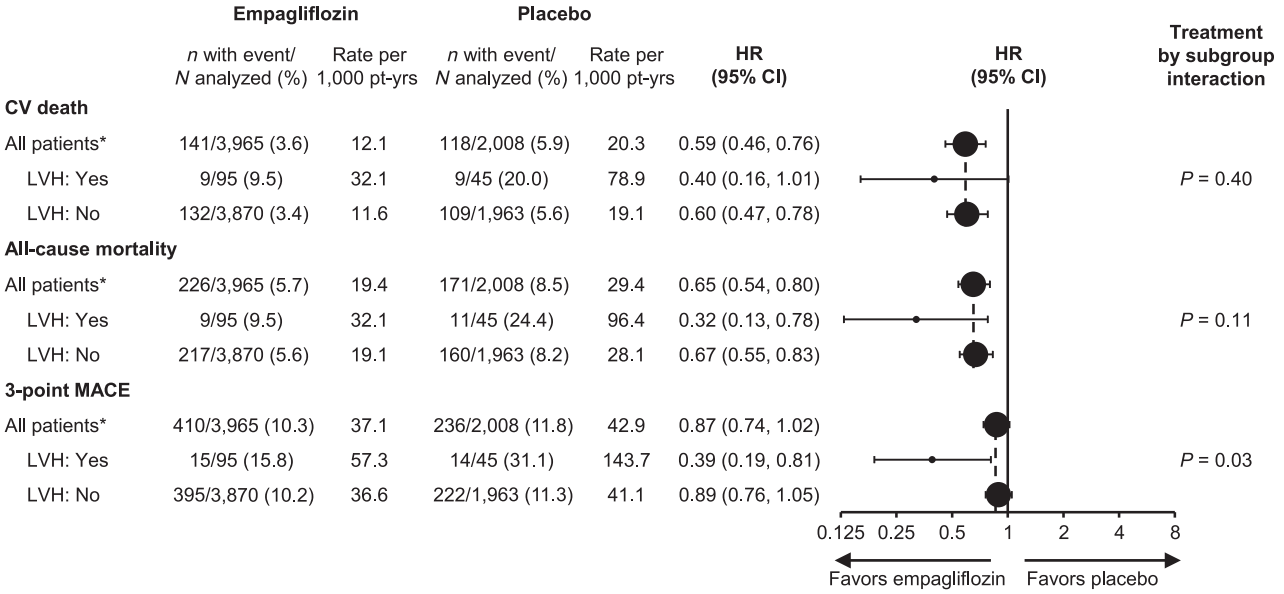

Figure 1—Outcomes by LVH subgroup. Cox regression analysis; subgroup interaction *P* value assesses the homogeneity of treatment group difference among subgroups with no adjustment for multiple tests. CV, cardiovascular; pt-yrs, patient-years. *Patients treated with one dose of the study drug who had a usable baseline ECG.

at baseline; hazard ratio (HR) 0.40 (95% CI 0.16, 1.01) vs. 0.60 (95% CI 0.47, 0.78) in patients with versus without LVH ($P = 0.40$ for interaction). Since the baseline risk was higher in patients with LVH, the absolute risk reductions with empagliflozin versus placebo were numerically higher in this cohort. Empagliflozin also reduced the risk of all-cause mortality irrespective of LVH at baseline ($P = 0.11$ for interaction). Statistical heterogeneity was observed in the reduction in 3-point MACE with empagliflozin ($P = 0.03$ for interaction); HR 0.39 (95% CI 0.19, 0.81) in patients with LVH vs. 0.89 (95% CI 0.76, 1.05) in patients without LVH. For the 3-point MACE components myocardial infarction and stroke, similar trends were observed; *P* values for interaction could not be calculated due to very low event numbers.

The presence of LVH was a strong determinant of cardiovascular events and mortality in patients with type 2 diabetes enrolled in the EMPA-REG OUTCOME trial. The sodium–glucose cotransporter 2 inhibitor empagliflozin consistently reduced the risks of cardiovascular and all-cause mortality in this population. The risk reduction for 3-point MACE appears to be larger in patients with type 2 diabetes and LVH than in those without LVH, although given the small numbers analyzed and the post hoc nature of the analysis, this remains hypothesis generating. It would be interesting to investigate, in future analyses, the relationship between empagliflozin effects and less stringent ECG criteria of LVH, such as RaVL ≥1.1 mV vs. the RaVL 1.3 mV criterion used in this analysis. Although various postulated mechanisms may explain the benefits of empagliflozin on the myocardium (5), whether empagliflozin causes a regression in left ventricular mass remains to be determined.

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