Circulation: Heart Failure

EDITORIAL

Targeting Iron Deficiency in Heart Failure

Existing Evidence and Future Expectations

Piotr Ponikowski, MD, PhD; Ewa A. Jankowska, MD, PhD

"The deepest sin against the human mind is to believe things without evidence."

—Thomas H. Huxley

Despite considerable improvements in the management of patients with heart failure (HF), the outcomes remain unsatisfactory. The analysis of temporal trends reveal growing problem of increasing rate of rehospitalization and urgent need to address HF-associated comorbidities, which adversely affect natural history of the disease and impact the management.[1] Only recently, iron deficiency (ID) has been recognized as a prevalent comorbidity in HF, related to exercise intolerance and poor quality of life, independently predicting poor outcome in chronic and acute settings.[2] In this issue of *Circulation*: *Heart Failure*, Mentz et al[3] present the rationale and design of the HEART-FID trial, which addresses the intriguing and still not definitively answered question whether long-term treatment of ID with intravenous iron improves mortality and morbidity. Here, we present brief overview of the current understanding of deleterious biological consequences of ID in HF together with existing evidence positioning ID as therapeutic target in HF to emphasize clinical need for the HEART-FID trial and its relevance.

See Article by Mentz et al

BACKGROUND OF IRON HOMEOSTASIS

Iron is an essential micronutrient involved in numerous biological processes within human body, including oxygen transport and storage, energy production in the mitochondria, oxidative metabolism in the skeletal muscles and cardiomyocytes, synthesis and degradation of proteins, lipids, and RNA.[4] The human body contains on average between 3 and 4 g of iron, majority of which is located intracellularly, either bound to heme in hemoglobin or myoglobin or bound to cytosolic iron-storage proteins (ferritin, hemosiderin) in macrophages or hepatocytes.[5] The extracellular iron constitutes only about 0.1% of the total body iron and is mainly bound to blood iron-transport protein—transferrin. From the blood, transferrin-bound iron enters the cells via transferrin receptor and subsequent internalization by endocytosis. In addition, in unbound form iron uptake can occur through a variety of different channels and transporters.[4,5] In humans, iron homeostasis is tightly controlled by 2 major regulatory systems: systemic iron metabolism (including iron transportation in the enterocytes and macrophages)—controlled by mechanisms involving hepcidin (small peptide hormone mainly synthesized by hepatocytes) and its transmembrane receptor (ferroportin), whereas intracellular iron metabolism is orchestrated by a complex of IRPs (iron-regulatory proteins) which secure iron availability for metabolic processes.[4,5] Functionally, hepcidin (via an interaction with ferroportin) blocks intestinal absorption of iron and inhibits the export of iron from the reticuloendothelial system. Hepcidin synthesis and release into the circulation are down-regulated by depleted iron stores, hypoxia and ineffective erythropoiesis, and induced by inflammation and infection.[4,5] Importantly, export through ferroportin is the only mechanism of iron removal from the cells.[4,5]

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Correspondence to: Piotr Ponikowski, MD, PhD, Department of Heart Diseases, Medical University, Wroclaw University Centre for Heart Diseases, University Hospital 50-556 Wrocław, Borowska 213, Poland. Email piotr.ponikowski@umed.wroc.pl

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DELETERIOUS BIOLOGICAL CONSEQUENCES OF ID

The role of iron in myriad key homeostatic processes explains clinical importance of dysregulation of iron metabolism in the form of ID, which is the most common nutritional deficiency worldwide. Iron is vital micronutrient for effective erythropoiesis in the bone marrow, thus ID is traditionally linked to anemia with deleterious effects being associated with low hemoglobin level (Figure). In clinical practice, it is referred to as ID anemia, often complicating natural course of chronic diseases (eg, chronic kidney disease, inflammatory bowel disease, malignancies, chronic skin disorders, rheumatoid diseases).[6] On the contrary, however, pathophysiological consequences of ID are far more extensive and independent of low hemoglobin level (Figure). ID alone results in decreasing oxygen storage, abnormal oxidative metabolism and cellular energy handling, impaired reactive oxygen species defense, all of which contribute mitochondrial dysfunction. Other deleterious consequences of ID (unrelated to anemia) comprise derangements in DNA replication, repairing and cell-cell regulation, abnormalities in the immune response and control within hormonal system[5–7] (Figure).

As iron is an essential cofactor for key energetic processes, tissues with high energetic demand (such as the skeletal muscle and cardiomyocytes) may be particularly susceptible for deleterious pathological effects of ID. The effect of myocardial ID on the function of the heart, such as a decrease in energy production in the mitochondria, inability to adapt to acute and chronic increases in workload and resultant impairment in cardiomyocyte contractility and relaxation, has been documented in the preclinical studies.[8–10] It appears that in advanced HF depleted intracellular iron is a characteristic feature of failing myocardium,[10–12] but there are also reports that mitochondrial iron and total cellular heme levels are elevated in advanced HF and the term myocardial iron disequilibrium (rather deficit) has been proposed.[13] At the level of the skeletal muscle, ID may be an important causative factor of loss of muscle oxidative capacity which contributes to abnormal muscle function with specific form of skeletal myopathy.[14]

ID IN HF: COMMON AND OMINOUS COMORBIDITY

ID is recognized as a prevalent comorbidity in HF, present in ≈50% of patients with chronic stable HF irrespective of the presence of anemia and up to 70% of patients hospitalized with acute HF.[2,5,15] The mechanisms underlying ID in HF remain unclear. ID may simply reflect depleted iron stores in the body resulting from reduced dietary intake (due to malnutrition, poor absorption due to impaired duodenal iron transport, interaction with certain drugs or food reducing iron absorption) and increased iron loses (due to edema of the gut, impaired integrity of intestinal mucosa, occult gastrointestinal/genitourinary bleeding due to use of antithrombotics).[5,6] Importantly, in certain conditions ID coincides with normal (or even increased) iron stores but with functional impairment of iron availability/utilization at the periphery.[5,6] It was suggested that proinflammatory activation seen in HF leads to an overexpression of hepcidin with resultant blockade of duodenal iron absorption and iron retention in the reticuloendothelial system.[5,6] This view has been recently challenged as the levels of hepcidin in HF are decreased and seem not to correlate with proinflammatory activation.[15,16]

In patients with HF, ID is accompanied by impaired functional capacity and decreased health-related quality of life.[2,5,6] In chronic ambulatory HFrEF and HFpEF, concomitant ID predicts increased long-term all-cause mortality independently of the presence of anemia.[2,5,6] Of note, ID in patients hospitalized due to acute HF was also found to be an independent predictor of poor outcome.[15] All these data suggest that ID may have a strong unfavorable impact on the natural history of clinical syndrome of HF beyond the CV status. Deterioration in energy homoeostasis, already impaired HF syndrome,[17] due to decreased iron delivery, content, and handling seems to accelerate progression of HF and lead to increased risk of poor outcomes. All these findings form strong background to expect beneficial effects of correcting ID in patients with HF.

ID IN HF AS THERAPEUTIC TARGET: EXISTING EVIDENCE

Intuitively, it might be expected that oral supplementation should be the first-line treatment in iron-deficient patients with HF. However, recent IRONOUT HF trial reported that in these population, oral iron supplementation was neither beneficial to correct ID nor to improve exercise capacity.[18] In contrast, several studies with intravenous iron used to correct ID in patients with HF proved to be effective in iron repletion and improvement of functional status, exercise capacity, and health-related quality of life[19–21] (Table 1). Consistent results of these studies have been acknowledged by recent European and US HF guidelines which recommend to consider intravenous iron in symptomatic patients with HF and ID to alleviate HF symptoms and improve exercise capacity and quality of life.[22,23]

Importantly, at this stage, the question of key importance for HF community is whether this therapy could favorably affect the outcomes in patients with HF with concomitant ID. An individual patient data meta-analysis reported that treatment with intravenous iron (in the form of FCM [ferric carboxymaltose]) was associated with reduction in combined all-cause death or cardiovascular hospitalization, and the risk of combined cardiovascular death or hospitalization for HF worsening but without the

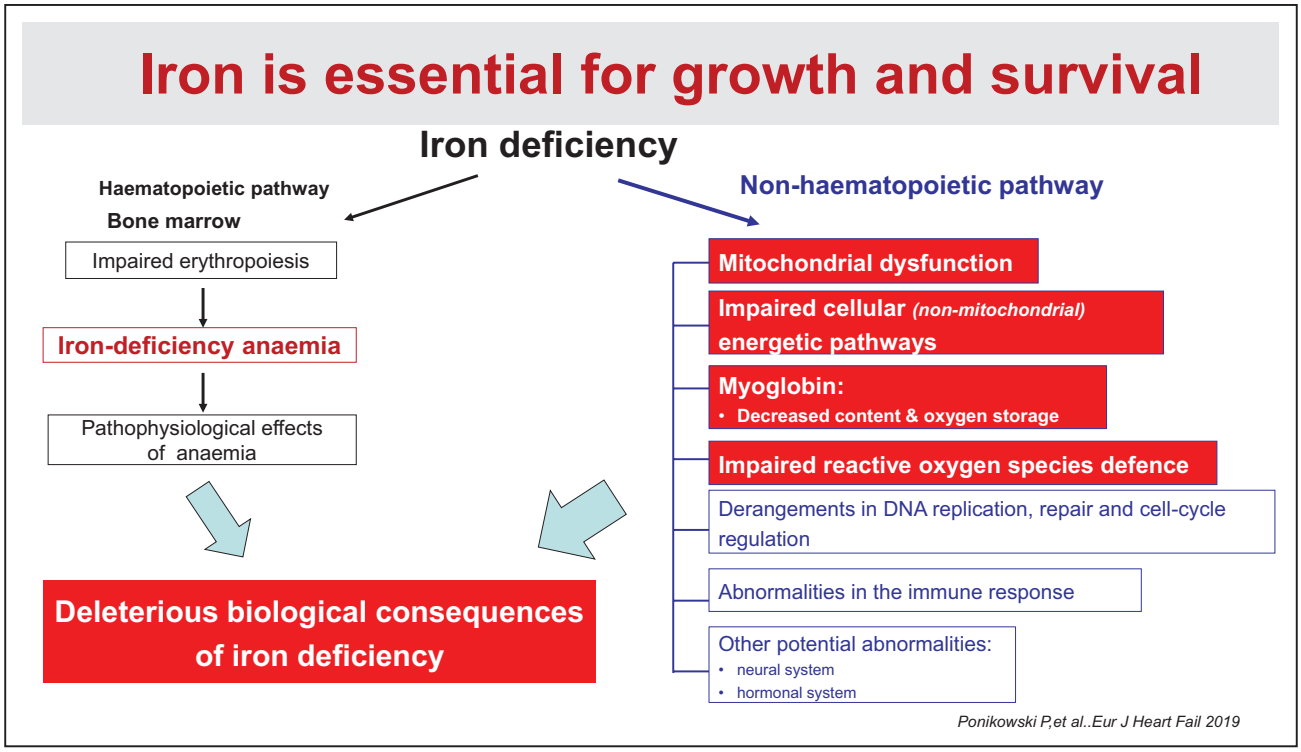

Figure. Deleterious biological consequences of iron deficiency.
Reproduced with permission from Ponikowski P et al. Rationale and design of the AFFIRM-AHF trial: A randomized, double-blind, placebo-controlled trial comparing the effect of intravenous ferriccarboxymaltose on hospitalizations and mortality in iron-deficient patients admitted for acute heart failure. Eur J Heart Fail. 2019;21:1651-1658. © 2019 The authors.

impact on either all-cause or cardiovascular mortality.[24] As of today, there is only one randomized clinical trial prospectively designed to evaluate the effect of intravenous iron (FCM) in patients with acute HF and ID on the outcomes—AFFIRM-AHF—results of which have been recently reported.[25]

AFFIRM-AHF was a multicenter, double-blind, randomized trial (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02937454) which comprised 1132 patients hospitalized for acute HF with concomitant ID (defined as ferritin <100 µg/L, or 100–299 µg/L with transferrin saturation <20%) with left ventricular ejection fraction of <50%. Before hospital discharge, participants were randomly assigned to receive intravenous FCM or placebo for up to 24 weeks, dosed according to the extent of ID. The primary outcome was a composite of total HF hospitalizations and cardiovascular death up to 52 weeks after randomization. Treatment with FCM, resulted in an rate ratio for the combined primary end point of 0.79 (95% CI, 0.62–1.01, *P*=0.059) which falls just short of conventional 5% statistical significance. The total number of HF hospitalizations was significantly lower in the FCM group compared with the placebo group (rate ratio, 0.74 [95% CI, 0.58–0.94], *P*=0·013). There was no difference in cardiovascular death between the 2 groups. Statistically significant treatment benefits of FCM compared with placebo were seen for the time to first HF hospitalization or cardiovascular death, and for days lost due to HF hospitalization and cardiovascular death.[25]

Considering the findings of the AFFIRM-AHF as strongly supporting the recommendation to administer intravenous FCM in patients with ID who are stabilized after an episode of acute HF to reduce the risk of HF hospitalizations, there is an undisputable need for additional randomized clinical trials adequately powered to evaluate the outcomes of iron supplementation in iron-deficient HF patients. Currently, there are 3 ongoing trials (Table 2), HEART-FID being one of them.[3] The unique features of this study[3] are as follows:

1. It is the largest of these 3 trials with ≈3014 patients with chronic, symptomatic, optimally managed HF (New York Heart Association class II–IV) and ID, planned to be randomized;
2. The primary end point is a hierarchical composite including death, HF hospitalization, and change in 6-minute walking test distance; of note, this end point was chosen not only to investigate the experience for patients in terms of mortality and morbidity but also allowing each participant to contribute to the primary end point (even if he/she does not experience a clinical event) through inclusion of 6-month 6-MWT distance[4];
3. Importantly, the study is also adequately powered to assess the effect of FCM on the top secondary

Table 1. Published Randomized Clinical Trials With Intravenous Iron Supplementation in Patients With Heart Failure and Iron Deficiency, Investigating the Effects on Exercise Capacity and Quality of Life

Trial	FAIR-HF (Anker et al[19])	CONFIRM-HF (Ponikowski et al[20])	EFFECT-HF (Veldhuisen et al[21])
Study population	Ambulatory, optimally treated, symptomatic patients with HF with LVEF ≤40% (for NYHA class II) or ≤45% (for NYHA class III)	Ambulatory, optimally treated, symptomatic patients with HF with LVEF ≤45%, NYHA II–III	Ambulatory, optimally treated, symptomatic patients with HF with LVEF ≤45%, NYHA II–III
Definition of iron deficiency	Ferritin <100 ng/mL or 100–299 ng/mL if transferrin saturation <20%	Ferritin <100 ng/mL, or 100–299 ng/mL if transferrin saturation <20%	Ferritin <100 ng/mL, or 100–299 ng/mL if transferrin saturation <20%
Interventions	FCM/placebo	FCM/placebo	FCM/standard of care
No. of participants	304/155	152/152	86/86
Duration of therapy	24 wk	52 wk	24 wk
Primary end points	PGA at wk 24 Δ NYHA class from baseline to wk 24	Δ 6MWT from baseline to wk 24	Δ pVO2 from baseline to wk 24

6MWT indicates 6-minute walk test; CONFIRM-HF, a study to compare the use of ferric carboxymaltose with placebo in patients with chronic heart failure and iron deficiency; EFFECT-HF, effect of ferric carboxymaltose on exercise capacity in patients with iron deficiency and chronic heart failure; FAIR-HF, ferinject assessment in patients with iron deficiency and chronic heart failure; FCM, ferric carboxymaltose; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PGA, patient global assessment; and pVO2, peak oxygen consumption.

composite (time to cardiovascular death or hospitalization for HF), as it will continue until preplanned number of participants with an event has occurred (771 participants with an event necessary to achieve the desired power for this top secondary end point);

4. The trial will provide robust evidence of postexposure efficacy and safety of FCM; in the AFFIRM-AHF trial, around 80% of patients in the active arm received only 2 doses of intravenous FCM at weeks 0 and 6, hence in the vast majority of patients the beneficial effects of this therapy on recurrent HF hospitalization seen already up to 12 months were in fact a consequence of a relatively short-term therapy administered to patients on discharge and few weeks later (and was on average of 1.4 g of FCM)[25]; the intervention in the HEART-FID trial will be administered chronically for few years of follow-up and cumulative doses of intravenous iron are

Table 2. Randomized Clinical Trials With Intravenous Iron Supplementation in Patients With Heart Failure and Iron Deficiency, Investigating the Long-Term Effects on Morbidity and Mortality

Trial acronym	HEART-FID	FAIR-HF2	IRONMAN
ClinicalTrials.gov Identifier	NCT03037931	NCT03036462	NCT02642562
Studied population	Stable HF (NYHA II–IV) on maximally tolerated background therapy for at least 2 wk before randomization	Patients with chronic HFrEF present for at least 12 mo	Patients with symptomatic HF (NYHA II–IV)
	LVEF ≤40% obtained during the screening visit or either of the following: (1) historical value of LVEF ≤40% within 24 mo of screening visit and (ii) historical value of LVEF ≤30% within 36 mo of screening visit		LVEF <45% within the prior 2 y using any conventional imaging modality (this should be the most recent assessment of LVEF)
	Either documented hospitalization for HF within 12 mo of enrollment or elevated natriuretic peptide level within 90 days of randomization (1) for patients in normal sinus rhythm: NT-proBNP >600 pg/mL or BNP >200 pg/mL and (2) for patients in atrial fibrillation: NT-proBNP >1000 pg/mL or BNP >400 pg/mL)		Evidence of being in a higher risk HF group: (1) current (with the expectation that patient will survive to discharge) or recent (within 6 mo) hospitalization for HF or (2) out-patients with NT-proBNP >250 ng/L in sinus rhythm or >1000 ng/L in atrial fibrillation (or BNP of >75 pg/mL or 300 pg/mL, respectively)
Definition of iron deficiency	Ferritin <100 ng/mL, or 100 to 300 ng/mL with transferrin saturation <20%	Ferritin <100 ng/mL, or 100-299 ng/mL if transferrin saturation <20%	Transferrin saturation <20% and/or ferritin <100 ug/L
Total number of participants	3014	1200	1300
	FCM/placebo	FCM/placebo	Iron isomaltoside/SOC
Primary end points	Composite of (1) incidence of death (time frame: 1 y), (2) incidence of hospitalization for HF (time frame: 1 y), and (3) change in 6MWT distance (time frame: 6 mo)	Combined rate of recurrent hospitalizations for HF and of CV death (number of events; time frame: at least after 12 mo of follow-up)	CV mortality or hospitalization for worsening HF (analysis will include first and recurrent hospitalizations; time frame: minimum 2.5 y follow-up from last patient recruited)

6MWT indicates 6-minute walk test; CV, cardiovascular; FAIR-HF2, intravenous iron in patients with systolic heart failure and iron deficiency to improve morbidity & mortality; FCM, ferric carboxymaltose; HEART-FID, randomized placebo-controlled trial of FCM as treatment for heart failure with iron deficiency; HF, heart failure; IRONMAN, intravenous iron treatment in patients with heart failure and iron deficiency; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and SOC, standard of care.

most likely to be much higher[3];
5. Last but not least, the data from the placebo arm in the HEART-FID trial will provide unique evidence on changes in iron status in patients with chronic HF during the long-term follow-up; the biological process of changes over time in iron status during the natural history still remains enigmatic, and comprehensive knowledge would definitively allow to address the problem of ID more specifically and more effectively in the future.

As the execution of this trial will be conducted in the era of coronavirus disease 2019 (COVID-19) pandemic, specific precautions may well be considered, as suggested by the recent expert consensus documents.[26,27] Particularly, patient safety, potential impact of COVID-19 on the data integrity, study execution and completeness of follow-up, fewer HF hospitalizations reported recently in Europe—all could have an impact on the treatment effects and need to be considered.

FUTURE DIRECTIONS

Beneficial effects of intravenous iron therapy in patients with HF (improving quality of life, attenuating HF symptoms and preventing HF hospitalizations) without a clear hint regarding the responsible pathomechanisms, fully justifies a rapidly growing interest in experimental and clinical research focusing on deranged iron metabolism in HF. In our opinion, the following concepts merit a particular attention and require properly designed mechanistic studies:

1. Although clinical benefits of intravenous ID have been demonstrated in patients with HF with a particular configuration of circulating iron biomarkers (ferritin, TSAT), the definition of ID to be applied in HF remains controversial. There are experimental presumptions that we need to distinguish between systemic and cellular iron status, and we see intuitively that changes in iron status within peripheral blood, myocardium, skeletal muscle, and bone marrow are not parallel. There is a pragmatic need to identify circulating iron biomarkers reliably characterizing iron status within tissues which seem to be targets for intravenous iron therapy in patients with HF and ID, which would also allow to monitor precisely efficacy and safety of such an intervention;
2. The origin of ID in patients with HF remains a key question. The elucidation of pathomechanisms leading to ID in patients with HF is critical, which would allow to counteract this process with specific therapies and prevent the development of ID. Currently, intravenous iron supplementation can only balance iron loss in the body of unknown origin;
3. Experimental studies reveal a myriad processes where iron is involved, and as a consequence depleted iron critically compromises homeostasis. There is a need for mechanistic studies linking the effects of iron repletion with the metabolism and functioning of myocardium, skeletal muscle, kidneys, and other tissues contributing to the pathophysiology of circulatory decompensation and HF progression;
4. There are presumptions that iron repletion could be positioned as therapy preventing HF. Recent data indicate a high prevalence of ID in acute coronary syndrome and its association with poor outcome.[28] Based on the promising results of the AFFIRM-AHF trial confirming that iron repletion prevents HF hospitalization, including patients with ischemic cause, one may hypothesize a similar potential also in patients with postacute coronary syndrome who have risk factors for the development of HF or the progression of HF after an ischemic event;
5. SGLT2 inhibitors appear to be a new class of drugs which soon become a fundamental part of HF pharmacological management. Interestingly, there are reports that SGLT2 inhibitors can stimulate erythropoietin production, resulting in an increase in hemoglobin and may interfere with iron metabolism, for example, increasing a need for iron for metabolic processes and leading to ID.[29] It seems to be tempting to speculate that a combination of SGLT2 inhibitor and intravenous iron therapy would augment the beneficial effects of these 2 therapies.

Nearly, 2 decades passed since the first report was published indicating ID as a frequent comorbidity complicating the natural course of HF. Following the quote from T.H. Huxley cardiology community remained somehow hesitant how to handle these findings expecting more evidence. It seems that over last years, we have accumulated more and more evidence proving clinical importance of ID and benefits of intravenous iron therapy in HF. However. declaring here our conflict of interest, we believe that the best is yet to come.

ARTICLE INFORMATION

Affiliations

Department of Heart Diseases, Wroclaw Medical University, Poland (P.P., E.A.J.). Centre for Heart Diseases, University Hospital, Wroclaw, Poland (P.P., E.A.J.).

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