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STATE-OF-THE-ART PAPER

Potential Interactions When Prescribing SGLT2 Inhibitors and Intravenous Iron in Combination in Heart Failure

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HIGHLIGHTS

- SGLT2 inhibitors change iron biomarkers in a manner that mimics iron deficiency.
- These changes reflect relief of inflammation-related changes in iron homeostasis, not a reduction in cytosolic iron.
- SGLT2 inhibitors alleviate iron deficiency, explaining their ability to promote erythrocytosis and cardiomyocyte ATP production.
- Further studies are needed before intravenous iron supplements are prescribed to patients receiving SGLT2 inhibitors.

ABSTRACT

In patients with heart failure, sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to decrease hepcidin and ferritin and increase transferrin receptor protein, changes that are typically indicative of worsening absolute iron deficiency, as would be seen with poor dietary intake or gastrointestinal bleeding, neither of which is provoked by SGLT2 inhibitors. Therefore, 2 alternative conceptual frameworks may explain the observed pattern of changes in iron homeostasis proteins. According to the "cytosolic iron depletion hypothesis," the effect of SGLT2 inhibitors to decrease hepcidin and ferritin and increase transferrin receptor is related to a decline in cytosolic Fe^{2+} that occurs after drug-induced erythropoietin-related increase in iron use. Erythropoietin-mimetics (eg, darbepoietin) elicit this type of iron-deficiency pattern of response, and it is typically accompanied by erythropoietin resistance that is alleviated by intravenous iron supplementation. In contrast, according to the "cytosolic iron repletion hypothesis," the effect of SGLT2 inhibitors to decrease hepcidin and ferritin and increase transferrin receptor represents a direct action of these drugs: 1) to reverse inflammation-related increases in hepcidin and ferritin, and, thus, alleviate functional blocks on iron utilization; and 2) to increase in sirtuin-1 signaling, which suppresses hepcidin, accelerates the degradation of ferritin, and up-regulates transferrin receptor protein. Through either or both mechanisms, direct suppression of hepcidin and ferritin would be expected to increase cytosolic Fe^{2+}, thus allowing an unattenuated erythrocytic response to erythropoietin without the need for intravenous iron supplementation. The totality of clinical evidence supports the "cytosolic iron repletion hypothesis" because SGLT2 inhibitors elicit a full and sustained erythrocytosis in response to erythropoietin, even in overtly iron-deficient patients and in the absence of intravenous iron therapy. Therefore, the emergence of an iron-deficiency pattern of response during SGLT2 inhibition does not reflect worsening iron stores that are in need of replenishment, but instead, represents potential alleviation of a state of inflammation-related functional iron deficiency that is commonly seen in patients with chronic heart failure. Treatment with intravenous iron may be unnecessary and theoretically deleterious.
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ABBREVIATIONS AND ACRONYMS

ATP = adenosine triphosphate

SGLT2 = sodium-glucose cotransporter 2

SIRT1 = sirtuin-1

Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of cardiovascular death and hospitalization for heart failure in patients with heart failure, whether the ejection fraction is reduced or preserved.[1] Although these drugs have an exceptional safety profile, a recent analysis from the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial investigators reported that the use of dapagliflozin in patients with heart failure with reduced ejection fraction led to significant worsening of biomarkers of iron deficiency.[2] After 12 months of therapy, patients in the dapagliflozin group were 70% more likely than in the placebo group to demonstrate new-onset iron deficiency, as defined by a serum ferritin <100 ng/mL or a transferrin saturation <20% combined with a serum ferritin <300 ng/mL. Perhaps more importantly, patients who already met these criteria at the start of the trial showed further worsening of their indices of iron homeostasis after SGLT2 inhibition.

In light of these findings, the authors suggested that patients receiving an SGLT2 inhibitor might benefit from the additional intravenous iron supplementation in the hope that the combination of the 2 treatments might provide therapeutic synergy. This possibility is based on the findings of randomized placebo-controlled trials showing that intravenous iron supplementation (in the absence of SGLT2 inhibition) can reduce worsening heart failure events and improve functional capacity in patients with heart failure with reduced ejection fraction who meet current criteria for iron deficiency.[3,4] It is noteworthy that nearly 50% of patients in the DAPA-HF trial were considered iron deficient at the start of the trial, and an additional 15% of the original cohort became newly iron deficient while treated with dapagliflozin.[2] Therefore, if conventional metrics of iron deficiency are used, nearly two-thirds of patients with heart failure with reduced ejection fraction would be considered candidates for iron supplementation therapy after several months of treatment with an SGLT2 inhibitor, suggesting that combination therapy might become a routine component of efforts to implement the use of foundational drugs in these patients. The public health and financial implications of these observations are substantial.

WHAT CAUSES WORSENING OF BIOMARKERS OF IRON DEFICIENCY DURING SGLT2 INHIBITION?

Iron is essential for the synthesis of heme and iron-sulfur clusters in the mitochondria of erythroid precursors (leading to the synthesis of hemoglobin) and in cardiomyocytes (leading to adenosine triphosphate [ATP] production). The iron that is directly responsible for these effects is the cytosolic pool of weakly bound highly reactive ferrous ion (Fe^{2+}), representing 5%-10% of intracellular iron stores.[5,6]

What determines the size of bioreactive cytosolic Fe^{2+} pool? Iron enters the bloodstream as ferric iron (Fe^{3+}), a process that is regulated by hepcidin (which blocks the absorption of iron from the gastrointestinal tract and the release of iron from macrophages involved in the recycling of senescent erythrocytes). Circulating Fe^{3+} is conveyed into cells when its transport protein (transferrin) attaches to transferring receptor protein 1, and the complex is internalized.[7] The reduction of Fe^{3+} releases Fe^{2+} into the bioreactive cytosolic pool, but the size of this pool is tightly regulated, and most intracellular iron is sequestered as inactive Fe^{3+} within a ferritin nanocage, which releases iron into the cytosol when needed. When body stores of iron are depleted (as in nutritional deficiency or gastrointestinal bleeding), down-regulation of hepcidin and up-regulation of transferrin receptor protein 1 act in concert to facilitate the absorption and entry of iron into heme-producing cells, and, at the same time, ferritin is degraded, which acts to release sequestered iron from intracellular storage sites.[7] Low levels of hepcidin and ferritin and high levels of transferrin receptor protein 1 (typically measured as soluble transferrin receptor) in circulating blood are conventionally considered to be indicative of iron deficiency.[8,9] However, this distinctive pattern of changes in iron homeostasis proteins is not a measure of the size of the cytosolic pool of Fe^{2+}; instead, these changes reflect the adaptive responses that are evoked when cytosolic Fe^{2+} is depleted and needs to be replenished.

ALTERNATIVE MECHANISTIC FRAMEWORKS TO EXPLAIN WORSENING OF IRON BIOMARKERS DURING TREATMENT WITH SGLT2 INHIBITORS. Although this pattern of changes in iron biomarkers is often

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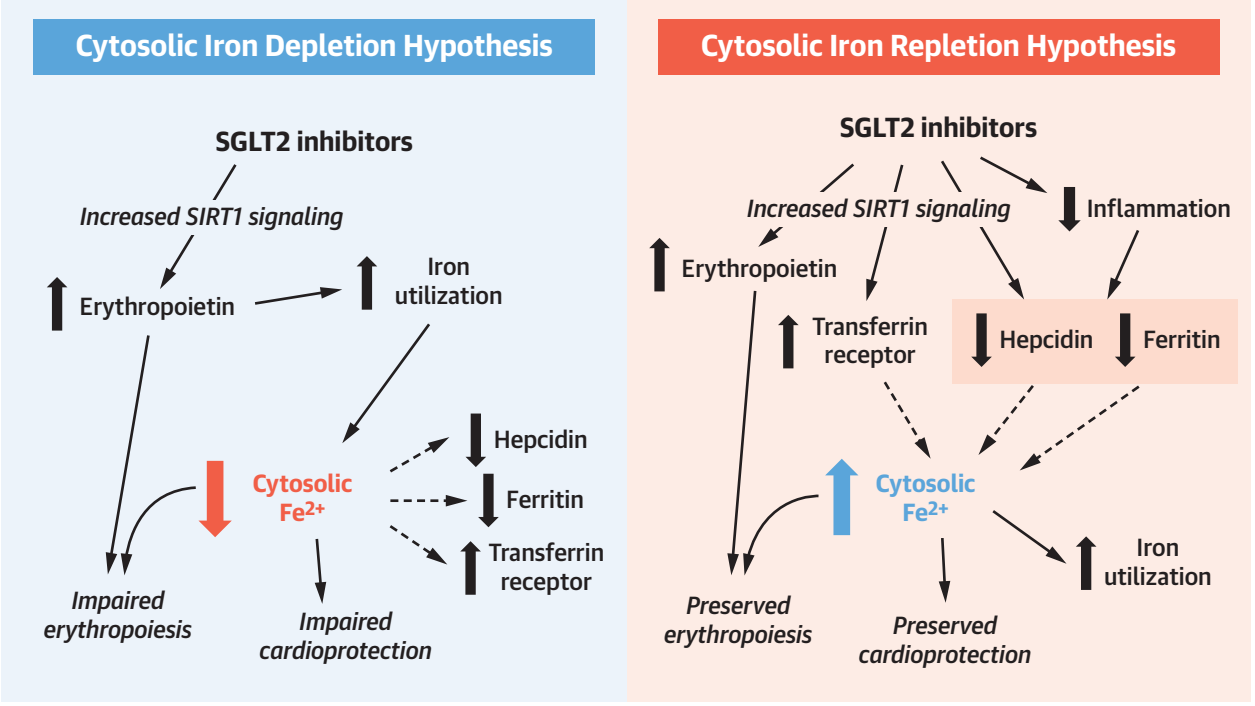
CENTRAL ILLUSTRATION **Two Conceptual Frameworks to Explain Worsening of Indices of Iron Deficiency During Treatment With SGLT2 Inhibitors**



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According to the "cytosolic iron depletion hypothesis," the effect of SGLT2 inhibitors to decrease hepcidin and ferritin and increase transferrin receptor is related to a decrease in cytosolic Fe^{2+} that occurs after erythropoietin-induced increase in iron use. In contrast, according to the "cytosolic iron repletion hypothesis," the effect of SGLT2 inhibitors to decrease hepcidin and ferritin and increase transferrin receptor represents a direct effect mediated by an increase in SIRT1 signaling (augmented by reversal of inflammation-related increases in hepcidin and ferritin), and these changes lead to an increase in cytosolic Fe^{2+}. If the cytosolic depletion hypothesis were true, low cytosolic Fe^{2+} would be expected to impair the erythropoietic and heart failure benefits of SGLT2 inhibitors, but such impairment is not seen in clinical trials. SGLT2 = sodium-glucose cotransporter 2; SIRT1 = sirtuin-1.

indicative of a depletion of the body's iron stores secondary to nutritional deficiency or gastrointestinal bleeding, 2 other pathophysiological states also lead to a distinctive pattern of decreasing hepcidin and ferritin coupled with an increase in soluble transferrin receptor (Central Illustration).

Enhanced erythropoiesis. Stimulation of erythropoiesis (regardless of cause) consumes cytosolic Fe^{2+} in the formation of heme, and the resulting decrease in cytosolic Fe^{2+} triggers decreases in hepcidin and ferritin and increases in soluble transferrin receptor, as an adaptive response to replenish iron capacity.[10,11] The concerted action of these proteins acts to maintain adequate levels of cytosolic Fe^{2+} to ensure that effective erythropoiesis can be sustained. Erythropoietin-mimetics (eg, darbepoietin) elicit an iron-deficiency pattern of response,[12,13] which likely reflects a clinically important decrease in cytosolic Fe^{2+} because: 1) patients with this pattern show blunted responsiveness to erythropoietin;[14,15] and 2) replenishment of cytosolic Fe^{2+} with the use of intravenous iron supplementation overcomes erythropoietin resistance.[16-18]

Systemic inflammation. In disease states characterized by chronic inflammation, cytokine activation directly stimulates the synthesis of hepcidin and ferritin.[19,20] These changes likely represent a profoundly ancient response intended to deprive inflammation-triggering invading organisms of the iron they needed to sustain their survival in the host.[21] Regardless of its primordial significance, the effect of inflammation on hepcidin and ferritin retards the amount of iron that can be absorbed from the duodenum or released from macrophages as well as the quantity of intracellular iron that can be freed from ferritin sequestration. The result is a state of

cytosolic Fe^{2+} deficiency, although systemic and intracellular Fe^{3+} stores are not depleted, that is, the state of cytosolic iron deficiency is functional, rather than absolute.[7]

Functional iron deficiency states can respond favorably to intravenous (but not to oral) iron administration.[22] However, if the state of chronic inflammation can be ameliorated, the biological stimulus to the synthesis of hepcidin and ferritin subsides, leading to an increase in bioreactive cytosolic Fe^{2+}, although circulating levels of hepcidin and ferritin are decreasing.[23] Under these circumstances, the emergence of an iron-deficiency pattern of response does not reflect the presence of an iron depletion state, but, instead, reflects the alleviation of the inflammation-related functional blocks on iron use. Reversal of inflammation-mediated functional iron deficiency produces changes in circulating iron biomarkers that closely mimic the development of an absolute iron-deficient state. However, because cytosolic levels of Fe^{2+} are supported and enhanced, the relief of functional iron deficiency is not accompanied by erythropoietin resistance, and iron supplementation is not required to maintain erythrocytosis.

Can either of these 2 alternative mechanisms explain the observed changes in iron- deficiency biomarkers seen during treatment with SGLT2 inhibitors in patients with heart failure? In placebo-controlled trials, SGLT2 inhibitors have been consistently shown to increase erythropoietin and soluble transferrin receptor while reducing hepcidin and ferritin.[2,24-27] Such changes are compatible with either of the 2 conceptual frameworks depicted in the **Central Illustration**. However, the first framework (left) is predicated on the assumption that cytosolic levels of Fe^{2+} are depleted by enhanced erythropoiesis, whereas the second framework (right) presumes that cytosolic levels of Fe^{2+} are being repleted by the relief of inflammation or by other actions that reduce cellular stress. The first framework leads to the conclusion that iron supplementation is vital for optimal patient outcomes, whereas the second framework suggests that iron supplements are unnecessary. Which framework explains the effects of SGLT2 inhibitors?

CELLULAR MECHANISMS INFLUENCING IRON HOMEOSTASIS DURING SGLT2 INHIBITION. According to the "cytosolic iron depletion hypothesis" (**Central Illustration**, left), SGLT2 inhibitors directly stimulate the production of erythropoietin, presumably through their established ability to up-regulate sirtuin-1 (SIRT1) signaling.[28] SIRT1 enhances the production of erythropoietin through its effect to activate hypoxia inducible factor-2α.[29] The action of erythropoietin to stimulate erythropoiesis depletes the cytosolic Fe^{2+} pool, thus triggering the suppression of hepcidin and ferritin and up-regulation of transferrin receptor protein as an adaptive response.[11-14] However, these reactive changes cannot restore cytosolic Fe^{2+} if dietary sources and/or macrophage and hepatic stores of iron are marginal. The depletion of cytosolic Fe^{2+} impairs the erythrocytic response to erythropoietin, resulting in a state of iron-dependent erythropoietin resistance, akin to that seen with the clinical use of erythropoietin-stimulating agents.[14-16]

According to the "cytosolic iron repletion hypothesis" (**Central Illustration**, right), up-regulation of SIRT1 signaling not only promotes the synthesis of erythropoietin, but it also directly causes decreases in hepcidin and ferritin and increases in transferrin receptor protein, independent of erythropoiesis. SGLT2 inhibitors exert important anti- inflammatory effects (likely mediated through SIRT1),[30,31] thus reversing the stimulus to both hepcidin and ferritin. SIRT1 inhibits the synthesis of hepcidin in both hepatocytes and macrophages;[32] SIRT1 activates peroxisome proliferator-activated receptor-gamma coactivator-1 alpha, which acts to up-regulate transferrin receptor protein;[33] and stimulation of hypoxia-inducible factor-2 alpha by SIRT1 increases expression of nuclear receptor coactivator 4,[34] which promotes ferritinophagy, thus degrading ferritin. Therefore, through an anti-inflammatory effect and other cellular actions that suppress hepcidin and ferritin (independent of erythropoiesis), SGLT2 inhibitors can directly overcome the internal functional blocks that are imposed on iron use as a result of systemic inflammation. Because cellular iron stores are not depleted in patients with functional iron deficiency, the reversal of functional blocks on iron use with the use of SGLT2 inhibitors acts to augment cytosolic Fe^{2+}, thus allowing for an unimpaired erythrocytic response, in the absence of iron supplementation.

CLINICAL EVIDENCE FAVORS THE CYTOSOLIC IRON REPLETION HYPOTHESIS. To determine which conceptual framework might be applicable during treatment with SGLT2 inhibitors, it would be ideal if investigators could measure the cytosolic Fe^{2+} pool, but that is not possible in the clinical setting. Nevertheless, 2 lines of evidence from clinical studies support the merits of the "cytosolic iron repletion hypothesis."

First, the iron deficiency state that is seen in 50% of patients with heart failure with reduced ejection

fraction is not caused by an absolute deficiency state related to poor dietary intake or gastrointestinal bleeding. Instead, the high prevalence of iron deficiency is caused by a functional block on the release of iron from existing stores.[35-37] Patients with heart failure have an inflammatory state that stimulates the production of both hepcidin and ferritin, explaining why serum hepcidin levels are increased in heart failure in parallel to the activation of proinflammatory pathways.[36-39] Similarly, patients with heart failure have increased levels of ferritin,[40] and the magnitude of this increase is so marked that the presence of heart failure changes the threshold levels of ferritin that are used for the diagnosis of iron deficiency states. Iron depletion in patients without heart failure is generally identified when serum ferritin decreases to <30 ng/mL. However, this threshold increases 10-fold in patients with heart failure, who can be diagnosed with iron deficiency with ferritin levels as high as 299 ng/mL (or even greater).[40] Although several studies have reported absolute iron deficiency in patients with heart failure, these have evaluated small highly selected cohorts who had a bone marrow examination,[41,42] which is notoriously difficult to interpret.[43,44] Although it is possible that some patients with advanced heart failure have depleted iron stores, most patients with heart failure have mild-to-moderate symptoms (as was the case in the DAPA-HF trial) and have a functional iron deficiency state.[39]

Second, if changes in iron biomarkers during SGLT2 inhibition were to represent worsening of iron deficiency,[2] then patients who are already iron-deficient before treatment would be expected to show an attenuated response to these drugs, with respect to their effects on both the bone marrow and the heart. Specifically, patients who are iron-deficient should show a blunted erythrocytic response because cytosolic Fe^{2+} depletion leads to erythropoietin resistance.[14-16] Furthermore, ATP is depleted in the failing heart, particularly when patients are iron deficient;[45-47] restoration of ATP is the basis for the use of intravenous iron supplements to reduce the risk of major heart failure events.[3,4] Therefore, if SGLT2 inhibitors were to lower cytosolic Fe^{2+}, they would be expected to aggravate iron deficiency-related depletion of ATP in the myocardium, leading to an increased risk of heart failure events and limiting the ability of SGLT2 inhibitors to reduce heart failure hospitalizations. However, in the DAPA-HF trial,[2] when compared with those who were iron replete, patients who were iron deficient at baseline showed similar increases in hemoglobin and experienced similar decreases in the risk of heart failure events in response to dapagliflozin, although biomarkers of iron deficiency worsened in these patients during treatment. Importantly, the magnitude of the erythrocytosis produced by SGLT2 inhibitors did not wane over time,[2] a finding that would be difficult to explain if patients were truly becoming progressively more iron deficient (**Central Illustration**).

It should be noted that—before treatment with an SGLT2 inhibitor—many patients in the DAPA-HF trial who were deemed to be iron deficient also had anemia, implying that the levels of cytosolic Fe^{2+} in erythroid precursors were insufficient to maintain adequate erythropoiesis.[2,48] However, after therapy with an SGLT2 inhibitor, patients who had iron-deficient anemia were likely to show correction of anemia, although <1% received intravenous iron supplementation.[48] This sequence of events is possible only if SGLT2 inhibition was acting to alleviate—not exacerbate—the low cytosolic levels of Fe^{2+} that acted to limit erythropoiesis in these anemic patients. Such alleviation is consistent with the "cytosolic iron repletion hypothesis," but it is inconsistent with the expectations of the "cytosolic iron depletion hypothesis."

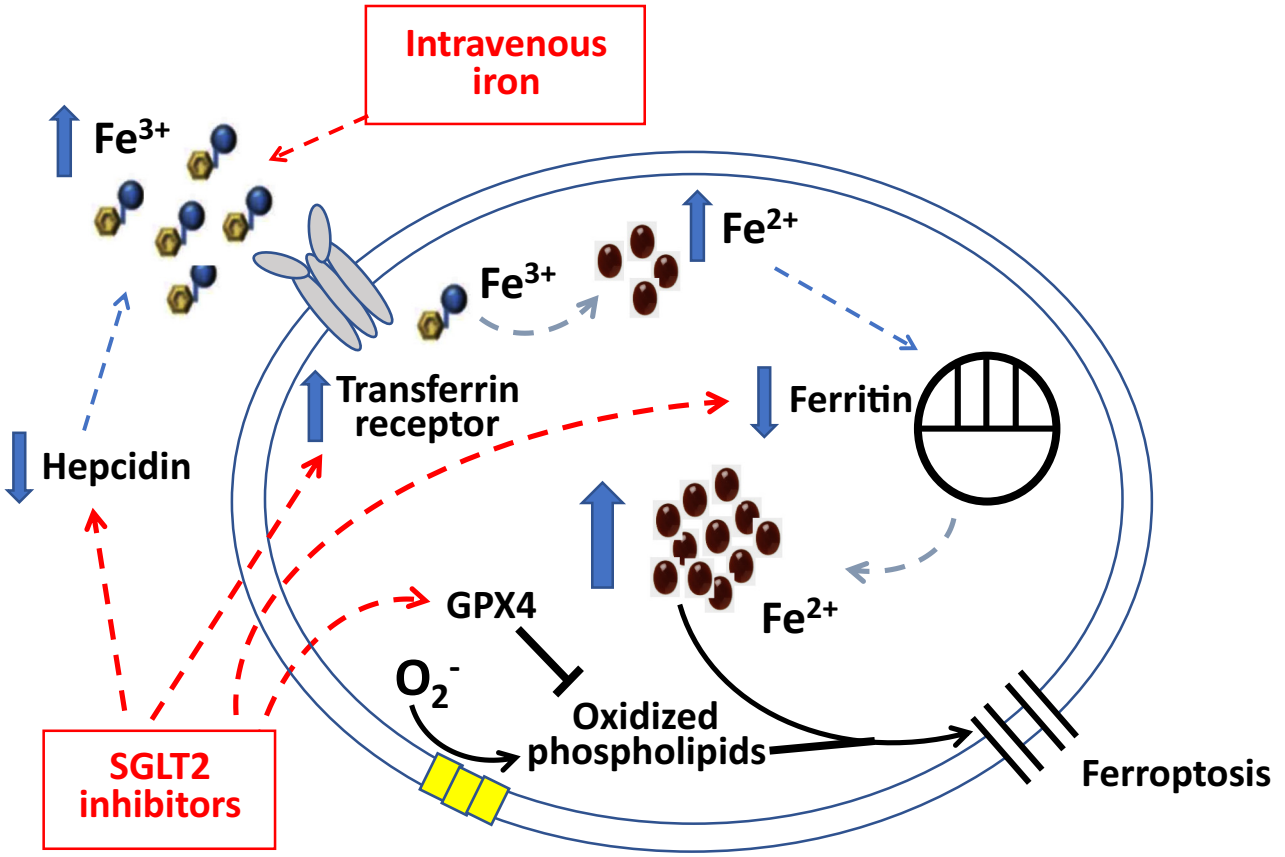
POTENTIAL ADVERSE CONSEQUENCES OF TREATING PATIENTS RECEIVING SGLT2 INHIBITORS WITH INTRAVENOUS IRON

If SGLT2 inhibitors act to replete cytosolic iron, the treatment of worsening biomarkers of iron deficiency with intravenous iron would be unnecessary, and it is possible that combined use of SGLT2 inhibitors and intravenous iron might have deleterious effects.

In states where glutathione-dependent antioxidant defenses are deficient, increased cytosolic free radicals steal electrons from membrane-bound phospholipids (particularly polyunsaturated fatty acids), a process known as lipid peroxidation. In the healthy heart, the consequences of lipid peroxidation are held in check by glutathione-dependent glutathione peroxidase 4,[49-51] yet, this defense mechanism is deficient in the failing heart.[52] Under these conditions, if cytosolic Fe^{2+} levels increase excessively and surpass the capacity for effective mitochondrial use, oxidatively damaged phospholipids coalesce leading to a specialized form of programmed cell death, known as ferroptosis.[49-54] Ferroptosis is characterized by defects in the cell membrane that promote excessive permeability, leading to cell swelling and demise.

The risk of ferroptosis is proportional to level of unbound bioreactive cytosolic Fe^{2+}. Accordingly, ferroptosis is diminished by iron chelation,[54,55] and it

FIGURE 1 Pathways by Which Combined Treatment of SGLT2 Inhibitors and Intravenous Iron Might Increase Free Cytosolic Fe^{2+} and Influence Ferroptosis in Cardiomyocytes



The availability of extracellular iron is increased by down-regulation of hepcidin and treatment with intravenous iron. Iron is transported into cardiomyocytes through the transferrin receptor, but unbound cytosolic levels of Fe^{2+} are constrained by ferritin. SGLT2 inhibitors act to decrease hepcidin and ferritin and up-regulate the transferrin receptor. These 3 effects, acting in concert, would be expected to increase free cytosolic Fe^{2+}, and excessive levels (in the presence of oxidized phospholipids) promote ferroptosis. Ferroptosis may be prevented if SGLT2 inhibitors act to up-regulate the activity of GPX4, which neutralizes the toxicity of oxidized phospholipids. GPX4 = glutathione peroxidase 4; SGLT2 = sodium-glucose cotransporter 2.

is enhanced by heme degradation (which releases Fe^{2+} into the cytosol)[49] and by the deletion of cardiac ferritin (which abolishes the capacity of cardiomyocytes to maintain cytosolic Fe^{2+} in a bound and nonreactive state).[56] Ferroptosis plays a seminal role in the development of a wide range of diverse cardiomyopathies, especially those related to doxorubicin toxicity or myocardial infarction, including those occurring in the clinical setting.[57-61]

Both SGLT2 inhibitors and intravenous iron can act individually to increase cytosolic Fe^{2+} within cardiomyocytes, and when used alone, neither drug increases the risk of heart failure events. However, with combined use, it is possible that cytosolic Fe^{2+} levels might increase to levels that could promote ferroptosis (Figure 1), especially if lipid peroxidation was not simultaneously inhibited. It is, therefore, noteworthy that SGLT2 inhibitors increase intracellular levels of glutathione and enhance sirtuin-1 signaling;[28,62] both effects can augment glutathione-dependent glutathione peroxidase 4.[51,63] As a result, SGLT2 inhibitors have been reported to decrease ferroptosis in experimental models of cardiomyopathy.[64] However, it is not clear whether the favorable effects of SGLT2 inhibitors on ferroptosis seen experimentally might be negated in the clinical setting if patients were receiving intravenous iron supplementation.

It should be noted that the development of SGLT2 inhibitors and intravenous iron supplements for heart failure has occurred in parallel, and large-scale trials with 1 drug typically did not enroll patients taking the

other agent. As a result, physicians do not know whether intravenous iron and SGLT2 inhibitors interact—favorably or unfavorably—if prescribed together. The coadministration of these drugs in clinical practice is particularly likely because SGLT2 inhibitors decrease serum ferritin and transferrin saturation,[2] and, thus, they heighten the probability that patients will be deemed to be iron deficient, and, thus, considered for therapy with intravenous iron.

CONCLUSIONS

The available evidence suggests that: 1) most patients with mild-to-moderate heart failure have an inflammatory state that promotes the development of functional iron deficiency; 2) the use of SGLT2 inhibitors appears to alleviate the state of functional iron deficiency in parallel with their anti-inflammatory effects, without the use of intravenous iron; and 3) SGLT2 inhibitors act to worsen circulating biomarkers that are commonly used to characterize the iron status of patients with heart failure, but these changes in iron biomarkers do not identify the existence of an intracellular iron deficit that limits the beneficial effects of these drugs in erythroid precursors or in cardiomyocytes. In fact, alleviation of functional iron deficiency during SGLT2 inhibition would be expected to obviate, rather than augment, the need for intravenous iron supplementation in these patients. Therefore, before intravenous iron is widely prescribed to patients with heart failure who appear to be iron deficient while receiving SGLT2 inhibitors, trials of the utility of combination therapy are needed to determine whether the "cytosolic iron repletion hypothesis" or the "cytosolic iron depletion hypothesis" has the greater merit. The efficacy and safety of the concurrent use of SGLT2 inhibitors and intravenous iron in patients with heart failure should be tested before combined therapy is recommended.

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During the past 3 years, Dr Packer has consulted for Abbvie, Actavis, Amarin, Amgen, AstraZeneca, Boehringer Ingelheim, Caladrius, Casana, CSL Behring, Cytokinetics, Imara, Lilly, Moderna, Novartis, Reata, Relypsa, and Salamandra.

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