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Ferric derisomaltose therapy and heart failure: implications and molecular insights

Konrad T. Sawicki & Hossein Ardehali

Iron is essential to the production of myocardial energy and proteins critical for cardiovascular function. Nearly 50% of patients with heart failure with reduced ejection fraction (HFrEF) meet current criteria for iron deficiency, and there has been considerable interest in intravenous repletion of iron stores as a therapeutic strategy to improve HFrEF outcomes. However, the data on intravenous iron therapy in HFrEF have been mixed.

At the American Heart Association (AHA) Scientific Sessions 2022 and in a simultaneous publication in *The Lancet*, Kalra et al.[1] recently reported the results of IRONMAN, the first large trial in patients with HFrEF and iron deficiency (ID)[2] evaluating intravenous ferric derisomaltose, a newer formulation of intravenous iron that can be given as a rapid, high-dose infusion[1]. IRONMAN was a prospective, randomized, open-label, blinded-endpoint trial of the safety and long-term effects of ferric derisomaltose treatment compared with usual care in 1,137 participants with HFrEF (ejection fraction <45%) and iron deficiency, defined as transferrin saturation (TSAT) <20% or serum ferritin <100 μg l^{-1}. Participants randomized to ferric derisomaltose infusion were redosed 4 weeks later, and then every 4 months if ferritin levels were <100 μg l^{-1}, or <400 μg l^{-1} if TSAT was <25%. Across 70 hospitals in the UK, the average age of participants was 73 years, 74% were men and >90% were white.

At a median follow-up of 2.7 years, intravenous ferric derisomaltose was not superior to usual care for the primary composite endpoint of reduction in recurrent HF hospitalizations and cardiovascular death (rate ratio (RR) = 0.82, 95% confidence interval (CI) 0.66–1.13; $P = 0.07$). The secondary outcomes of a reduction in the rate of HF hospitalizations (RR = 0.80, 95% CI 0.62–1.03; $P = 0.085$) and risk of cardiovascular death (hazard ratio = 0.86, 95% CI 0.67–1.10; $P = 0.23$) were also not significantly different between groups. Although intravenous ferric derisomaltose was borderline associated with short-term improvements in subjective HF symptoms at 4 months, as measured by change in the Minnesota 'living with heart failure questionnaire' (−3.33, 95% CI −6.67 to 0.0; $P = 0.05$), this was no longer significant by 20 months (−2.57, 95% CI −6.72 to 1.59; $P = 0.23$). Perhaps the most sobering finding of IRONMAN was that the mortality rate did not differ significantly between the groups: an overall all-cause mortality of 33% over a median of only 2.7 years.

The findings of IRONMAN were reminiscent of the AFFIRM-AHF trial, which enrolled patients with HFrEF at the time of an acute decompensation and used a different intravenous iron formulation, ferric carboxymaltose (FCM)[3]. Both IRONMAN and AFFIRM-AHF failed to show a significant benefit of intravenous iron treatment for their primary composite endpoint of total HF hospitalizations and cardiovascular death. The findings of the IRONMAN and AFFIRM-AHF trials also do not support a reduction in cardiovascular mortality with intravenous iron, which now seems to be a class effect across different formulations. Of note, IRONMAN and AFFIRM-AHF faced challenges due to the COVID-19 epidemic, and in sensitivity analyses with follow-up censored for the pandemic, both trials showed greater reductions in the primary composite outcome.

The observations from IRONMAN may have notable public health and financial implications. The use of intravenous iron in patients with HF largely depends on reimbursement policies, which are related to

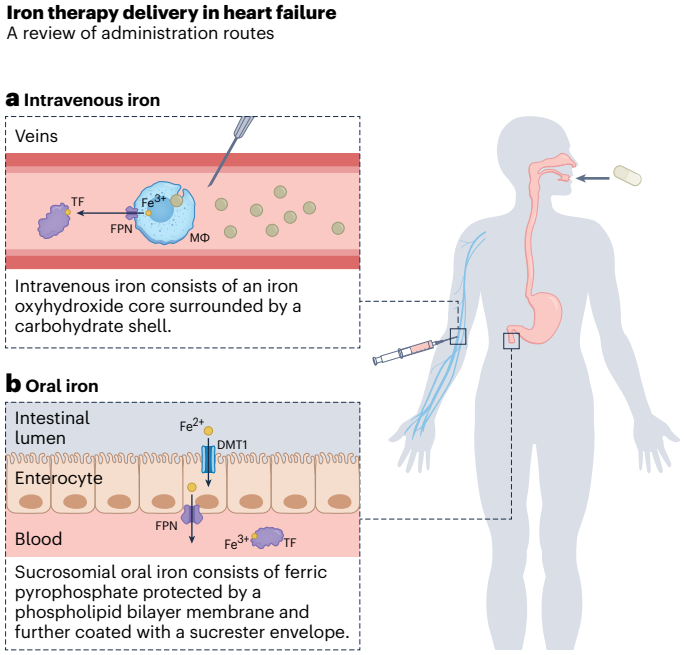

Fig. 1 | Iron therapy delivery in heart failure. a, Intravenous iron introduces a large bolus of non-transferrin-bound iron directly into the systemic circulation. Non-transferrin-bound iron is redox active and may promote the production of reactive oxygen species, which can be damaging to endothelial cells and target cells. Intravenous iron is taken up by circulating macrophages (MΦ) and the iron core is then released into the circulation by ferroportin (FPN), which requires higher hepcidin levels for suppression than does intestinal FPN. **b**, Absorbed oral ferric iron (Fe^{3+}) is reduced to ferrous iron (Fe^{2+}) at the brush border of enterocytes in the small intestine. Ferrous iron is imported by divalent metal transporter 1 (DMT1) and exported through FPN, which is under major regulatory control from hepcidin. Released iron is oxidized and incorporated into transferrin (TF), rendering it redox inactive. TF-bound iron circulates in plasma until it reaches target cells.

Table 1 | Overview of IRONMAN and upcoming intravenous iron trials in patients with HFrEF and iron deficiency.

	IRONMAN	FAIR-HF2	HEART-FID
NCT number	NCT02642562	NCT03036462	NCT03037931
Design	Multicenter RCT	Multicenter RCT	Multicenter RCT
Blinding	Open-label	Double-blind	Double-blind
Patient population	Chronic HFrEF	Chronic HFrEF	Chronic HFrEF
Iron product	Ferric derisomaltose	FCM	FCM
Definition of iron deficiency	TSAT <20% or ferritin <100 μg l^{-1}	Ferritin <100 μg l^{-1} or 100–299 μg l^{-1} with TSAT <20%	Ferritin <100 μg l^{-1} or 100–300 μg l^{-1} with TSAT <20%
Enrollment	1,137	1,200	3,014
Duration	2.7 years (median)	>12 months	12 months
Primary endpoint	HF hospitalization and CV mortality (RR = 0.82, 95% CI: 0.66–1.13; *P* = 0.07)	HF hospitalization and CV mortality	HF hospitalization and CV mortality, and 6MWT (change from baseline to 6 months)
Trial status	Complete	Recruiting	Active, not recruiting

Abbreviations: 6MWT, 6-minute walk test; CI, confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NCT, National Clinical Trial; RCT, randomized controlled trial; RR, relative rate; TSAT, transferrin saturation.

professional guideline recommendations. The European Society for Cardiology (ESC) HF guidelines recommend the screening of patients with HF for iron deficiency and treatment with intravenous FCM in symptomatic patients with iron deficiency to improve symptoms and quality of life[4]. The AHA and American College of Cardiology (ACC) HF guidelines also recommend screening patients with HF for iron deficiency, but there is no strong indication for intravenous iron repletion[5]. Given the failure of ferric derisomaltose to meet its primary or key secondary endpoints in IRONMAN, the study is unlikely to justify expansion of intravenous iron use in clinical practice.

An important distinction between IRONMAN and AFFIRM-AHF was the use of different criteria to identify iron deficiency. IRONMAN defined iron deficiency as a TSAT <20% or ferritin <100 μg l^{-1}, whereas AFFIRM-AHF defined it as ferritin <100 μg l^{-1}, or ferritin 100–299 μg l^{-1} with TSAT <20%. This highlights a critical question in the field: what definition of iron deficiency should be used for patients with HF[6]? Iron deficiency occurs in the forms of (i) absolute iron deficiency, reflected by the absence of iron in the bone marrow; or (ii) functional iron deficiency, due to impaired gastrointestinal absorption or iron sequestration in hepatocytes and macrophages related to chronic inflammation. The assessment of iron deficiency in HF is complex, and patients with HF can have absolute iron deficiency, functional iron deficiency or both. Many patients with mild to moderate HF have a low-grade inflammatory state that promotes the development of functional iron deficiency, as evidenced by increased hepcidin and ferritin levels in most patients with HF until the development of end-stage disease[7]. However, current criteria for functional and absolute iron deficiency were based on expert opinion over 15 years ago and derived from patients with chronic kidney disease. In addition, previous reports estimating the prevalence of absolute iron deficiency in patients with HF were based on small sample sizes, did not include bone marrow iron staining as the gold standard and involved a highly selected group of participants with advanced HF, and is likely to have overestimated the rates of absolute iron deficiency[8].

It is commonly believed that circulating iron indices for systemic iron deficiency also identify the existence of an intracellular iron deficiency that limits cardiovascular function, but this assumption may not be valid. Although myocardial iron staining is reduced in HF, this does not necessarily reflect a lack of bioavailable iron at the level of the cardiomyocyte due to dysregulated cellular iron homeostasis[9]. These observations raise important questions about our current reliance on circulating iron indices to infer intracellular iron levels in cardiomyocytes and other cardiovascular cell types when patients are being considered for iron repletion therapy. Myocardial iron deficiency at the level of the cardiomyocyte may be best identified by an increase in myocardial transferrin receptor (TFR1) expression and a corresponding decrease in myocardial ferritin levels[10]. Thus, current criteria may misclassify a significant number of individuals who are not truly iron deficient at the cellular level in the cardiovascular system.

It is also important to note that the investigation of novel therapies for guideline-directed medical therapy (GDMT) and intravenous iron repletion in HF have largely occurred in parallel, with little overlap. In IRONMAN, the use of optimal GDMT among participants was relatively low, and only 3% of participants were on sodium–glucose cotransporter-2 (SGLT2) inhibitors. Therefore, there is a gap in knowledge regarding any potential synergistic or antagonistic interactions between contemporary GDMT and intravenous iron. This may be particularly relevant for the combination therapy of SGLT2 inhibitors and intravenous iron. Dapagliflozin has been shown to increase hematocrit and erythropoiesis, with corresponding reductions in circulating ferritin and TSAT levels[11]. These reductions in circulating ferritin and TSAT levels with dapagliflozin do not suggest a reduction in intracellular iron stores but rather relief of inflammation-mediated changes in iron homeostasis, which could render treatment with intravenous iron unnecessary.

It is also possible that the coadministration of SGLT2 inhibitors and intravenous iron in certain patients may have deleterious effects by raising intracellular myocardial iron to levels that promote ferroptosis, an iron-mediated cell death pathway that has been heavily implicated in HF[12]. Thus, trials evaluating the efficacy and safety of optimal GDMT with and without intravenous iron may be beneficial before intravenous iron is commonly prescribed to patients with HF who appear to be iron deficient by current criteria.

No significant safety concerns were seen with intravenous ferric derisomaltose during the follow-up period of IRONMAN. However, there are risks and logistical challenges associated with intravenous iron. Hypophosphatemia has been observed following both ferric derisomaltose and FCM administration, particularly in patients with iron deficiency anemia due to inflammatory bowel disease[13]. The pro-oxidative effects of free iron may also theoretically destabilize plaques in patients with atherosclerosis[14]. Furthermore, the cost of intravenous iron is high and its availability in the outpatient setting limited in the USA.

In IRONMAN, the usual-care group could include oral iron supplementation, which accounted for 17% of patients in the control group. The lack of superiority in regard the primary and secondary endpoints may be partially due to oral iron repletion in the control group diluting any potential beneficial effect for intravenous iron in the treatment group. It is unknown whether similar HF benefits could be achieved using oral iron supplementation. There is a relative paucity of evidence supporting intravenous over oral iron repletion in patients with HFrEF and iron deficiency (Fig. 1)[15]. Oral iron is safe and inexpensive, and newer formulations are well tolerated. The effects of contemporary oral iron formulations on HF outcomes have not yet been studied in large-scale clinical trials.

In conclusion, the results of IRONMAN add to the body of evidence demonstrating that intravenous iron repletion in patients with HFrEF and iron deficiency improves quality of life and possibly reduces HF hospitalizations in certain populations, but with no significant change in hard endpoints such as cardiovascular mortality. Patients with HF should be screened for iron deficiency, regardless of anemia status, and if they are found to have iron deficiency there should be a patient–provider discussion about the risks and benefits of iron repletion options. Two large ongoing trials, FAIR-HF2 and HEART-FID, will help to answer remaining questions about intravenous iron repletion in patients with HFrEF and iron deficiency (Table 1).

Konrad T. Sawicki [1,2] **& Hossein Ardehali** [1,2] ✉

[1]Feinberg Cardiovascular and Renal Research Institute, Northwestern University, Chicago, IL, USA. [2]Division of Cardiology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA.

✉e-mail: h-ardehali@northwestern.edu

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