

Perspective

Combining Iron Supplements With SGLT2 Inhibitor-Stimulated Erythropoiesis in Heart Failure: Should We Be Worried About Thromboembolic Events?

MILTON PACKER, MD,^{1,2} AND JOHN G.F. CLELAND, MD³*Dallas, USA; and London, and Glasgow, UK*

Milton Packer



Physicians have long believed that anemia might contribute to the progression of heart failure (HF). A decade ago, clinical trials investigated whether erythropoiesis-stimulating agents could increase hemoglobin levels in patients with anemia in the hope that enhancing oxygen delivery would improve outcomes.

The RED-HF Trial and Trials With Prolyl Hydroxylase Inhibitors

In the RED-HF (Reduction of Events by Darbepoietin Alfa in Heart Failure) trial,¹ 2278 patients with HF, reduced ejection fraction, hemoglobin

9.0–12.0 g/dL, and transferrin saturation (TSAT) \geq 15% (median 24%) were randomized to placebo or darbepoietin, a synthetic analogue of erythropoietin. Darbepoietin was given monthly to maintain the hemoglobin levels between 13.0 and 14.5 g/dL; iron supplements (usually oral) were coadministered when the TSAT was $<$ 20% and were prescribed in \approx 80% of patients. Darbepoietin did not reduce the primary endpoint of all-cause mortality or hospitalizations for HF, but it did increase the risk of thromboembolic events (13.5% vs 10.0%; $P=0.009$). Similarly, in the TREAT (TRial to EvaluAte Tranexamic acid therapy in Thrombocytopenia) trial,² darbepoietin increased the risk of stroke in patients with diabetes, chronic kidney disease or anemia.

Why did darbepoietin increase the risk of thromboembolic events? Darbepoietin (with iron supplementation) increased hemoglobin by \approx 1.5 g/dL to achieve a median of 13.0 g/dL (IQR 12.4–13.4), rising meaningfully during the first 3 months, with a peak after 6 months. Increases in hemoglobin of this magnitude might enhance blood viscosity. Recent experience with prolyl-hydroxylase inhibitors in patients with chronic kidney disease underscores these findings. These drugs potentiate the action of hypoxia-inducible factors (HIF-1 α and HIF-2 α), which are the primary endogenous stimuli for erythropoietin production. In trials of patients receiving intravenous iron, the prolyl-hydroxylase inhibitor roxadustat yielded a greater increase in hemoglobin but also a higher risk of thromboembolic events³ when compared with darbepoietin—a striking finding, given that darbepoietin itself promotes thromboembolic events.^{1,2}

The totality of evidence indicates that the increases in hemoglobin that follow erythropoiesis stimulation combined with iron supplementation appear to augment thromboembolic risk in patients with cardiovascular disease. Currently, most physicians using erythropoiesis-stimulating agents in

From the ¹Baylor Heart and Vascular Institute, Dallas, TX, USA; ²Imperial College, London, UK and ³British Heart Foundation Centre of Research Excellence, School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK.

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Reprint requests: Milton Packer, MD, Baylor Heart and Vascular Institute, 621 North Hall Street, Dallas, TX 75226, USA. Tel: +1 214 820 7500. E-mail: milton.packer@baylorhealth.edu

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chronic kidney disease target a hemoglobin level no higher than 10–11 g/dL.

Simultaneous Erythropoietin Stimulation and Iron Supplementation in Patients With Chronic Heart Failure in the Modern Era

Although anemia has negative prognostic implications in patients with HF,⁴ most of the essential medicines for the treatment of HF lead to a decrease in hemoglobin and increase the proportion of patients with anemia, even though they reduce mortality rates and hospitalizations due to HF.^{5,6} Should we, therefore, be concerned about increases in hemoglobin when erythropoiesis stimulation and iron supplementation are combined in the modern era of HF management?

Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization due to HF for a broad range of patients, and they may reduce the risk of cardiovascular death in those with reduced ejection fraction.^{7,8} Initiation of SGLT2 inhibitors is accompanied by an increase in hemoglobin, which averages ≈ 0.7 g/dL, with a mean achieved hemoglobin level of ≈ 14.5 g/dL; the magnitude of the increase is similar in patients with and without anemia.^{7–9} The increase occurs over the first 4 weeks and plateaus after 4–8 months; the early increase in hemoglobin levels is a statistical marker of the action of these medicines to reduce hospitalizations due to HF.¹⁰ Although there has been much

speculation about the action that causes hemoconcentration, SGLT2 inhibitors increase hemoglobin primarily by stimulating the endogenous production of erythropoietin,^{11,12} which may reflect enhanced nutrient deprivation and HIF-2 α signaling, the latter effect being akin to that of prolyl hydroxylase inhibitors.¹² However, the use of iron supplementation in trials of SGLT2 inhibitors was very low (< 5%).

Intravenous iron improves symptoms and exercise capacity in patients with HF and reduced ejection fraction who fulfill current criteria for iron deficiency; most of them had mild anemia (mean hemoglobin level of ≈ 12.0 – 12.5 g/dL).^{13,14} In 2 trials (AFFIRM-AHF [Randomised, Double-Blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and Mortality in Iron Deficient Patients Admitted for Acute Heart Failure] and IRONMAN [Intravenous Iron or Placebo for Anaemia in Intensive Care]),^{15,16} intravenous iron supplementation (with ferric carboxymaltose or ferric derisomaltose) reduced the risk of hospitalization for HF with no conclusive effect on mortality rates. Intravenous iron increased hemoglobin by ≈ 0.6 – 1.0 g/dL, with a mean achieved hemoglobin of ≈ 12.5 – 13.0 g/dL; the increase occurred within 4 weeks and plateaued after 4–12 months.^{13–16} Increases in hemoglobin levels were most apparent in those with anemia at baseline, but iron alone did not always correct the anemia.¹³ The use of SGLT2 inhibitors in trials of iron supplementation was low (< 5%).¹⁶

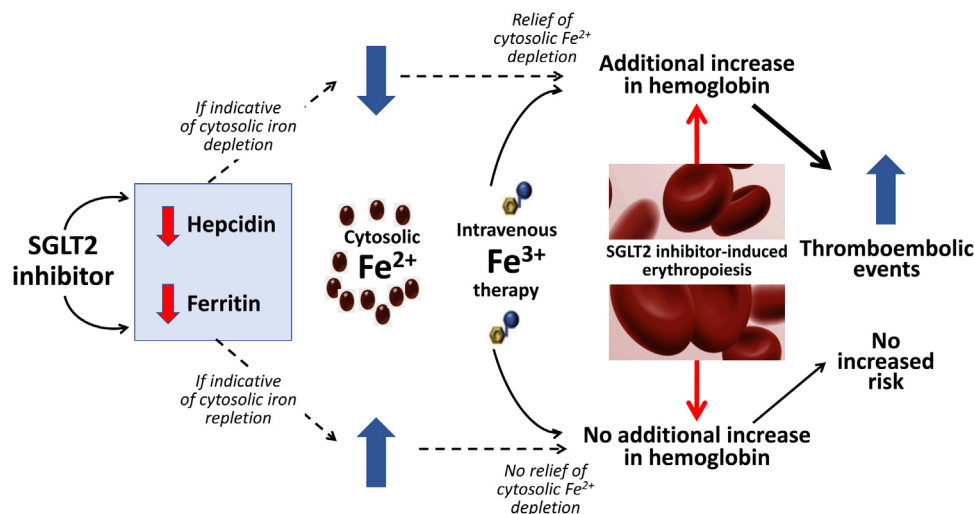


Fig. 1. Potential influence of intravenous iron on SGLT2 inhibitor-induced erythropoiesis in patients with heart failure who fulfill conventional criteria for iron deficiency. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to reduce hepcidin and ferritin in randomized controlled trials. On the one hand, changes in these iron biomarkers might reflect worsening of cytosolic iron deficiency, and if intravenous iron were administered, the action of SGLT2 inhibitors to stimulate erythropoiesis would be potentiated, leading to additional increases in hemoglobin and, possibly, to an increased risk of thromboembolic events. On the other hand, the declines in hepcidin and ferritin might reflect an anti-inflammatory action of SGLT2 inhibitors, which would be expected to alleviate a cytosolic iron-deficiency state. Under such circumstances, intravenous iron therapy would not be expected to produce further increases in hemoglobin or enhance thromboembolic risk. SGLT2, sodium-glucose cotransporter 2.

In the absence of treatment with an SGLT2 inhibitor, $\approx 50\%$ of patients with HF and reduced ejection fraction appear to be iron deficient and would be considered candidates for intravenous iron.¹⁷ SGLT2 inhibitors decrease both hepcidin and ferritin,¹⁸ which may be related to their erythropoietic action or to their ability to minimize systemic inflammation or cellular stress.¹⁹ SGLT2 inhibition also produce a slight decrease in TSAT due to an increase in transferrin, with little change in serum iron concentrations.¹⁸ The decreases in TSAT and ferritin may be interpreted by clinicians as worsening iron deficiency; thus, during SGLT2 inhibition, the proportion of patients deemed to be iron deficient by current criteria increases to nearly 70%.¹⁸ Thus, most patients treated with an SGLT2 inhibitor might be considered for intravenous iron therapy.

What can we expect when SGLT2 inhibitors and intravenous iron are combined? There are 2 possibilities (Fig. 1). On the one hand, the decrease in serum hepcidin during SGLT2 inhibitor use should increase the duodenal absorption of iron and enhance the release of iron from the reticuloendothelial system. Simultaneously, the effect of SGLT2 inhibitors in lowering ferritin can reduce the sequestration of intracellular iron, thus enhancing release of iron into the cytosolic pool. The action by SGLT2 inhibitors to decrease both hepcidin and ferritin would, therefore, lead to an increase in iron availability, thus alleviating intracellular iron deficiency.¹⁹ Under these circumstances, iron supplementation would be expected to have little effect on erythropoiesis. On the other hand, if worsening of conventional iron biomarkers during SGLT2 inhibition were to reflect the depletion of cytosolic iron (which would limit erythrocyte production), then iron supplementation would potentiate the increase in hemoglobin produced by these drugs. If the 2 treatments had additive effects, we would expect a hemoglobin level of 12.0 g/dL to rise to ≈ 13.5 g/dL for patients with HF and iron deficiency, and patients without anemia might achieve even higher hemoglobin concentrations. Increases in hemoglobin of this magnitude, driven by darbepoetin in patients with HF or with prolyl hydroxylase inhibitors in chronic kidney disease, increase the risk of thromboembolic events.^{1,2} Concerns have been raised that the increase in hemoglobin levels produced by SGLT2 inhibitors alone might explain why these drugs do not reduce the risk of stroke.²⁰

If SGLT2 inhibitors cause cytosolic iron depletion (as is commonly believed⁹), the concurrent treatment of patients with SGLT2 inhibitors and intravenous iron may amplify the erythrocytic response, leading, potentially, to a greater improvement in symptoms but, possibly, to an increased risk of thromboembolic events. Based on the lessons of

RED-HF, we cannot assume that the greater increases in hemoglobin are safe. However, if SGLT2 inhibitors cause cytosolic iron repletion (as has been recently proposed¹⁹), worrisome erythrocytosis will be avoided, and the need for intravenous iron therapy reduced. Therefore, there is an urgent need for additional clinical trial evidence to understand the benefits and risks of prescribing intravenous iron together with SGLT2 inhibitors before the combination is widely deployed.

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