Direct effects of empagliflozin on erythropoiesis in heart failure: data from the Empire HF trial

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Background: Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a newly recommended treatment of heart failure with reduced ejection fraction (HFrEF). The consistently observed increase in haematocrit with SGLT2 inhibition is associated with a large proportion of the observed clinical benefit in different type 2 diabetes (T2D) populations. Whether the increase in haematocrit is caused by diuresis-associated haemoconcentration or is due to a direct effect on erythropoiesis is unknown. We have previously observed a decrease in ferritin alongside increases in haematocrit and haemoglobin with empagliflozin, thus indicating a direct effect on erythropoiesis.

Purpose: To investigate the effect of the SGLT2 inhibitor empagliflozin on erythropoiesis in patients with HFrEF.

Methods: The Empire HF trial was an investigator-initiated, double-blind, randomised, placebo-controlled trial conducted at two Danish university hospitals with enrolment of 190 patients from five outpatient heart failure clinics. Patients with a left ventricular ejection fraction (LVEF) of 40% or lower, with New York Heart Association (NYHA) Class I, II, or III symptoms, and on stable doses of guideline-directed HFrEF therapy were randomly assigned (1:1) to receive empagliflozin 10 mg or matching placebo once daily for 12 weeks. The present biomarker endpoints were analysed according to the intention-to-treat principle in analyses of covariance models with baseline adjustments.

Results: A minimum of 91 patients (96%) in each group had complete data and were included in the present analyses. Baseline characteristics were well-balanced between the allocated groups [mean age: 64 (SD 11) years; male: 85%; mean LVEF: 29 (SD 8) %; NYHA Class II: 78%; T2D: 13%; anaemia: 28%]. Serum-erythropoietin increased in the empagliflozin group compared to placebo from baseline to 12 weeks [adjusted mean difference 2.6 IU/L (95% CI 0.8–4.4; P=0.0052)]. Moreover, plasma-hepcidin decreased [adjusted ratio of change 0.68 (95% CI 0.22–1.02; P=0.067)], and mean corpuscular volume increased [adjusted ratio of change 1.01 (95% CI 1.00–1.02; P=0.0033)] compared to placebo, while no changes were observed for mean corpuscular haemoglobin concentration or plasma-iron (P>0.05).

Conclusion: The consistently observed increase in haematocrit with SGLT2 inhibitor treatment may not exclusively be due to diuresis-associated haemoconcentration as previously suspected. The present analyses suggest that empagliflozin increases erythropoiesis and induces changes in iron metabolism in a population of patients with HFrEF, primarily without diabetes. The observed decrease in hepcidin, and in ferritin as we have previously reported, further implies an anti-inflammatory effect, all of which may contribute to the cardioprotective properties of empagliflozin.