**Empagliflozin reduces the risk of a broad spectrum of heart failure outcomes regardless of heart failure status at baseline**

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In the EMPA-REG OUTCOME trial (NCT01131676), empagliflozin reduced the primary composite outcome of CV mortality (CVM), nonfatal myocardial infarction, or nonfatal stroke, driven by a reduction in CVM, as compared to placebo in patients with type 2 diabetes and established CV disease. These results led to the first approval of a glucose-lowering drug for CV death prevention in the United States. Furthermore, hospitalization for heart failure (HHF) was reduced by 35% (4.1% vs. 2.7%, HR [95%CI] 0.65 [0.50-0.85]), and the composite of HHF and CVM by 34% (8.5% vs. 5.7%, HR[95% CI] 0.66 [0.55-0.79 ]) [1], with similar effect in those with and without HF at baseline (interaction p >0.05) [2]. Subsequent analyses of those without established HF at baseline revealed consistent effects of empagliflozin on HF outcomes across the spectrum of HF risk [3], suggesting that empagliflozin reduced not only HHF but also prevented new-onset HF. In addition to adjudicated HF outcomes (HHF, and HHF or CVM), investigator reported HF and first introduction of loop diuretics were reduced by empagliflozin in the overall study population[2]. However, the study of these additional outcomes in patients with and without HF has not yet been explored. The potential interest of the study of these subpopulations is to explore whether empagliflozin may be helpful in treating HF but also in preventing new-onset HF.

In the CANVAS Program (Canagliflozin Cardiovascular Assessment Study), canagliflozin, another SGLT2 inhibitor, also reduced HHF and HHF or CVM[4] but heterogeneity was observed in patients with and without HF at baseline for HHF or CVM. Such a heterogeneity was not observed in the DECLARE-TIMI 58 trial [5], and a meta-analysis combining the results from these three trials showed similar effect on HHF or CVM in those with or without HF[6]. In this context, we re-evaluated the robustness of EMPA-REG findings and further explored the effect of empagliflozin on a broad spectrum of endpoints not yet reported for the subgroups of patients with and without HF at baseline. The additional HF-related outcomes explored are the first introduction of loop diuretic, the composite outcome of first introduction of loop diuretic or first HHF, first mention of edema, and first investigator reported HF based on the narrow standardized MedDRA query (SMQ) adverse event definition of ‘cardiac failure’. We compare pooled empagliflozin and placebo groups in an intention-to-treat manner using a Cox proportional hazards model with covariate adjustment for treatment, age, sex, geographical region, HbA1c, estimated GFR, and BMI. Patients already using a loop diuretic at

baseline were not included for the analyses of endpoints including first introduction of loop diuretic. However, in order to capture all composite events, patients that experienced an event of HHF were included in the analysis of first introduction of the composite of loop diuretic or HHF regardless of baseline medication. Subgroup analyses were conducted by HF status at baseline, adding this factor and the interaction with treatment to the Cox model. The median follow-up time was 3.1 years.

At baseline, 80.7% were already using an ACE inhibitor or angiotensin receptor blocker, 64.9% were using a beta blocker, and 43.2% were using a diuretic. During the trial these drugs were newly introduced in 27.4%, 19.1% and 21.5% of the study population, respectively. Empagliflozin reduced the occurrence of first introduction of loop diuretic: HR (95% CI) 0.62 (0.53-0.73), the composite outcome of HHF or first introduction of loop diuretic: HR (95% CI) 0.63 (0.54-0.73), investigator reported HF: HR (95% CI) 0.70 (0.56-0.87) or edema onset: HR (95% CI) 0.51 (0.43-0.61), with no significant heterogeneity between patients with and without HF at baseline (interaction p >0.05 for all the studied outcomes). **Figure 1**.

The biological mechanisms for the reduction in HF events with SGLT2 inhibitors remain largely unknown. However, the pronounced effect on "congestion signs", such as edema and the decrease in diuretic need, suggest an important hemodynamic effect. Thus, the reduction in volume and sodium load, yielding reduced ventricular filling pressures and cardiac workload, could be an important mechanism for both HHF reduction and incident HF prevention. A mediation analysis of the EMPA-REG Outcome study associated 50% of the reduction of CVM and HHF with the increase in hematocrit, in combination with a plasma volume contraction and reduction of pre-load[7]. Additional suggested mechanisms to explain the benefit of empagliflozin include improved tissue oxygenation owing to increased hematocrit, a cardioprotective state related to inhibition of myocardial sodium/hydrogen co-transport ion channels, as well as shift in fuel substrate from fatty acids and glucose towards the more energy efficient ketones. Ongoing clinical trials in patients with HF (the EMPEROR Program [NCT03057951 and NCT03057977] and the EMPERIAL Trials [NCT03448406 and NCT03448419]), including patients with reduced or preserved ejection fraction, should help

inform our understanding of the clinical benefits with empagliflozin, and future studies could assess the effect of empagliflozin for HF prevention.

In conclusion, empagliflozin reduces the risk of a broad spectrum of HF outcomes with no heterogeneity observed in patients with or without HF at baseline. These results underline the robustness of empagliflozin effects on the reduction and prevention of HF events in type 2 diabetes patients with established CV disease.

**Disclosures**

Dr. Januzzi has received income for consulting and participation on Cardiology Endpoint Adjudication Committees for Boehringer Ingelheim and Janssen. Drs. Brueckmann, Ofstad, Zeller and George are full time employees of Boehringer Ingelheim International GmbH, Germany. Dr. Fitchett reports CME honoraria and consultation fees from Boehringer Ingelheim, Lilly, Sanofi, Astra Zeneca, and Amgen and DSMB honoraria from NovoNordisc. Dr Petrie has received speaker fees or consulting honoraria from Takeda, Novartis, Astra Zeneca, Vifor, Maquet, Novo Nordisk, Boehringer-Ingelheim, Pfizer, Daiichi Sankyo, Servier, Eli-Lilly and served on clinical events committees for Novo Nordisk, Roche, Bayer, Stealth Biotherapeutics, Takeda, Astra Zeneca, Glaxo Smith Kline, Astellas, Novartis, Cardiorentis, Resverlogix and Boehringer-Ingelheim. Dr Zannad has received fees for serving on the board of Boston Scientific; consulting fees from Novartis, Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, Servier, Boston Scientific, Bayer, Johnson & Johnson, and Resmed; and speakers' fees from Pfizer and AstraZeneca. He is CardioRenal co-founder. Dr Ferreira has no conflicts of interest with regards to the present manuscript.

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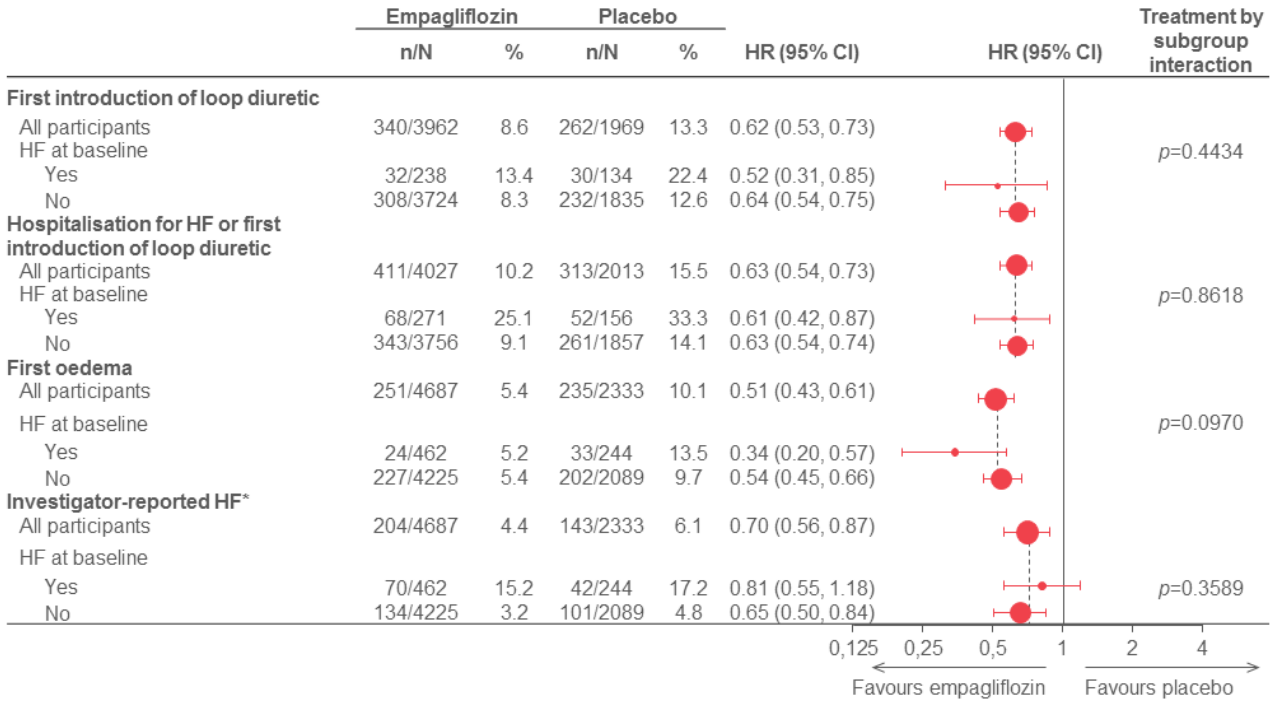
Figure 1. Investigator-reported heart failure outcomes in EMPA-REG OUTCOME overall and in patients with or without heart failure at baseline




Legend: * based on narrow standardised MedRA query (SMQ) ‘cardiac failure’.