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Anemia and erythrocytosis with empagliflozin in HFpEF: an EMPEROR- Preserved analysis

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Introduction

Many patients with heart failure and a preserved ejection fraction (HFpEF), have anemia as a consequence of “chronic disease”. Anemia worsens HF symptoms and has been associated with poor cardiovascular outcomes.¹ Sodium glucose co-transporter 2 inhibitors (SGLT2i) increase hemoglobin (and hematocrit), often leading to the correction of anemia and, in some patients, SGLT2i use may lead to erythrocytosis.²⁻⁵

While the association of anemia with poor outcomes has been documented in HF, the association of erythrocytosis with outcomes in HF is less well established.⁵

The association of anemia and erythrocytosis with clinical outcomes, the impact of SGLT2i on anemia and erythrocytosis throughout the follow-up, and the effect of SGLT2i on cardiovascular and kidney outcomes in patients with and without anemia or erythrocytosis are explored herein using the EMPEROR-Preserved (NCT03057951) data.

Methods

The design and primary results of the EMPEROR-Preserved trial have been published previously.⁶ The median follow-up was 26.2 months. The primary endpoint was a composite of cardiovascular death or hospitalization for HF. Additionally, the individual components of the primary outcome; a kidney composite outcome of sustained $\geq 40\%$ estimated glomerular filtration rate (eGFR) decline from baseline, dialysis, transplantation, or end-stage renal disease; a composite of myocardial infarction, stroke, or cardiovascular death; deep venous thrombosis or pulmonary thromboembolism (DVT or PTE); and all-cause mortality, were also studied.

Anemia and erythrocytosis were classified according to the World Health Organization (WHO) definition of hemoglobin level < 12.0 g/dL in women and < 13.0 g/dL in men, and hemoglobin level > 16.0 g/dL in women and > 16.5 g/dL in men, respectively.

Hemoglobin (and hematocrit) was obtained from the laboratory results at the main study visits (i.e., baseline, and weeks 4, 12, 32, 52 and every 24 weeks thereafter). The effect of empagliflozin (vs placebo) on hemoglobin (and hematocrit) over time, was studied using a mixed model for random effects with a treatment-by-visit

interaction, and random effects at the patient level, adjusting on previously specified variables.⁶ All analyses were performed using Stata®, v18. All analyses were performed within the Vivli® (<https://vivli.org/>) platform with the Vivli ID: 00009383. The trial sponsor was not involved in this analysis.

Results

Patient's characteristics by anemia and erythrocytosis status

Of the 5988 patients enrolled in the trial, at baseline, 1703 (28.4%) had anemia. The mean hemoglobin (hematocrit) level in patients with anemia was 11.6±0.9 g/dL (35.8±2.9 %) and in patients without anemia was 14.0±1.2 (42.9±3.7 %). Compared to patients without anemia, those with anemia were older, more frequently men, with diabetes, HF of ischemic etiology, poorer renal function, and higher NT-pro BNP levels. At baseline, 127 (2.1%) patients had erythrocytosis. The mean hemoglobin (hematocrit) level in patients with erythrocytosis was 17.2±0.8 g/dL (52.6±3.1 %) and in patients without erythrocytosis was 13.2±1.5 (40.7±4.5 %). Compared to patients without erythrocytosis, those with erythrocytosis were younger, more often smokers, with pulmonary disease.

Outcome associations by anemia and erythrocytosis status

In the placebo group, the presence of anemia at baseline was independently associated with an increased risk (1.4x to 2.0x) of occurrence of all studied outcomes (see Methods section) compared to patients without anemia. The adjusted hazard ratio (HR) and 95% confidence interval (95%CI) for the primary outcome was 1.66 (1.38-1.99), P<0.001.

The presence of erythrocytosis at baseline was not associated with any of the studied outcomes compared to patients without erythrocytosis. The adjusted HR (95%CI) for the primary outcome was 0.90 (0.51-1.61), P=0.73. The occurrence of erythrocytosis during the follow-up (in time-updated models) was not associated with atherothrombotic events.

Effect of empagliflozin according to anemia and erythrocytosis status

The presence of anemia did not modify the effect of empagliflozin on the studied outcomes (all interaction P-values>0.1). The empagliflozin vs placebo HR (95%CI) for the primary outcome in patients with anemia was 0.83 (0.68-1.01) and in patients

without anemia was 0.77 (0.64-0.91), interaction P-value=0.56. Despite a similar relative reduction in events with empagliflozin (vs placebo), the absolute risk reduction (ARR) was greater among patients with anemia at baseline who had a higher absolute risk of events. *Figure 1A.*

The presence of erythrocytosis also did not modify the effect of empagliflozin on the studied outcomes (all interaction P-value>0.05). However, despite the small number of events (24 events in total), a tendency to an increased risk of primary outcome events with empagliflozin was observed among patients with erythrocytosis at baseline: no erythrocytosis HR (95%CI) 0.78 (0.68-0.89) and erythrocytosis 1.65 (0.74-3.68), interaction P-value=0.069.

Effect of empagliflozin on hemoglobin and hematocrit over time

Throughout the follow-up, the average (standard error) hemoglobin level in the placebo group was 13.24 (0.01) g/dL and 13.79 (0.01) g/dL in the empagliflozin group, with a between-group (empagliflozin vs placebo) difference of 0.55 (0.02) g/dL, joint-P-value<0.001. *Figure 1B.* The corresponding average (standard error) hematocrit level increase with empagliflozin (vs placebo) was 1.94 (0.06) %, joint-P-value<0.001. The presence of CKD did not modify the effect of empagliflozin on hemoglobin levels, interaction P-value=0.69. *Figure 1C.*

Empagliflozin (vs placebo) reduced the odds of experiencing anemia by 40% at week 52: odds ratio (OR) 0.58, 95%CI 0.50-0.66, P<0.001. On the other hand, empagliflozin (vs placebo) increased the odds of experiencing erythrocytosis by 3.3x at week 52: OR 3.29, 95%CI 2.39-4.53, P<0.001. *Figure 1D.*

An increase in hemoglobin levels was associated with higher odds of meaningful (≥ 5 points) KCCQ-CSS improvement (and lower odds of deterioration) among patients randomized to empagliflozin but not among those randomized to placebo.

Discussion

The present study adds novel and clinically relevant information: 1) the treatment effect of empagliflozin was not influenced by anemia status and empagliflozin led to an important reduction of anemia throughout the follow-up; 2) increment in hemoglobin and anemia correction with empagliflozin was of similar magnitude regardless of chronic kidney disease; and 3) empagliflozin increased the proportion

of patients with erythrocytosis throughout the follow-up, but erythrocytosis was not associated with atherothrombotic events. Still, among patients with erythrocytosis at baseline, empagliflozin use was associated with a tendency towards an increased risk of primary outcome events, a finding limited by the small number of events and by the small number of patients with erythrocytosis.^{7,8}

In conclusion, empagliflozin increased hemoglobin levels and substantially reduced the incidence of anemia. While there was an increase in erythrocytosis this was not associated with atherothrombotic events. Further studies should clarify the risk factors for the occurrence of erythrocytosis with SGLT2i and whether there is an erythrocytosis threshold above which the risk of atherothrombotic events may be increased.

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Data availability

Data are available through the Vivli® platform.

Disclosures

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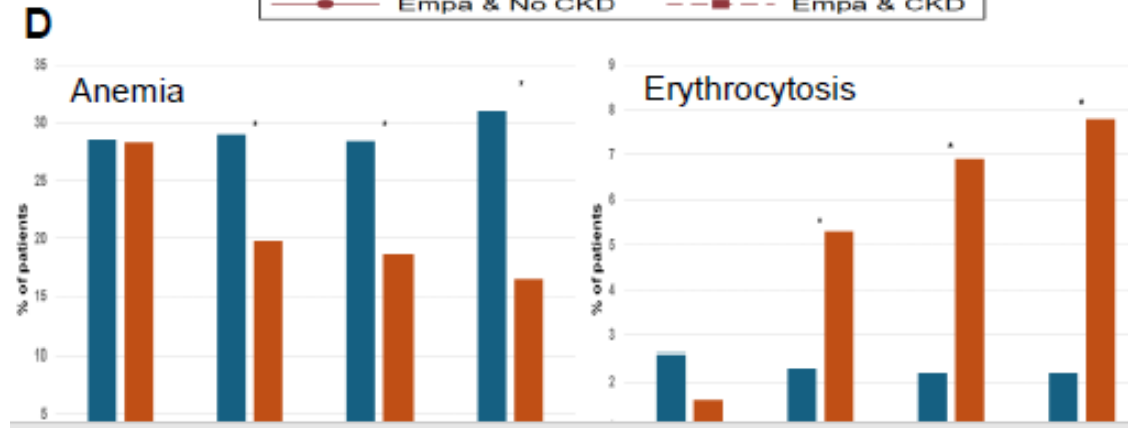
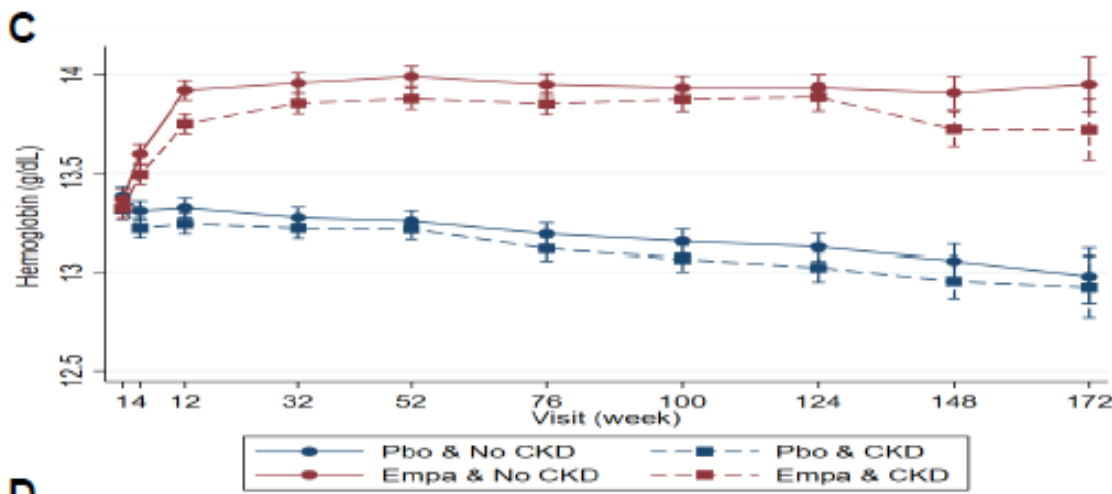
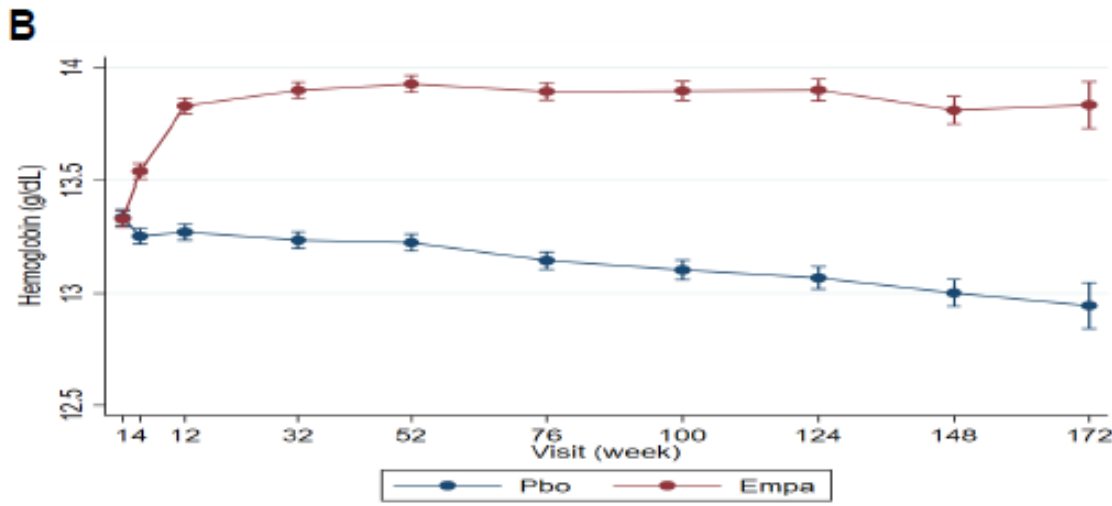
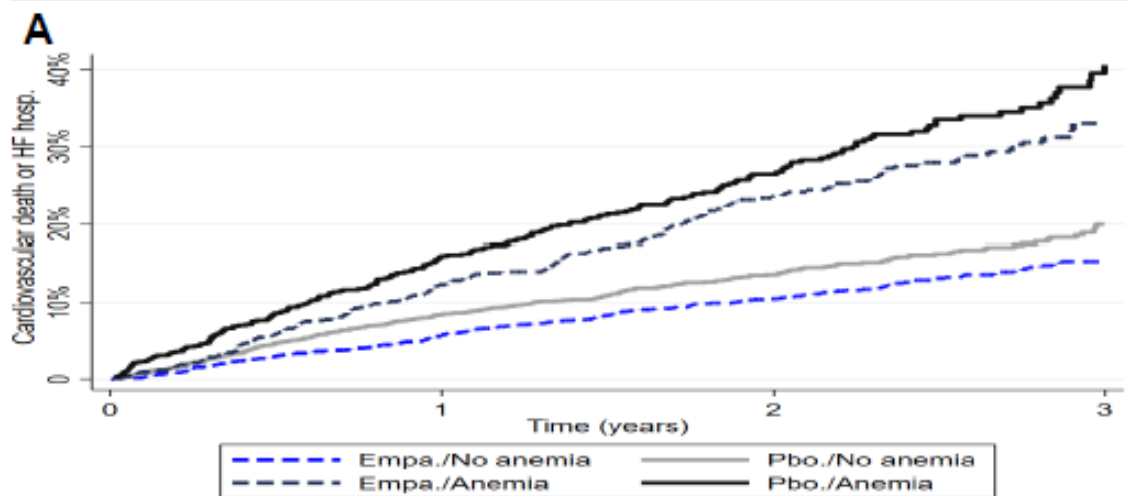


Figure 1. Anemia and erythrocytosis in EMPEROR-Pre served

A. Primary outcome occurrence according to anemia status and treatment group

- B. Effect of empagliflozin on hemoglobin levels over time
- C. Effect of empagliflozin on hemoglobin levels over time among patients with and without CKD
- D. Effect of empagliflozin on anemia and erythrocytosis over time

Legend: Empa., empagliflozin; Pbo., placebo; SE, standard error; CKD, chronic kidney disease; OR, odds ratio; *P-value <0.001. Panel A. Cumulative incidence of primary outcome events expressed in %. Caption Panel A: Despite a higher risk of primary outcome events among patients with anemia, the relative reduction of events with empagliflozin (vs placebo) was similar regardless of anemia status. Notes Panel B: Throughout the follow-up, the average (standard error) hemoglobin level in the placebo group was 13.24 (0.01) g/dL and 13.79 (0.01) g/dL in the empagliflozin group, with a between-group (empagliflozin vs placebo) difference of 0.55 (0.02) g/dL, joint P-value <0.001. Regarding specific time-points, at baseline the between-group difference was 0.01 (0.03) g/dL, at week 12 was 0.58 (0.03) g/dL, at week 52 was 0.74 (0.03) g/dL, and at week 100 was 0.82 (0.03) g/dL. Notes Panel C: Among patients without CKD, throughout the follow-up, the average (standard error) hemoglobin level in the placebo group was 13.29 (0.02) g/dL and 13.85 (0.02) g/dL in the empagliflozin group, with a between-group (empagliflozin vs placebo) difference of 0.56 (0.03) g/dL, joint P-value <0.001. Regarding specific time-points, at baseline the between-group difference was 0.00 (0.04) g/dL, at week 12 was 0.62 (0.04) g/dL, at week 52 was 0.78 (0.04) g/dL, and at week 100 was 0.81 (0.04) g/dL. Among patients with CKD, throughout the follow-up, the average (standard error) hemoglobin level in the placebo group was 13.18 (0.02) g/dL and 13.72 (0.02) g/dL in the empagliflozin group, with a between-group (empagliflozin vs placebo) difference of 0.54 (0.03) g/dL, joint P-value <0.001. Regarding specific time-points, at baseline the between-group difference was 0.02 (0.04) g/dL, at week 12 was 0.55 (0.04) g/dL, at week 52 was 0.70 (0.04) g/dL, and at week 100 was 0.83 (0.05) g/dL. No CKD vs CKD interaction P-value =0.69. Notes Panel D Anemia: At specific time points, the corresponding anemia n/N (%) and odds ratios were: Baseline: placebo 852/2989 (28.5) vs empagliflozin 848/2998 (28.3), OR 0.99, 95%CI 0.88-1.11, P =0.85. Week 12: placebo 803/2767 (29.0) vs empagliflozin 552/2787 (19.8), OR 0.60, 95%CI 0.53-0.68, P <0.001. Week 52: placebo 661/2329 (28.4) vs empagliflozin 433/2332 (18.6), OR 0.58, 95%CI 0.50-0.66, P <0.001. Week 100: placebo 448/1445 (31.0) vs empagliflozin 237/1434 (16.5), OR 0.44, 95%CI 0.37-0.53, P <0.001. Notes Panel D Erythrocytosis: At specific time points, the corresponding erythrocytosis n/N (%) and odds ratios were: Baseline: placebo 79/2989 (2.6) vs empagliflozin 47/2998 (1.6), OR 0.60, 95%CI 0.42-0.86, P =0.006. Week 12: placebo 64/2767 (2.3) vs empagliflozin 149/2787 (5.3), OR 2.36, 95%CI 1.78-3.14, P <0.001. Week 52: placebo 51/2329 (2.2) vs empagliflozin 160/2332 (6.9), OR 3.29, 95%CI 2.39-4.53, P <0.001. Week 100: placebo 32/1445 (2.2) vs empagliflozin 112/1434 (7.8), OR 3.74, 95%CI 2.51-5.58, P <0.001.