Iron Deficiency in Heart Failure
An Overview

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ABSTRACT
Iron deficiency is an extremely common comorbidity in patients with heart failure, affecting up to 50% of all ambulatory patients. It is associated with reduced exercise capacity and physical well-being and reduced quality of life. Cutoff values have been identified for diagnosing iron deficiency in heart failure with reduced ejection fraction as serum ferritin, <100 μg/l, or ferritin, 100 to 300 μg/l, with transferrin saturation of <20%. Oral iron products have been shown to have little efficacy in heart failure, where the preference is intravenous iron products. Most clinical studies have been performed using ferric carboxymaltose with good efficacy in terms of improvements in 6-min walk test distance, peak oxygen consumption, quality of life, and improvements in New York Heart Association functional class. Data from meta-analyses also suggest beneficial effects for hospitalization rates for heart failure and reduction in cardiovascular mortality rates. A prospective trial to investigate effects on morbidity and mortality is currently ongoing. This paper highlights current knowledge of the pathophysiology of iron deficiency in heart failure, its prevalence and clinical impact, and its possible treatment options. (J Am Coll Cardiol HF 2019;7:36–46) © 2019 by the American College of Cardiology Foundation.

Iron is an essential element for all forms of human life, mostly for its ability to accept and to donate electrons, thereby switching between its ferrous (bivalent, Fe²⁺) and its ferric (trivalent, Fe³⁺) form (1). Iron deficiency (ID), on the other hand, affects up to one-third of the world’s population (2). Populations at high risk include infants, young children, adolescents, elderly persons, and women, the last particularly during menstrual periods and pregnancy. The past decades have seen tremendous research effort into ID in patients with chronic diseases with underlying inflammatory activation, and these efforts have finally yielded the understanding that patients with heart failure (HF), chronic kidney disease, cancer, and inflammatory bowel disease are likewise at increased risk of developing ID. Thus, it is now understood that childhood growth and blood loss as well as inflammatory activity, even when only just detectable as cytokine or C-reactive protein activation, are risk factors for ID. This review paper traces the history of ID and iron supplementation in HF and summarizes the available data from clinical trials in order to guide clinicians in their treatment decisions.

HISTORY OF TREATING IRON DEFICIENCY IN HF
Patients with HF are affected by severely reduced exercise capacity and quality of life. On the lookout for new ways of improving exercise capacity, researchers from Tel Aviv started in the late 1990s to...
treat anemic patients with HF with a combination of subcutaneous erythropoietin and intravenous (IV) iron sucrose (2). Mean hemoglobin concentration, left ventricular ejection fraction (LVEF), and New York Heart Association (NYHA) functional classes improved significantly over 6 months of treatment (3). These findings sparked an avalanche of research into treatment of anemia in HF, culminating in a program of large trials of the novel long-acting erythropoietin derivative darbepoetin-alfa (Online Refs. 1,2). The anemia treatment pathway was ultimately left only after a large trial of darbepoetin-alfa ended in disappointment. Indeed, the RED-HF (Reduction of Events by Darbepoetin Alfa in Heart Failure) study, a randomized, double-blind, placebo-controlled trial in 2,278 patients with systolic HF and mild to moderate anemia did not show any improvement in the primary endpoint of death from any cause or hospitalization for worsening HF; however, there was an increased rate of thromboembolic events (13.5% vs. 10.0%, respectively; p = 0.009) and an increased risk of ischemic stroke (4.5% vs. 2.8%, respectively; p = 0.03) (4). In retrospect, it can be said that the early study design, consisting of a combination therapy of erythropoietin and IV iron, hampered the discovery that ID treatment may be worthwhile even in the absence of anemia.

Shortly before the results of RED-HF were published, a small open-label, nonrandomized, noncontrolled study in 16 patients with hemoglobin of ≤12 g/dl and ferritin of ≤400 μg/l in NYHA functional class II (56%) or III (44%) using IV iron administration alone showed improvements in quality of life and physical well-being over 3 months of follow-up (5). At the end of the study, all patients were in NYHA functional class II, their hemoglobin had risen, and their quality-of-life score had improved. This point is interesting, because the trials of darbepoetin-alfa had all underutilized iron. Therefore, the confirmation of these early results in a double-blind, randomized, placebo-controlled trial in 40 patients with symptomatic HF was important (6). Another small, randomized, observer-blinded study of IV iron sucrose also showed that improvements in exercise capacity measured by spiroergometry were possible (Online Ref. 3).

**DIAGNOSING IRON DEFICIENCY IN HF**

The dilemma of correctly diagnosing ID arises from the distinction between stored and circulating iron and from the difference between mobilizable and immobilizable iron. Because chronic HF, like chronic kidney disease, inflammatory bowel disease, or cancer, has been associated with increased systemic inflammation, the patient’s status plays an important role leading to functional ID. Hepcidin, a peptide encoded by the HAMP gene on chromosome 19 and secreted chiefly by hepatocytes, is the main regulator of iron uptake and release (1). Hepcidin controls the activity of ferroportin, a transmembrane iron exporter out of different cell types, that is, at the site of iron absorption (gut mucosa cells in the duodenum), as well as at the site of iron storage (hematocytes, macrophages). Once ferroportin is bound by hepcidin, it is destroyed in the lysosome, leading to reduced iron release (7). Because bacteria are largely dependent on the presence of iron for reproduction, the peptide that inhibits its uptake and its mobilization during periods of increased inflammatory activity was originally named liver-expressed antimicrobial protein (LEAP)-1. It was discovered in 2000 and later renamed hepatic bactericidal protein, or hepcidin.

When research of ID started in cardiology, it was unclear how to correctly arrive at its diagnosis. Reliable cutoff values were not available for HF but only for kidney disease or cancer. Early studies of ID in HF, therefore, used a ferritin concentration of ≤400 μg/l or <100 μg/l or a combination of ferritin concentrations ranging between 100 and 299 μg/l together with a transferrin saturation (TSAT) level of <20% as identifying criterion. After the latter cutoff values were validated in a double-blind trial, they were accepted and have been entered into the HF guidelines of the European Society of Cardiology (ESC) (8). Consequently, current ESC HF guidelines give a Class Ic recommendation to screen all HF patients for the presence of ID by using serum ferritin and TSAT measurement (8). Because these values are significantly different from the cutoff values used in subjects without chronic inflammation (usually ferritin concentration of <20 μg/l), the point of alternative diagnostic cutoffs is worth stressing. Treatment should be considered regardless of the presence of anemia. Table 1 highlights the most important cutoff values for diagnosing ID across different clinical entities in internal medicine.

**PREVALENCE AND CLINICAL EFFECTS OF IRON DEFICIENCY IN HF**

ID is highly prevalent in patients with chronic and acute HF; however, studies have used different definitions (13). A Canadian study in 12,065 patients with newly diagnosed HF found 21% of all anemic patients had absolute ID, as detected using discharge
TABLE 1 Relevant Cut-Offs for the Diagnosis of ID in Different Fields of Internal Medicine

| Study name (Ref. #) | Clinical Trial | Diagnosis | Number of patients | Randomization | Duration | Definition of iron deficiency | Hemoglobin | Natriuretic peptides | Change in VO2 | Change in peak VO2 | Change in 6-MWT | Change in absolute pVO2
|---------------------|----------------|-----------|--------------------|---------------|-----------|-----------------------------|------------|---------------------|--------------|------------------|----------------|--------------------|
|                     |                | HFrEF     | 35                 | 2:1 (iron:placebo) | 16 weeks  | Serum ferritin <100 ng/ml, or serum ferritin 100-299 ng/ml with TSAT <20%, ferritin <100 ng/ml | <12.5 g/dl | Not included | from baseline to week 18 | from baseline to week 24 | to baseline to week 24 | to baseline to week 16
|                     |                | HFrEF     | 40                 | 1:1 (iron:placebo) | 25 weeks  | Serum ferritin <100 ng/ml, or serum ferritin 100-299 ng/ml with TSAT <20%, ferritin <100 ng/ml | ≥12.5 g/dl | NT-proBNP | 200 mg iron sucrose weekly for 5 weeks | Change in absolute VO2 (ml/min) | Change in 6-MWT | Change in peak VO2
|                     |                | HFrEF     | 459                | 2:1 (FCM:placebo) | 24 weeks  | Serum ferritin <100 ng/ml, or serum ferritin 100-299 ng/ml with TSAT <20%, ferritin <100 ng/ml | ≥12.5 g/dl | Not included | 200 mg ferric carboxymaltose | Change in absolute VO2 (ml/min) | Change in 6-MWT | Change in peak VO2
|                     |                | HFrEF     | 304                | 1:1 (FCM:placebo) | 52 weeks  | Serum ferritin <100 ng/ml, or serum ferritin 100-299 ng/ml with TSAT <20%, ferritin <100 ng/ml | ≥12.5 g/dl | BNP >100 pg/ml, NT-proBNP >400 pg/ml | 200 mg ferric carboxymaltose | Change in self-reported PGA score and NYHA class from baseline to week 24 | Change in 6-min walk distance from baseline to week 24 | Change in absolute VO2 (ml/min) | Change in peak VO2 (ml/min) from baseline to week 16
|                     |                | HFrEF     | 174                | 1:1 (FCM:placebo) | 90 days   | Serum ferritin <100 ng/ml, or serum ferritin 100-299 ng/ml with TSAT <20%, ferritin <100 ng/ml | ≥12.5 g/dl | NT-proBNP >4,000 pg/ml | Ferrous sulfate 200 mg 3 times daily for 90 days | Change in peak VO2 from baseline to 90 days | Change in 6-MWT | Change in peak VO2
|                     |                | HFrEF     | 54                 | 1:1 (FCM:placebo) | 225       | Serum ferritin <100 ng/ml, or serum ferritin 100-299 ng/ml with TSAT <20%, ferritin <100 ng/ml | ≥12.5 g/dl | NT-proBNP | 150 mg oral iron polysaccharide iron complex (Feramax) twice daily | Change in peak VO2 from baseline to week 16 | Change in 6-MWT | Change in peak VO2
|                     |                | HF        | 225                | 1:1 (FCM:placebo) | 24 weeks  | Serum ferritin <100 ng/ml, or serum ferritin 100-299 ng/ml with TSAT <20%, ferritin <100 ng/ml | ≥12.5 g/dl | NT-proBNP | 150 mg oral iron polysaccharide iron complex (Feramax) twice daily | Change in peak VO2 from baseline to week 16 | Change in 6-MWT | Change in peak VO2

BNP = B-type natriuretic peptide; FCM = ferric carboxymaltose; Hb = hemoglobin; HF = heart failure; HFrEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MR-proANP = mid-regional atrial natriuretic peptide prohormone; NT-proBNP = N-terminal BNP prohormone; NYHA = New York Heart Association; PGA = patient global assessment; TSAT = transferrin saturation.

international classification of disease codes, implying complete or nearly complete depletion of iron stores (Online Ref. 4). Nanas et al. (Online Ref. 5), on the other hand, showed that a diagnosis based on serum values of ferritin might be misleading. Those authors used bone marrow biopsies from 37 anemic patients with end-stage HF. They found that 27 patients (73%) presented with ID in the bone marrow, even though they had normal or nearly normal serum ferritin levels. Several studies have applied the defining criteria named above, that is, serum ferritin of <100 μg/l or serum ferritin ranging from 100 to 299 μg/l in combination with a TSAT value of <20%. Using data from 546 consecutive ambulatory patients...
with HF, Jankowska et al. (14) found ID was present in 37%. Another study, in outpatients in German office-based cardiology practices, using data from 1,198 patients with HF, found a prevalence of ID reaching 42.5% (15). Acknowledged risk factors for the development of ID include female sex, a more advanced stage of HF, higher levels of N-terminal-pro-B-type natriuretic peptide (NT-proBNP), and higher serum levels of C-reactive protein (14). In addition, the presence of ID is an independent predictor of poor exercise capacity (15) and worse survival (14,16).

**IRON METABOLISM IN HUMANS**

Iron itself is potentially toxic, because intracellular reduction of molecular oxygen leads to the formation of free radicals, which can cause oxidative stress and damage to cells. However, iron also plays a vital role in many cellular processes, including the production of ATP and the formation of heme, which is essential for the function of many enzymes.

**TABLE 1 Continued**

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Recruiting</th>
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<td>≥45% together with evidence of diastolic dysfunction</td>
<td>≥45%</td>
<td>&lt;50%</td>
<td>&lt;35%</td>
<td>≥40%</td>
<td>&lt;45%</td>
<td>&lt;40% or ≥40% with left atrial volume index &gt;28 ml/m² and/or left ventricular mass index &gt;95 g/m² (women) or &gt;115 g/m² (men)</td>
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<td>Serum ferritin &lt;100 ng/ml, or serum ferritin 100-299 ng/ml with TSAT &lt;20%</td>
<td>Serum ferritin &lt;100 ng/ml, or serum ferritin 100-299 ng/ml with TSAT &lt;20%</td>
<td>Serum ferritin &lt;100 ng/ml, or serum ferritin 100-299 ng/ml with TSAT &lt;20%</td>
<td>Serum ferritin &lt;100 ng/ml or 100-300 ng/ml with TSAT &lt;20%</td>
<td>Serum ferritin &lt;100 ng/ml, or serum ferritin 100-299 ng/ml with TSAT &lt;20%</td>
<td>Serum ferritin &lt;100 ng/ml, or serum ferritin 100-299 ng/ml with TSAT &lt;20%</td>
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<td>&gt;9.5-14 g/dl</td>
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<td>&lt;9.0 and &lt;13.5 g/dl (women) or &lt;15.0 g/dl (men)</td>
<td>&lt;13 g/dl for men and &lt;12 g/dl for women</td>
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<td>Not included</td>
<td>Not included</td>
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<td>4 weeks</td>
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<td>500-2,000 mg ferric carboxymaltose according to Hb and weight value</td>
<td>500-2,000 mg ferric carboxymaltose according to Hb and weight value</td>
<td>500-2,000 mg ferric carboxymaltose according to Hb and weight value</td>
<td>500-2,000 mg ferric carboxymaltose according to Hb and weight value</td>
<td>750 mg ferric carboxymaltose</td>
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<td>Change in 6-min walk distance from baseline to week 24</td>
<td>Combined rate of recurrent hospitalizations for HF and of cardiovascular death from baseline to at least 12 months of follow-up</td>
<td>HF hospitalizations and cardiovascular death up to 52 weeks after randomization</td>
<td>Incidence of death and incidence of hospitalization for heart failure at least 12 months of follow-up and change in 6MWT distance after 6 months</td>
<td>Evaluate the effect of ferric carboxymaltose on mitochondrial gene activation pattern after 12 weeks of treatment</td>
<td>Change in skeletal muscle mitochondrial oxidative capacity</td>
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</tbody>
</table>
of reactive oxygen species. Therefore, intracellular and intravascular iron requires a “detoxifier,” intracellularly in the form of ferritin and intravascularly by binding to transferrin. Intravenously administered iron preparations likewise require such a “detoxifier” that usually has a composition similar to the “envelope” function of ferritin (Figure 1). Side effects of IV iron usually occur as a result of the “envelope” composition rather than as a result of the iron itself.

Oral iron tablets are prone to cause gastrointestinal side effects, mostly as a result of direct iron effects on the gut wall. Indeed, most oral iron preparations contain ferrous iron (Fe$^{2+}$) that is directly absorbed through divalent metal transporter (DMT)-1 into the gut mucosa cell. Nonheme (ferric) iron present in vegetables and fruits is less well absorbed and requires reduction by ferrireductase, an enzyme likewise present in the gut mucosa, before absorption. Ferrous iron (Fe$^{2+}$), however, cannot bind to transferrin and ferritin, and therefore a reduction is necessary to enable such binding (Figure 2) (17).

Inside the human body, iron not only plays a role in oxygen transport but also in skeletal muscle, the thyroid gland, the central nervous system, and in immune function. In a single person, the overall amount of iron is approximately 3 to 5 g, two-thirds of which resides inside hemoglobin (18). Stored iron bound to ferritin in several cell types has a much smaller part: 800 to 1,000 mg in men and 300 to 500 mg in women, thus explaining the higher prevalence of ID in female patients. With regard to function, the body always prioritizes the use of iron for metabolic purposes, with erythropoiesis having relative priority over other functions (19). Because no means of iron excretion exists, only the uptake in the duodenum and the upper jejunum is regulated (20). Normal food contains mostly nonheme (Fe$^{3+}$) iron, approximately 5 to 6 mg per 1,000 kcal, a form that is less well absorbed than heme iron (Fe$^{2+}$) found in meat (Online Ref. 6). Daily consumption is approximately 12 to 15 mg, but only 1 to 2 mg of this is ultimately absorbed.

**ESTIMATING THE IRON DEFICIT**

Conventionally, the iron deficit seen in patients with chronic disease had been estimated using Ganzoni’s formula published in 1970 (21). This equation assumes an ideal (target) hemoglobin value of 15.0 g/dl (body weight of >35 kg) or 13.0 g/dl (lower body weight). Because Ganzoni’s formula does not consider replenishment of iron stores, an extra depot dose of 500 mg is usually added, as follows:

$$\text{Iron deficit (mg)} = \left( \frac{\text{body weight (kg)}}{2} \right) \times \left( \frac{\text{target Hb} - \text{actual Hb}}{2.4 + \text{depot iron}} \right)$$

The calculated result is 1,000 mg or higher in most cases. Therefore, modern IV iron products provide guidance for dosages listed in the drug information sheet. Ferric carboxymaltose, for example, is usually administered at a dose between 1,000 and 2,000 mg to replenish iron stores; however, dosages should not exceed 1,000 mg per week, which implies that a heavy patient needs to return for a second dose in the week after the first dose.

**ORAL IRON THERAPY**

Oral iron preparations usually contain Fe$^{2+}$ (Online Ref. 7). Problems include the small amount of iron absorbed in the gut, a metallic taste, and the fact that up to 40% of patients experience side effects, most frequently gastrointestinal discomfort such as nausea, flatulence, abdominal pain, diarrhea, constipation, and black staining of the stool (Online Ref. 8). Oral iron preparations should be taken 30 to 60 mins before to meals because iron absorption is highest in the fasting state. The normal dosage is 100 to 200 mg per day. Success is usually assumed when an increase in reticulocytes or hemoglobin is observed after 1 or 3 weeks, respectively. Replenishing iron stores usually takes 2 to 6 months (Online Ref. 9).

Two clinical studies evaluated the use of oral iron preparations in patients with HF. The first study, published in 2013, was named IRON 5-(Short Term Oral Iron Supplementation in Systolic Heart Failure Patients Suffering From Iron Deficiency Anemia) HF and enrolled patients with an LVEF of <40% in NYHA functional classes II to IV who had a hemoglobin concentration between 9 and 12 g/dl, a TSAT level of >20%, and a ferritin concentration of <500 µg/l. Patients were randomized to 1 of 3 groups: 1) an oral ferrous sulfate therapy, 200 mg 3 times daily, plus IV placebo; 2) an oral placebo plus IV iron sucrose, 200 mg weekly; or 3) an oral and IV placebo. Oral iron was administered over 8 weeks and IV iron over 5 weeks. The calculated sample size was 39 per group, making it the only clinical study in HF to compare IV and oral iron supplementation. All treatments were performed in a double-blinded fashion (Online Ref. 10). Unfortunately, the trial was terminated early after prolonged recruitment and funding problems, with only 23 patients in the database.
A significant increase in the patients’ peak oxygen consumption was noted in the IV iron group after 3 months but not in the other groups (22). The mean change in the patients’ TSAT level was 10 percentage points with IV iron and 5 and 2 percentage points with oral iron and placebo, respectively. Serum ferritin increased from $167 \pm 149 \mu g/l$ to $293 \pm 270 \mu g/l$ in the IV iron group and from $115 \pm 141$ to $218 \pm 189 \mu g/l$ in the oral iron group, but only the latter change was statistically significant. These data, however, need to be interpreted with caution, as most of the nonsignificant results are probably explained by $\beta$-error.

The second trial to use oral iron therapy in HF was the IRONOUT HF (Oral Iron Repletion Effects On Oxygen Uptake in Heart Failure) trial, a phase II double-blind, randomized, placebo-controlled trial of 225 patients with HF, an LVEF of <40%, and ID defined as ferritin concentration of 15 to 100 $\mu g/l$ or ferritin 101 to 299 $\mu g/l$ with TSAT of <20% (12). Patients received oral iron polysaccharide, 150 mg twice daily over 16 weeks. The primary endpoint of the trial, a change in peak oxygen uptake from baseline to 16 weeks, was not significantly different between the 2 groups at the end of follow-up (iron: +23 ml/min vs. placebo: −2 ml/min; $p = 0.5$). Likewise, no significant change was noted for the secondary endpoints, 6-min walk test and NT-proBNP levels. A mild increase in serum ferritin (+11.3 $\mu g/l$; $p = 0.06$) and TSAT (+3.3%; $p = 0.003$) was noted with oral iron therapy (12). The authors concluded that “these results do not support use of oral iron supplementation in patients with HF with reduced ejection fraction.”

**INTRAVENOUS IRON THERAPY**

Since the beginning of ID treatment in HF, oral iron preparations were not the most promising treatment approach due to pathophysiological considerations such as the established overactivity of inflammatory mediators in HF (23). Indeed, serum levels of tumor necrosis factor (TNF) and interleukin (IL)-6 are known to be elevated in patients with HF and are independent predictors of poor survival (Online Ref. 11). In addition, the gut wall itself has been shown to display increased thickness in cases of HF (Online Ref. 11). Therefore, early intervention trials were carried out with IV iron treatment using 1 of the several different formulations available on the market. Presently, the usual route of administration is the IV route, and treatment options are iron(III) gluconate, iron(III) hydroxide sucrose, iron(III) hydroxide polymaltose complex (ferric carboxymaltose), and ferumoxytol (Online Ref. 13). A combination of the products in 1 sitting is generally not recommended. The latest additions to the portfolio, that is, iron sucrose, ferric carboxymaltose, and ferumoxytol, permit the application of higher doses of iron in 1 sitting. Most studies in patients with HF and ID have used either iron sucrose (maximum dose in 1 sitting: 200 mg) or ferric carboxymaltose (1,000 mg). Iron dextran does not play a major role anymore in clinical routine (24).

The early small studies of IV iron in HF are summarized in Table 2 and Figure 3. The first large-scale, double-blind, placebo-controlled multicenter trial of ferric carboxymaltose in patients with chronic HF was published in 2009 (Online Ref. 14). This study, the FAIR-HF (Ferinject Assessment in patients with IRon deficiency and chronic Heart Failure) trial recruited 459 patients in NYHA functional class II (LVEF ≤40%) or NYHA functional class III (LVEF ≤45%). With a hemoglobin concentration ranging between 9.5 and 13.5 g/dl, the recruitment of anemic patients was not a prerequisite. Patients had to have ID, defined as serum ferritin of <100 $\mu g/l$ or ferritin ranging from 100 to 300 $\mu g/l$, with TSAT of <20%. Patients were randomly allocated in a 2:1 fashion to receive IV ferric carboxymaltose or placebo and entered the trial in the so-called correction phase, during which their calculated iron deficit (Ganzoni’s formula) was replenished by weekly doses of 200 mg. A maintenance phase was added during which patients received 200 mg of ferric carboxymaltose per month. After 24 weeks of follow-up, 50% of patients in the ferric carboxymaltose group had improved according to the self-reported patient global assessment (PGA), the primary end point of the study, compared to 28% in the placebo group (odds ratio [OR] for being in a better rank: 2.51;
95% confidence interval [CI]: 1.75 to 3.61; \( p < 0.001 \) \( ^{(27)} \)). The PGA describes the patient’s overall well-being compared to the last assessment. Secondary endpoints included NYHA functional class, 6-min walk distance, and quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire and showed, likewise, a statistically significant improvement. These effects were seen regardless of whether anemia was present at baseline. Publication of the FAIR-HF study results yielded the first recommendation to consider IV ferric carboxymaltose in the 2012 ESC HF guidelines \( ^{15} \), which followed the 2011 update of the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand guidelines for the management of HF (grade B recommendation) \( ^{16} \).

The second large-scale trial of ferric carboxymaltose in HF, the CONFIRM-HF (ferric CarboxymaltOse evaluatiOn on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure) trial, showed results very similar to those of the FAIR-HF study. Likewise, CONFIRM-HF was a double-blind, multicenter, prospective, randomized controlled trial that enrolled ambulatory patients with symptomatic HF in NYHA functional class II or III with an LVEF of \( \leq 45\% \) and an elevated level of either NT-proBNP or B-type natriuretic peptide (BNP) \( ^{17} \). Patients received between 500 and 2,000 mg of iron or placebo within the first 6 weeks in the study. Thereafter, patients received 500 mg of ferric carboxymaltose at each visit in weeks 12, 24, and 36 if ferritin and/or TSAT still indicated ID \( ^{17} \). Randomization was performed in 1:1 fashion, and treatment duration was 52 weeks. The primary endpoint was the change in the 6-min walking distance from baseline to 24 weeks. Additional assessments were done at 6, 36, and 52 weeks, also including secondary endpoints such as PGA score and safety. At 24 weeks, patients in the ferric carboxymaltose group had a significantly greater

Iron uptake in the duodenum and iron release from cells of the reticuloendothelial system by ferroportin, whose expression is tightly regulated by the expression of the acute-phase reactant hepcidin. Adapted from von Haehling \( ^{(17)} \).

<table>
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<th>TSAT, %</th>
<th>Ferritin, ( \mu g/l )</th>
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<tr>
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<tr>
<td>Cancer and chemotherapy-associated anemia</td>
<td>Without inflammatory activity</td>
<td>&lt;20</td>
</tr>
<tr>
<td></td>
<td>With inflammatory activity</td>
<td>&lt;20</td>
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Adapted from von Haehling \( et \) al. \( ^{9} \).

HF = heart failure; ID = iron deficiency; TSAT = transferrin saturation.
improvement in their 6-min walk distances than patients taking placebo (difference: 33 ± 11 m; p = 0.002), and this effect was maintained to week 52 (28). A more recent clinical study named EFFECT-HF (Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency) (29) showed that IV administration of ferric carboxymaltose can also improve patients’ peak oxygen consumption, as measured by spiroergometry (2). A total of 174 patients were randomized, unfortunately in a nonblinded fashion, to ferric carboxymaltose therapy or standard of care (i.e., no intervention) and were followed for 24 weeks. Most patients were in NYHA functional class II at baseline. Ferric carboxymaltose significantly increased serum ferritin and transferrin saturation. At 24 weeks, peak oxygen consumption had decreased in the control group (least square means: −1.19 ± 0.389 ml/min/kg) but was maintained in the ferric carboxymaltose group (−0.16 ± 0.387 ml/min/kg; p = 0.02). This result was achieved by imputation of missing data by the last-observation-carried-forward approach. In a sensitivity analysis, in which missing data were not imputed, peak oxygen consumption at 24 weeks decreased by −0.63 ± 0.375 ml/min/kg in the control group and by −0.16 ± 0.373 ml/min/kg in the IV iron group; p = 0.23.

Two meta-analyses were published between 2016 and 2017 with regard to IV iron treatment in HF. Jankowska et al. (30) included 5 clinical studies yielding a total number of 851 patients, 509 of whom received iron sucrose or ferric carboxymaltose. IV iron therapy was found to reduce the risk of the combined endpoint of all-cause death or cardiovascular hospitalization (OR: 0.44; 95% CI: 0.30 to 0.64; p < 0.0001) and the combined endpoint of cardiovascular death or hospitalization for worsening HF (OR: 0.39; 95% CI: 0.24 to 0.63; p = 0.0001). With regard to overall well-being and quality of life, IV iron therapy resulted in a reduction in NYHA functional class (p = 0.001), an increase in the 6-min walking test distance (+31 m; 95% CI: 18 to 43; p < 0.0001), and an improvement in quality of life, using different assessment tools (all p ≤ 0.01) (30). A second meta-analysis was published in 2017, using data from 4 randomized controlled trials including 839 patients, 504 of whom had received ferric carboxymaltose (31). Patients taking ferric carboxymaltose had lower rates of recurrent cardiovascular hospitalizations and cardiovascular mortality (OR: 0.59; 95% CI: 0.40 to 0.88; p = 0.009). Treatment with ferric carboxymaltose also reduced recurrent HF hospitalizations and cardiovascular mortality (OR: 0.53; 95% CI: 0.33 to 0.86; p = 0.011) and recurrent cardiovascular hospitalizations and

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**FIGURE 3** Major Publications in the Field of Iron Deficiency and Anemia in Heart Failure

- **Ferric carboxymaltose**
- **Iron sucrose**
- **Polysaccharide iron**
- **Erythropoietin**

- **2001**
  - Szwarcberg et al.
  - Sonnenberg et al.

- **2002**
  - Sonnenberg et al.

- **2003**
  - Mantovani et al.

- **2004**
  - Nuetzelunger et al.

- **2005**
  - Tobias et al.

- **2006**
  - Tobio et al.

- **2007**
  - Schmiedt et al.

- **2008**
  - FERRIC-HF (Ferric Carboxymaltose in Heart Failure)

- **2009**
  - EFFECT-HF (Effect of Ferric Carboxymaltose on Exercise Capacity in Patients with Chronic Heart Failure and Iron Deficiency)

- **2010**
  - CONVINCI-HF (Conference on the Use of Intravenous Iron in Chronic Heart Failure)

- **2011**
  - IRON-HF (Iron Sucrose in Heart Failure)

- **2012**
  - IRONOUT-HF (Iron Outcomes in Heart Failure)

- **2013**
  - Kato et al.

- **2014**
  - Kato et al.

- **2015**
  - Kato et al.

- **2016**
  - Two meta-analyses were published between 2016 and 2017 with regard to IV iron treatment in HF. Jankowska et al. (30) included 5 clinical studies yielding a total number of 851 patients, 509 of whom received iron sucrose or ferric carboxymaltose. IV iron therapy was found to reduce the risk of the combined endpoint of all-cause death or cardiovascular hospitalization (OR: 0.44; 95% CI: 0.30 to 0.64; p < 0.0001) and the combined endpoint of cardiovascular death or hospitalization for worsening HF (OR: 0.39; 95% CI: 0.24 to 0.63; p = 0.0001). With regard to overall well-being and quality of life, IV iron therapy resulted in a reduction in NYHA functional class (p = 0.001), an increase in the 6-min walking test distance (+31 m; 95% CI: 18 to 43; p < 0.0001), and an improvement in quality of life, using different assessment tools (all p ≤ 0.01) (30). A second meta-analysis was published in 2017, using data from 4 randomized controlled trials including 839 patients, 504 of whom had received ferric carboxymaltose (31). Patients taking ferric carboxymaltose had lower rates of recurrent cardiovascular hospitalizations and cardiovascular mortality (OR: 0.59; 95% CI: 0.40 to 0.88; p = 0.009). Treatment with ferric carboxymaltose also reduced recurrent HF hospitalizations and cardiovascular mortality (OR: 0.53; 95% CI: 0.33 to 0.86; p = 0.011) and recurrent cardiovascular hospitalizations and

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von Haehling et al.  
Iron Deficiency in Heart Failure
ID in HF with reduced ejection fraction has received increasing attention over the last 18 years. The prevalence of ID reaches 50% among ambulatory patients with HF, and ID is an independent predictor of reduced exercise capacity, quality of life, and survival. Risk factors include female sex, more advanced stage of HF, higher levels of NT-proBNP, and higher serum levels of C-reactive protein. Relevant cutoff values are ferritin of <100 µg/l or ferritin 100 to 300 µg/l when TSAT is <20%. It has been convincingly shown that IV iron application leads to improvements in quality of life, physical well-being, and exercise capacity. Most studies, particularly those of relevant size, have been conducted with ferric carboxymaltose and have good overall safety profiles. Data from 2 meta-analyses suggest beneficial effects in terms of reduced hospitalization rates for HF and cardiovascular mortality. A large-scale prospective morbidity and mortality trial is underway. The situation in HF with preserved ejection fraction (HFpEF) is less clear, and another prospective trial, the FAIR-HFpEF trial commenced recruitment late in November 2017. Likewise, uncertainty remains with regard to the

CONCLUSIONS AND OUTLOOK

Since 2012, the ESC guidelines have recommended that all patients with HF should undergo testing for ID by using serum assessment of ferritin and TSAT (Online Ref. 17). Anemia should be ruled out by using full blood count assessment, both are Class I, Level of Evidence: C recommendations. This point has not been changed in the 2016 version of the guidelines (8), in which the treatment recommendation had been updated after the publication of the CONFIRM-HF trial to Class IIa, Level of Evidence: A. The statement reads, “IV ferric carboxymaltose should be considered in symptomatic patients (serum ferritin <100 µg/l, or ferritin between 100 to 299 µg/l and TSAT <20%) in order to alleviate HF symptoms and improve exercise capacity and quality of life” (8). The Central Illustration shows the diagnostic algorithm for the treatment of iron deficiency in patients with HF as recommended by current ESC guidelines (32). The joint guidelines of the American Heart Association and American College of Cardiology published in 2013 were less enthusiastic (33); however, the 2017 update now states that “in patients with NYHA functional class II and III HF and iron deficiency (ferritin <100 µg/l or 100 to 300 µg/l if TSAT is <20%), IV iron replacement might be reasonable to improve functional status and quality of life giving this recommendation a IIb level of evidence” (34). The European guidelines currently advocate only the use of ferric carboxymaltose, because large-scale trials have been undertaken, and the drug’s safety has been demonstrated in the HF population only with this drug. The U.S. guidelines do not mention a specific type of iron but rather mention IV iron administration. Previous smaller trials have also used other iron preparations, particularly iron sucrose, but large-scale trials that could have been considered by the guideline committees are still missing. Therefore, it remains unclear if these are able to achieve similar results.

TREATMENT OF IRON DEFICIENCY IN HF GUIDELINES

Adapted with permission from Doehner et al. (32). *If anemia is significant, initiate an evaluation. **Re-evaluate iron status after 3 to 6 months.

ideal time point of IV application after cardiac decompensation. The AFFIRM-AHF (Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency) trial, a randomized, double-blind placebo-controlled trial comparing the effect of IV ferric carboxymaltose in patients with ID who are hospitalized for acute HF, is aimed at elucidating effects on hospitalization rates and mortality in this population. Table 2 highlights published and currently ongoing studies with relevance to ID in HF.

For the time being, it appears sensible to test all symptomatic patients with HF with reduced ejection fraction for the presence of ID. A full blood count needs to be performed as well. When ID is diagnosed, IV ferric carboxymaltose can be administered as a bolus injection or as an infusion over 15 mins. The label permits the use of ferric carboxymaltose up to a hemoglobin concentration of 15 g/dl. A single dosage cannot exceed 1,000 mg per week; dilutions can be made in 0.9% sodium chloride. A typical response is a sharp increase in the patient’s ferritin level following the infusion, which can easily exceed 500 µg/l and will decline only very slowly over several weeks to months. Reassessment of iron status is useful after approximately 3 to 6 months. However, whether this time frame is optimal has not been prospectively tested, and it remains unclear if 1,000 mg or higher doses are optimal for all patients.

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KEY WORDS ferric carboxymaltose, heart failure, iron deficiency, treatment

APPENDIX For supplemental references, please see the online version of this paper.