Empagliflozin in the treatment of heart failure with reduced ejection fraction in addition to background therapies & therapeutic combinations (EMPEROR-Reduced): a post-hoc analysis of a randomised, double-blind trial

Background

It is important to evaluate whether a new treatment for heart failure with reduced ejection fraction (HFrEF) provides additive benefits to background foundational treatments. As such, we aimed to evaluate the efficacy and safety of empagliflozin in patients with HFrEF in addition to baseline treatment with specific doses and combinations of disease-modifying therapies.

Methods

We performed a post-hoc analysis of the EMPEROR-Reduced randomised, double-blind, parallel-group trial, which took place in 520 centres (hospitals and medical clinics) in 20 countries in Asia, Australia, Europe, North America, and South America. Patients with New York Heart Association (NYHA) classification II–IV with an ejection fraction of 40% or less were randomly assigned (1:1) to receive the addition of either oral empagliflozin 10 mg per day or placebo to background therapy. The primary composite outcome was cardiovascular death and heart failure hospitalisation; the secondary outcome was total heart failure hospital admissions. An extended composite outcome consisted of inpatient and outpatient HFrEF events was also evaluated. Outcomes were analysed according to background use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) or angiotensin receptor neprilysin inhibitors (ARNIs), as well as β blockers and mineralocorticoid receptor antagonists (MRAs) at less than 50% or 50% or more of target doses and in various combinations.

Findings

In this post-hoc analysis of 3730 patients (mean age 66·8 years [SD 11·0], 893 [23·9%] women; 1863 [49·9%] in the empagliflozin group, 1867 [50·1%] in the placebo group) assessed between March 6, 2017, and May 28, 2020, empagliflozin reduced the risk of the primary outcome (361 in 1863 participants in the empagliflozin group and 462 of 1867 in the placebo group; HR 0·75 [95% CI 0·65–0·86]) regardless of background therapy or its target doses for ACE inhibitors or ARBs at doses of less than 50% of the target dose (HR 0·85 [0·69–

1·06]) and for doses of 50% or more of the target dose (HR 0·67 [0·52–0·88]; $p_{interaction}$=0·18). A similar result was seen for β blockers at doses of less than 50% of the target dose (HR 0·66 [0·54–0·80]) and for doses of 50% or more of the target dose (HR 0·81 [0·66–1·00]; $p_{interaction}$=0·15). Empagliflozin also reduced the risk of the primary outcome irrespective of background use of triple therapy with an ACE inhibitor, ARB, or ARNI plus β blocker plus MRA (given combination HR 0·73 [0·61–0·88]; not given combination HR 0·76 [0·62–0·94]; $p_{interaction}$=0·77). Similar patterns of benefit were observed for the secondary and extended composite outcomes. Empagliflozin was well tolerated and rates of hypotension, symptomatic hypotension, and hyperkalaemia were similar across all subgroups.

Interpretation

Empagliflozin reduced serious heart failure outcomes across doses and combinations of disease-modifying therapies for HFrEF. These data suggest that empagliflozin might be considered a foundational therapy in patients with HFrEF regardless of their existing background therapy.