



# Effect of Dapagliflozin on Hematocrit in Patients With Type 2 Diabetes at High Cardiovascular Risk: Observations From DECLARE-TIMI 58

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There is a growing body of evidence for sodium–glucose cotransporter 2 (SGLT2) inhibitors, supporting their use in a wide spectrum of patient populations. Their indications have now expanded beyond patients with type 2 diabetes (T2D) to patients with heart failure and chronic kidney disease, regardless of T2D status (1–3). Several mechanisms are postulated to explain their favorable effects, such as their natriuretic, diuretic, and glucosuric properties, among many others. Consistent evidence suggests a relationship between SGLT2 inhibitors and increased hematocrit (Hct)/hemoglobin/erythropoietin levels (4). Whether this reflects hemoconcentration due to diuretic effects, expansion of red blood cell (RBC) mass due to increased erythropoietin, or both remains unclear. In BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), empagliflozin was associated with increased Hct (5). In Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), anemia was more frequently corrected with dapagliflozin than with placebo (3). To that effect, we analyzed data from the

longer and larger Dapagliflozin Effect on Cardiovascular Events trial (DECLARE-TIMI 58), which included a broader population of patients with T2D, to assess effects of dapagliflozin (DAPA) versus placebo on Hct (1).

DECLARE-TIMI 58 was a randomized, double-blinded, placebo-controlled trial of DAPA in 17,160 patients with T2D with, or at high risk for, atherosclerotic cardiovascular (CV) disease (1). After the demonstration of the efficacy of empagliflozin in the EMPA-REG OUTCOME trial (5), including reduced risk for the composite of CV death/myocardial infarction/stroke and for hospitalization for heart failure and attenuated progression of chronic kidney disease, similar findings were corroborated with DAPA in the DECLARE-TIMI 58 trial on heart failure and kidney outcomes but without superior efficacy for CV death/myocardial infarction/stroke.

In DECLARE-TIMI 58, DAPA versus placebo increased Hct levels at 12, 24, 36, and 48 months (Fig. 1A and B). For instance, at 4 years, the median (interquartile range) Hct in the DAPA group had increased from a baseline of 42.1% (39.4, 44.8) to 44.6% (41.5, 47.5),

reflecting a 5.7% (0.9, 10.5) relative change. Over the same time period, the placebo group baseline median Hct of 42.1% (39.4, 44.8) remained stable at 41.8% (38.9, 44.5). When comparing DAPA with placebo in the first, second, and third Hct tertiles, the relative percent change from baseline in median Hct was 3.1% (1.1, 5.2) vs. 0.7% (–1.4, 2.5), 3.1% (1.1, 5.2) vs. 0.7% (–1.4, 2.5), and 1.8% (–0.3, 3.5) vs. –1.2% (–3.2, 0.6), respectively. Stratified by baseline estimated glomerular filtration rate, relative percent change from baseline in median Hct was 5.6% (0.5, 10.9) vs. –1.0% (–5.8, 3.7), 2.4% (0.5, 4.3) vs. –0.4% (–2.4, 1.5), and 2.4% (0.5, 4.3) vs. –0.1% (–2.0, 1.8) in the first, second, and third estimated glomerular filtration rate tertiles, respectively. At 1 and 4 years, the placebo-subtracted least squares mean estimates of absolute Hct percent were 2.5 (SE 0.05) and 2.6 (SE 0.06), corresponding to relative percent changes of 5.9% (SE 0.12) and 6.2% (SE 0.15), respectively ( $P < 0.001$  in all cases). Absolute and relative percent changes in Hct by randomized group at 1 year are presented in Fig. 1C and D. Diuretic use at the end of the

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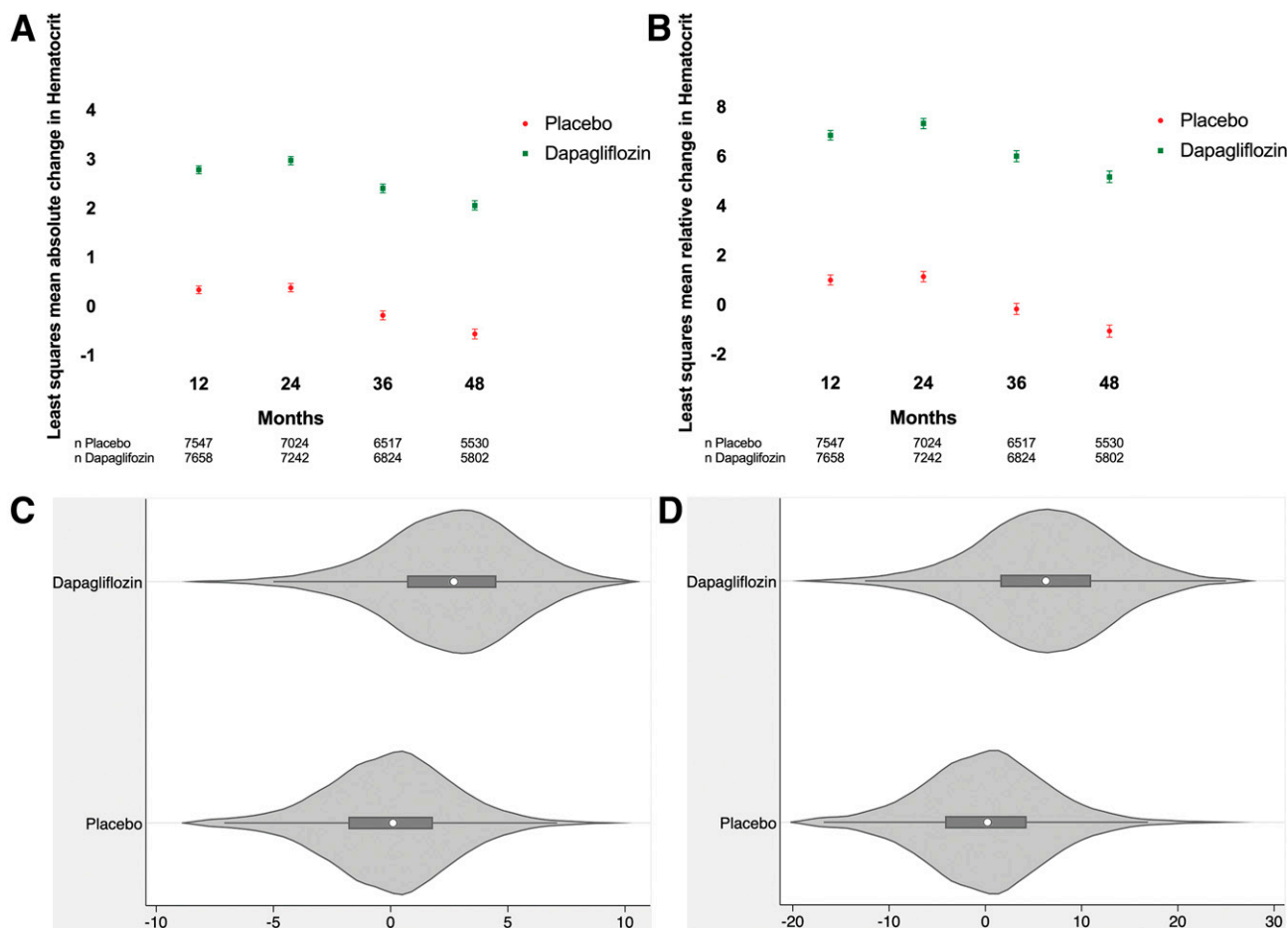
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**Figure 1**—Effect of DAPA vs. placebo on Hct in the DECLARE-TIMI 58 trial. **A:** Least squares mean absolute change in Hct from baseline over time. **B:** Least squares mean relative change in Hct from baseline over time. **C:** Absolute Hct change from baseline to 1 year. **D:** Relative percent change of Hct from baseline to 1 year.

study was 41.6% (3,571/8,582) and 44.3% (3,798/8,578) in the DAPA and placebo groups, respectively ( $P < 0.001$ ).

The present observations with regard to DAPA effects on Hct are in line with previously reported data from the EMPA-REG OUTCOME trial of empagliflozin but extend them to a broader population with longer follow-up duration. While the EMPA-REG OUTCOME investigators speculated that the increase in Hct was due to plasma volume contraction and hemoconcentration (5), others have postulated that the increase in Hct with SGLT2 inhibitors is more likely due to hematopoiesis/RBC mass expansion associated with increased erythropoietin (4). The lower diuretic use in the DAPA group argues against this being a pure hemoconcentration effect. A prominent theory as to how SGLT2 inhibition induces

erythropoietin, leading to increased RBC mass, includes the reversal of relative tissue hypoxia surrounding the proximal convoluted tubules as a result of the diminished action of the ATP/oxygen-consuming  $\text{Na}^+/\text{K}^+$  ATPase pump, a secondary effect of SGLT2 inhibition. This, in turn, may result in the restoration of the erythropoietin production capacity of fibroblasts surrounding the proximal convoluted tubules, stimulating hematopoiesis (4). In addition, inhibiting the highly metabolically efficient glucose and sodium reuptake by SGLT2 relegates their reclamation to more distal mechanisms with less energy efficiency (e.g., sodium-hydrogen exchanger, SGLT1, and epithelial sodium channel) and potentially inducing regional tissue hypoxia in zone 3 of the renal medulla, further inducing erythropoietin from interstitial fibroblasts. The present findings support

but cannot address these hypotheses, limited by lack of measurement of erythropoietin levels, RBC mass, reticulocyte count, and plasma volume. Further explorations regarding the consistent finding of Hct increase across the SGLT2 inhibitor class, its clinical relevance, and its mechanistic underpinnings are necessary.

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