REVIEW ARTICLE

Iron deficiency in heart failure: a 2020 update

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ABSTRACT
Iron deficiency (ID) constitutes an important comorbidity affecting symptoms and outcomes in patients with heart failure (HF). Recent experimental studies and randomized clinical trials have demonstrated important novel data regarding either the mechanisms of this comorbid condition or the beneficial effects of intravenous iron therapy in patients with HF. In this review we summarize new developments regarding ID in patients with HF with either reduced or preserved ejection fraction, along with brief description of ongoing morbidity and mortality trials in this field—4 years after the release of the 2016 European Society of Cardiology guidelines that clearly recommend to screen for, and consider treatment of, ID in patients with HF with reduced ejection fraction.

Introduction The process of optimizing risk stratification and therapeutic algorithms in patients with heart failure (HF) remains challenging.[1] In recent years, iron deficiency (ID) has received special clinical attention as an important comorbidity affecting symptoms and outcomes in patients with HF mainly in a stable (chronic) but also acute clinical setting.[2-4] Since ID was included in the 2016 European Society of Cardiology (ESC) guidelines[5] as one of relevant comorbidities occurring in patients with HF (along with, eg, atrial fibrillation, depression, chronic obstructive pulmonary disease, anemia), research on the condition has been boosted and each year there are several new studies released that investigate this condition—from pathophysiological experiments to new clinical trials. Furthermore, the awareness of ID in HF was extrapolated to other patient populations, including those with myocardial infarction, aortic stenosis, diabetes, coronary artery disease, or even pediatric patients with HF.[2,6-8] In this review, we summarize new data available regarding ID in HF—4 years after the presentation of the current ESC guidelines for the management of HF[5] which clearly recommend to screen for, and consider treatment of, ID (with intravenous ferric carboxymaltose [FCM]) in this population to obtain clinical benefits.

Epidemiology and pathophysiology

A notable prevalence of ID in stable patients with HF has been confirmed in several new trials applying guideline-based diagnostic criteria. Moreover, promising data regarding patients with HF (who can be effectively treated with FCM) have instigated studies in other cardiovascular disease populations. In a recent analysis in elderly patients referred for transcatheter aortic valve implantation, ID was not only a common condition but also independent predictor of worse outcomes.[9] Importantly, the treatment with intravenous iron before transcatheter aortic valve implantation in iron-deficient individuals resulted in an improvement of iron parameters and clinical symptoms 1 month thereafter.[9] ID was also the subject of interest in patients with acute coronary syndrome. Cosentino et al[10] have shown that more than half of patients hospitalized for ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention have absolute or functional ID. Surprisingly, although iron-deficient patients had higher admission circulating cell-free mitochondrial DNA (reflecting mitochondrial injury) and cardiac troponins, they had better prognosis as compared with patients without ID.[10] Potential explanations of this paradox are currently not known.

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The exact etiology of negative systemic iron balance in the course of HF is still poorly elucidated.[11] The first potential explanation is a merely nutritional character of iron deficits.[12] Indeed, HF is accompanied by many nutritional deficiencies, including dietary iron, and there are several contributing and overlapping patomechanisms of nutritional abnormalities in this population.[13] It needs to be acknowledged that not only iron but also other dietary deficiencies negatively affect patient health-related quality of life and outcomes.[14] Nevertheless, many patients have proper body iron stores but the availability of iron for metabolic purposes and for iron-utilizing tissues (eg, bone marrow) is markedly reduced. Indeed, in several chronic diseases (not only HF but also chronic renal insufficiency, chronic obstructive pulmonary disease, and diabetes mellitus, to name a few) deranged iron status is attributed to the magnitude of systemic inflammation and circulating proinflammatory mediators, such as the thoroughly investigated interleukin 6.[15-17] It needs to be emphasized, however, that in patients with HF, the complex pathophysiological interplay between chronic low-grade inflammation and systemic iron status is not fully understood. Moreover, some iron biomarkers play a role in the immune system and response, for example, ferritin, which is an acute-phase reactant. From this point of view, interesting data have been demonstrated for hepcidin, which is not only the key iron regulator (it lowers circulating iron bound to transferrin in a negative feedback mechanism) but also an element of an innate immune response.[18] However, in stable patients with heart failure with reduced ejection fraction (HFrEF), hepcidin correlates neither with low hemoglobin levels nor inflammation, and is increased only in early stages of the disease.[19]

The fundamental differences between "systemic" iron status (reflected by circulating iron biomarkers such as widely assessed serum ferritin and transferrin saturation [TSAT]) and intracellular iron (mitochondrial vs extramitochondrial pool) need to be acknowledged. Analyzing either mechanistic and translational studies (eg, cell culture experiments) or large RCTs (with FCM or other iron formulations, intravenous or oral), we should make an elegant distinction between general systemic decrease in iron availability for target tissues (due to depleted iron stores or dysfunctional/restricted utilization of this micronutrient) and subtle well-balanced iron homeostasis within specific cells, in particular these with an extraordinarily high energy demand, such as cardiac or skeletal myocytes.[20-23] Although ID is considered an "energetic insult" for tissues utilizing high amounts of energy, the complex interplay between systemic, intercellular, and mitochondrial ID and iron overload is still not fully understood, in particular in cardiomyocytes and the heart as a whole.[24,25] Indeed, novel proteins and mechanisms have been investigated in animal models such as ferroportin (FPN), the protein increasing circulating iron (bound to transferrin). FPN has been traditionally considered as the exporter of iron to systemic circulation from the liver, duodenum, and mononuclear phagocytes (previously known as the reticuloendothelial system).[26] Interestingly, it is found also in the heart, where its role is not fully understood (there is evidence that cardiac FPN regulates cardiomyocyte iron).[26] To answer the question of how circulating iron regulator hepcidin affects cardiac FPN (in the context of systemic versus intracellular iron status), further mechanistic studies are required.

ID appears as a relevant comorbidity also in patients with HF with preserved ejection fraction (HFpEF), in whom it negatively impacts exercise tolerance and quality of life.[27,28] In a recent systematic review and meta-analysis of 11 studies yielding a total number of more than 1800 patients with HFpEF, ID was highly prevalent and associated with decreased exercise capacity (but not worse outcomes).[29] In another large observational study, nearly 1200 patients with HF were divided into 3 subgroups based on guideline-based strata of left ventricular ejection fraction (reduced, midrange, and preserved).[30] ID was present in more than 50% of patients and was related to decreased exercise capacity (as assessed by oxygen consumption) and worse outcomes in all 3 predefined subgroups.[30] There is one ongoing RCT to evaluate whether the use of FCM improves exercise capacity and symptoms of the disease in patients with HFpEF and ID (FAIR-HFpEF trial; ClinicalTrials.gov identifier, NCT03074591).

It is still not fully understood how intravenous FCM improves exercise capacity in patients with HFrEF and concomitant ID, especially that the therapeutic effect is independent of anemia,[31] so the basic explanation that FCM increases iron and consequently hemoglobin concentrations (with the latter resulting in improved oxygen supply to high-energy–demand tissues) is considered insufficient.[32] There are important patophysiological links between ID and skeletal muscle dysfunction,[33] and we have recently postulated that decreased exercise capacity in iron-deficient patients with HF can be due to impaired skeletal and respiratory muscle performance.[21] For example, in men with HFrEF, low circulating ferritin correlates with inspiratory muscle weakness, which is independent of the skeletal muscle mass.[34] Other important findings come from the study by Charles-Edwards et al,[35] who investigated the effects of intravenous iron isomaltoside on skeletal muscle energetics in patients with chronic HF with concomitant ID in a randomized double-blind placebo-controlled trial of mechanistic

design. The authors have demonstrated that this supplementation therapy improves energetics of skeletal muscles in these patients, which is reflected by shorter phosphocreatine recovery half-times as assessed on phosphorus magnetic resonance spectroscopy.[35] Further translational studies are needed and warranted regarding this potential mechanism of action of intravenous iron in patients with HF (with special emphasis on systemic versus intracellular iron evaluation in these patients).[20]

Acute/decompensated heart failure ID is frequent and clinically relevant in patients hospitalized for decompensated HF,[36] including those with HFpEF.[37] Importantly, iron status is not constant in these patients.[38-40] In general, acute HF is characterized by dynamic changes in clinical and laboratory characteristics of a patient even during the period of in-hospital stay.[41-43] It is, therefore, reasonable to reassess iron parameters few weeks or months after discharge even in patients with normal baseline iron parameters (during hospitalization / on discharge). With regard to the etiology of ID in acute HF, in a large biomarker profile analysis trial (BIOSTAT-CHF substudy)[44] in more than 2000 patients with worsening HF, the etiology of this comorbidity was attributed mainly to low iron uptake, deranged utilization / storage (eg, due to inflammation) and eventually blood loss associated with antiplatelets.

ID constitutes an important negative prognosticator in acute HF, and there is evidence that it correlates with longer in-hospital stay.[37] Patients hospitalized for acute HF with unmet iron cell requirements as reflected by high circulating soluble transferrin receptor levels and elevated lactate concentrations on admission have markedly decreased 1-year survival rates as compared with those without aforementioned abnormalities.[45] Indeed, ID defined based on pathophysiological approach as low hepcidin levels (depleted stores of this micronutrient) with concomitant high soluble transferrin receptor concentrations identifies patients with acute HF with highest risk of long-term mortality.[46]

Completed and ongoing clinical trials In patients with HFrEF, FCM, which is intended for those with concomitant ID irrespective of anemia (but contraindicated when hemoglobin concentration is higher than 15 g/dl—there are no data on safety in this group of patients), constitutes one of the novel promising therapeutic options (beyond angiotensin inhibitor-neprilysin inhibition, sodium glucose cotransporter 2 inhibition, and potassium binders),[47] with several ongoing RCTs aiming to expand the current body of knowledge on which groups of patients benefit the most from such a therapy.[48] Available data supports the use of FCM in patients with HF as this pharmacological intervention is either simple to initiate (and monitor / maintain) or cost-effective.[49-51]

The 2016 ESC guidelines on HF[5] recommended to consider intravenous FCM in patients with symptomatic HFrEF and ID (serum ferritin <100 µg/l, or ferritin between 100–299 µg/l and TSAT <20%) based on 2 large RCTs (pioneering FAIR-HF trial [Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure] published in 2009[52] and CONFIRM-HF trial [A Study to Compare the Use of Ferric Carboxymaltose with Placebo in Patients with Chronic Heart Failure and Iron Deficiency] from 2015)[53], which have demonstrated that such therapy improves symptoms, exercise capacity, and quality of life in these patients.[54] Since the publication of the 2016 guidelines, there have been a few new RCTs and subanalyses regarding either oral or intravenous iron in patients with HF. A lesson from IRONOUT HF trial (Oral Iron Repletion Effects on Oxygen Uptake in Heart Failure)[55] is that oral iron is not working in HFrEF with ID, as high-dose oral iron did not increase peak oxygen consumption over 16 weeks of therapy. In turn, in the EFFECT-HF trial (Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure) the group of van Veldhuisen et al[56] investigated how intravenous FCM affects objective measures of exercise capacity (obtained during cardiopulmonary exercise testing) in patients with HFrEF and ID. The authors have demonstrated that therapy with intravenous iron versus standard care has beneficial effects on the change in peak oxygen consumption from baseline to week 24; however, the imputation strategy for primary endpoint in patients who died (peak oxygen consumption of 0 at week 24) needs to be acknowledged.[56]

There are a few meta-analyses regarding intravenous iron in HF, which confirm clinical benefits of such therapy.[57,58] Furthermore, there are a few important ongoing clinical trials investigating different effects of intravenous iron in patients with HF.

The Affirm-AHF trial (Study to Compare Ferric Carboxymaltose with Placebo in Patients With Acute Heart Failure and Iron Deficiency; ClinicalTrials.gov identifier, NCT02937454) is to evaluate the effect of intravenous FCM in 1100 patients with acute HF and ID on the primary endpoint of recurrent HF hospitalizations and cardiovascular death during the 52-week follow-up. Patients will be enrolled during hospitalization (index hospitalization) after clinical stabilization.

The major inclusion criteria are, first, currently hospitalized for an episode of acute HF, where acute HF was the primary reason for hospitalization. All of the following items must apply:

1 Persistent dyspnea at rest in a recumbent sitting position (30°–45°) or with minimal exertion on admission due to acute HF episode
2 At least 2 of the following clinical findings present on or during acute HF admission: congestion on a chest X-ray; rales on chest auscultation; edema of 1+ or higher on a 0 to 3+ scale; elevated jugular venous pressure (≥8 cm H_2O)
3 Natriuretic peptide levels, measured during 72 hours from acute HF admission: B-type natriuretic peptide (BNP) level of 400 pg/ml or higher or N-terminal-pro-B-type natriuretic peptide (NT-proBNP) level of 1600 pg/ml or higher; or BNP level of 600 pg/ml or higher or NT-proBNP level of 2400 pg/ml or higher for patients presenting with atrial fibrillation when the blood sample was taken. In patients treated with an angiotensin receptor neprilysin inhibitor in the previous 4 weeks prior to randomization, only NT-proBNP values should be considered.
4 Acute HF episode treated with minimally 40 mg of intravenous furosemide (or equivalent intravenous loop diuretic defined as 20 mg of torasemide or 1 mg of bumetanide

The second inclusion criterion is ID defined as serum ferritin level of less than 100 ng/ml or 100 to 299 ng/ml if TSAT is less than 20%. The last criterion is left ventricular ejection fraction (LVEF) of less than 50% (assessed and documented within 12 months prior to randomization).

The HEART-FID trial (Randomized Placebo-controlled Trial of FCM as Treatment for Heart Failure with Iron Deficiency; ClinicalTrials.gov identifier, NCT03037931) is testing the effects of intravenous FCM compared with placebo (a 1:1 ratio) on the 12-month rate of death, hospitalization for worsening HF, and the 6-month change in the 6-minute walk test (6MWT) (primary endpoint) in 3014 patients with HF and ID. Drug administration occurs on day 0 and day 7 as an undiluted slow intravenous push (FCM, 15 mg/kg to a maximum individual dose of 750 mg 7 days apart and a maximum combined dose of 1500 mg), with additional follow-up visits planned at 3 month intervals, and additional dosing administered every 6 months as applicable.

Major inclusion criteria include:
1 Stable HF (the New York Heart Association class II–IV) on maximally-tolerated background therapy for at least 2 weeks prior to randomization
2 Reduced LVEF—assessment must be performed at least 12 weeks after a major cardiac surgical intervention including coronary artery bypass graft, valvular repair / replacement, or cardiac resynchronization therapy device implantation. LVEF of 40% or less obtained during the screening visit or either historical value of LVEF of 40% or less within 24 months of screening visit or historical value of LVEF of 30% or less within 36 months of screening visit.
3 Hemoglobin levels higher than 9.0 g/dl and less than 13.5 g/dl (women) or less than 15.0 g/dl (men) within 28 days of randomization
4 Serum ferritin level of less than 100 ng/ml or 100 to 300 ng/ml with TSAT of less than 20%
5 Either documented hospitalization for HF within 12 months of enrollment or elevated NT-proBNP concentrations within 90 days of randomization (for patients in normal sinus rhythm: NT-proBNP levels of more than 600 pg/ml or BNP levels of more than 200 pg/ml; for patients in atrial fibrillation: NT-proBNP levels of more than 1000 pg/ml (or BNP >400 pg/ml).

The IRONMAN trial (Intravenous Iron Treatment in Patients with Heart Failure and Iron Deficiency; ClinicalTrials.gov identifier, NCT02642562) will address whether the additional use of intravenous iron on top of standard care will improve the outcomes of 1300 patients with HF and ID. The primary endpoint is cardiovascular mortality or hospitalization for worsening HF (analysis will include first and recurrent hospitalizations) (minimum 2.5 years of follow-up). One group of patients will receive treatment with iron injections (administered as iron [III] isomaltoside 1000 mg) and the other group will not receive any iron injections. Iron will be infused over a minimum of 15 minutes for doses up to and including 1000 mg, and a minimum of 30 minutes for doses higher than 1000 mg.

Additional scheme:
1 Body weight of less than 50 kg: 20 mg/kg
2 Hemoglobin level of 10 g/dl or higher and body weight of 50 to 69 kg: 1000 mg
3 Hemoglobin level of 10 g/dl or higher and body weight of 70 kg or higher: 20 mg/kg up to a maximum of 1500 mg
4 Hemoglobin level of less than 10 g/dl and body weight of 50 to 69 kg: 20 mg/kg
5 Hemoglobin level of less than 10 g/dl and body weight of 70 kg or higher: 20 mg/kg up to a maximum of 2000 mg.

Major inclusion criteria were: 1) LVEF of less than 45% within the last 6 months using any conventional imaging modality; 2) the New York Heart Association class II–IV; 3) ID defined as TSAT of less than 20% and / or ferritin level of less than 100 µg/l; 4) evidence of being in a higher-risk HF group (current [with intention to discharge in the next 48 hours] or recent [within 6 months] hospitalization for HF, or 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]).

The FAIR-HF2 trial (Intravenous Iron in Patients with Systolic Heart Failure and Iron Deficiency to Improve Morbidity and Mortality; ClinicalTrials.gov identifier, NCT03036462) will investigate whether intravenous iron supplementation using FCM reduces hospitalization and mortality rates in 1200 patients with ID and HF. The primary

endpoint includes a combined rate of recurrent hospitalizations for HF and of cardiovascular death (number of events) (at least after 12 months of follow-up). Intravenous iron administration in the form of FCM will be carried out according to the summary of product characteristics. Bolus administration (1000 mg) will be followed by an optional administration of 500 to 1000 mg within the first 4 weeks (up to a total of 2000 mg) according to approved dosing rules, followed by administration of 500 mg FCM at every 4 months, except when hemoglobin level is higher than 16.0 g/dl or ferritin level is higher than 800 µg/l.

Major inclusion criteria were: patients with chronic HF present for at least 12 months; confirmed presence of ID; hemoglobin levels of 9.5 to 14.0 g/dl.

Summary ID constitutes an important comorbid condition in patients with HF, with several negative consequences for the disease symptomatology and prognosis. The current guidelines[5] recommend that intravenous FCM should be considered in patients with symptomatic HFrEF and concomitant ID to improve symptoms, exercise tolerance, and quality of life. There are some indirect premises from meta-analyses of RCTs that in HFrEF with ID intravenous iron therapy can improve outcomes[57,58]; however, there has been no large sufficiently powered RCT conducted to confirm this hypothesis prospectively. Ongoing RCTs on morbidity and mortality rates will soon answer this important clinical question.

ARTICLE INFORMATION

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