





# Iron deficiency in heart failure

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## Abstract

Iron deficiency is a major heart failure co-morbidity present in about 50% of patients with stable heart failure irrespective of the left ventricular function. Along with compromise of daily activities, it also increases patient morbidity and mortality, which is independent of anaemia. Several trials have established parenteral iron supplementation as an important complimentary therapy to improve patient well-being and physical performance. Intravenous iron preparations, in the first-line ferric carboxymaltose, demonstrated in previous clinical trials superior clinical effect in comparison with oral iron preparations, improving New York Heart Association functional class, 6 min walk test distance, peak oxygen consumption, and quality of life in patients with chronic heart failure. Beneficial effect of iron deficiency treatment on morbidity and mortality of heart failure patients is waiting for conformation in ongoing trials. Although the current guidelines for treatment of chronic and acute heart failure acknowledge importance of iron deficiency correction and recommend intravenous iron supplementation for its treatment, iron deficiency remains frequently undertreated and insufficiently diagnosed in setting of the chronic heart failure. This paper highlights the current state of the art in the pathophysiology of iron deficiency, associations with heart failure trajectory and outcome, and an overview of current guideline-suggested treatment options.

**Keywords** Iron deficiency; Heart failure; Ferric carboxymaltose; Quality of life; Exercise capacity

Received: 19 October 2020; Revised: 20 January 2021; Accepted: 4 February 2021

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## Epidemiology

Iron deficiency (ID) is one of the most common nutritional deficiencies worldwide, affecting approximately one-third of the general population.<sup>1</sup> Reaching a prevalence of 30–50% in patients with stable chronic heart failure (HF), ID is recognized as major cause of anaemia in these patients, regardless of sex, race, and left ventricular ejection function.<sup>2–4</sup> At the same time, more than 40% of the patients with chronic HF without anaemia or abnormalities in haematological indices exhibit laboratory abnormalities of depleted iron stores.<sup>5</sup> Furthermore, ID in acute decompensated HF can be detected in up to 80% of evaluated patients, which further underlines the importance of research efforts towards understanding of aetiology of ID in HF.<sup>6–8</sup>

Heart failure, as a chronic disabling syndrome, represents a leading cause of frequent hospitalizations and high health costs worldwide.<sup>9</sup> A myriad of co-morbidities complicate the natural course of HF and exhibit deleterious impact on disease progression. Intuitively, these co-morbidities also constitute targets for potential intervention to improve quality of life and patient outcome. As such, ID gained substantial importance as a part of comprehensive medical treatment of HF in past years. Remarkably, ID seems to have greater clinical repercussions on HF trajectory than anaemia *per se*, and the causal associations with worsened exercise capacity, oxygen consumption, hospitalization, and mortality are stronger for ID compared with anaemia in HF patients.<sup>10,11</sup>

## Pathophysiology of iron deficiency

Iron is an essential trace element, involved in plethora of crucial biochemical pathways and important for tissue metabolism.<sup>12,13</sup> In the human body, iron exists in the ferrous intracellular form ( $\text{Fe}^{2+}$ ) and in the ferric form ( $\text{Fe}^{3+}$ ), which is mainly extracellular and circulating.<sup>14,15</sup> The most prominent role of iron is in oxygen homeostasis, including oxygen transport and storage, oxidative metabolism in skeletal and cardiac muscle, mitochondrial function and metabolism of proteins, lipids, and ribonucleic acids.<sup>16–18</sup> As a cofactor for enzymes or an element of proteins with distinct cellular functions, iron is key factor in the maintenance of cellular energy and metabolism of extra-haematopoietic tissues.<sup>19</sup>

The main consequence of ID in HF is impaired erythropoiesis, while erythroblasts and reticulocytes are major iron consumers in human body.<sup>20,21</sup> Generally, cells with a high mitogenic potential (neoplastic and immune) are particularly sensitive to reduced iron supplies or dysregulated iron utilization.<sup>22</sup> Cardiac myocytes as tissue with high energy demand are especially sensitive to limited iron utilization and decreased iron supplies, which has potential impact on HF pathophysiology.<sup>23</sup>

Skeletal muscle functioning is also affected by ID, mainly in the context of impaired energetic metabolism through switch from oxidative metabolism to glycolysis, as well as through alterations in both carbohydrate and fat catabolic processing.<sup>24</sup> ID leads to ultra-structural alterations in skeletal muscle, as well. Histological examination of skeletal muscle in patients with HF reveals changes in fibre composition with an increased contribution of fast glycolytic fibres.<sup>25</sup> At the cellular level, decreased total number/volume of mitochondria, diminished mitochondrial volume density, and reduction of mitochondrial cristae surface density represent hallmark of rearrangement of myocyte energy centres induced through ID, where intravenous iron substitution restores muscle energetic and mitochondrial function.<sup>26</sup> In men with HF with reduced ejection fraction, low ferritin reflecting depleted iron stores is associated with inspiratory muscle weakness.<sup>27</sup>

Average iron intake is 10–20 mg/day.<sup>28</sup> The iron homeostasis is exclusively regulated through iron absorption by the apical surface of enterocytes in the duodenum and the upper jejunum, because no means of iron excretion exists. Normally, only ~15% of dietary iron is absorbed.<sup>29</sup> Dietary iron is found in two distinct different molecular forms, inorganic (non-haem) and organic (haem). Inorganic dietary iron is absorbed via the divalent metal transporter 1 on the surface of enterocytes, where in next step membrane ferrioreductases reduce ferric to ferrous iron. On the other hand, for hem iron, there is specific haem carrier protein, associated with inducible hemoxygenase 1, which reduces iron before entering the cytosol. Intracellular iron is secreted to the circulation using ferroportin 1 after membrane enzyme hephaestin

oxidizes iron to ferric form, which is in the circulation transported bound to transferrin.<sup>30,31</sup>

There are in general two different iron transport pathways with inherent regulatory mechanisms. First embrace transport from site of absorption to different tissues (systemic iron metabolism), and second intracellular iron transport, is responsible for transport between organelles within the cell.<sup>32</sup>

Systemic iron metabolism is predominantly regulated by hormone hepcidin and ferroportin, the only iron export protein known in mammals.<sup>33</sup> Hepcidin, a small peptide hormone synthesized mainly by hepatocytes, interacts with ferroportin on target cells in negative feedback fashion, causing (i) reduced expression of proteins involved in transmembrane iron import to enterocytes and (ii) internalization of ferroportin.<sup>34</sup> Hence, hepcidin blocks intestinal absorption of iron and diverts iron from the circulation, trapping it in enterocytes, hepatocytes, and macrophages.<sup>33</sup> Decreased intestinal iron absorption together with its accumulation in the reticuloendothelial stores reduces the availability of iron to target tissues (*Figure 1*). Major stimuli decreasing hepcidin expression in the liver and its release into the circulation are depleted iron stores, hypoxia, and ineffective erythropoiesis, whereas inflammation produces the opposite effect.<sup>35</sup> Conversely, Ganz *et al.* showed that even a mild transient increase in the serum iron is sufficient to dramatically rise hepcidin level, blocking iron absorption and release in extracellular compartment and circulation.<sup>36</sup>

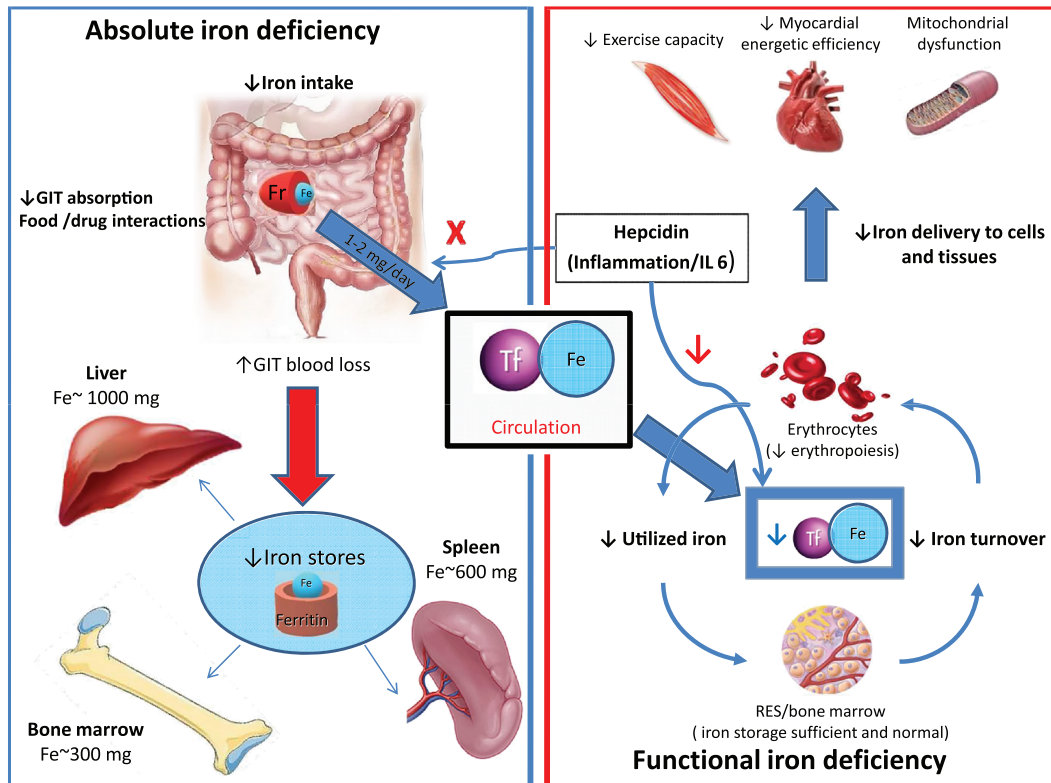
Because HF is characterized through high circulatory levels of inflammatory cytokines, it was initially postulated that, similar to chronic inflammatory states, HF patients have elevated levels of serum hepcidin.<sup>37,38</sup> However, recent studies in chronic as well as acute HF showed that hepcidin levels are actually decreased in HF.<sup>39,40</sup> Accordingly, initial premise that ID in HF is induced through limited circulatory iron availability due to metabolic mechanisms triggered by chronic inflammation is replaced with hypothesis that actually depleted iron stores are responsible for ID in HF.<sup>33</sup>

## Classification and diagnosis of iron deficiency in heart failure

For clinical and didactical purposes, two different types of ID are distinguished: absolute and functional (*Figure 1*).<sup>41</sup> Absolute ID is characterized through depleted iron stores, although iron transport, regulatory mechanisms, and erythropoiesis are undisturbed.<sup>42</sup> Contrary, functional ID represents a mismatch between iron demand and tissue supply, mostly due to iron utilization and iron maldistribution.<sup>43</sup>

Although mechanisms underlying the development of ID in HF have not been rigorously investigated, generally ID arises as a consequence of impaired iron absorption, augmented gastrointestinal loss, and reduced availability of utilizable iron

**Figure 1** Basic physiological principles involved in iron absorption, transport and storage, as well as pathophysiological cascades responsible for absolute and functional iron deficiency. Fe, iron; Fr, ferroportin; GIT, gastrointestinal; RES, reticuloendothelial system; Tf, transferrin.



from the reticuloendothelial system.<sup>44</sup> In setting of HF, disease-specific pathophysiological consequences (intestinal oedema, insufficient dietary intake, drug interactions due to polypharmacy, and polymorbidity) further perpetuate depletion of iron storages.<sup>45,46</sup>

In order to optimize the detection and classification of ID, as well as to ensure optimal and timely management of carefully selected candidates for iron replenishment, development of diagnostic algorithms advanced significantly over the last 10 years (Figure 2).<sup>47</sup> Albeit considered as a gold standard, due to its invasiveness and potential harmful side effects, a bone marrow biopsy for evaluating iron stores is replaced in clinical practice by the measurement of several blood biomarkers.<sup>48</sup>

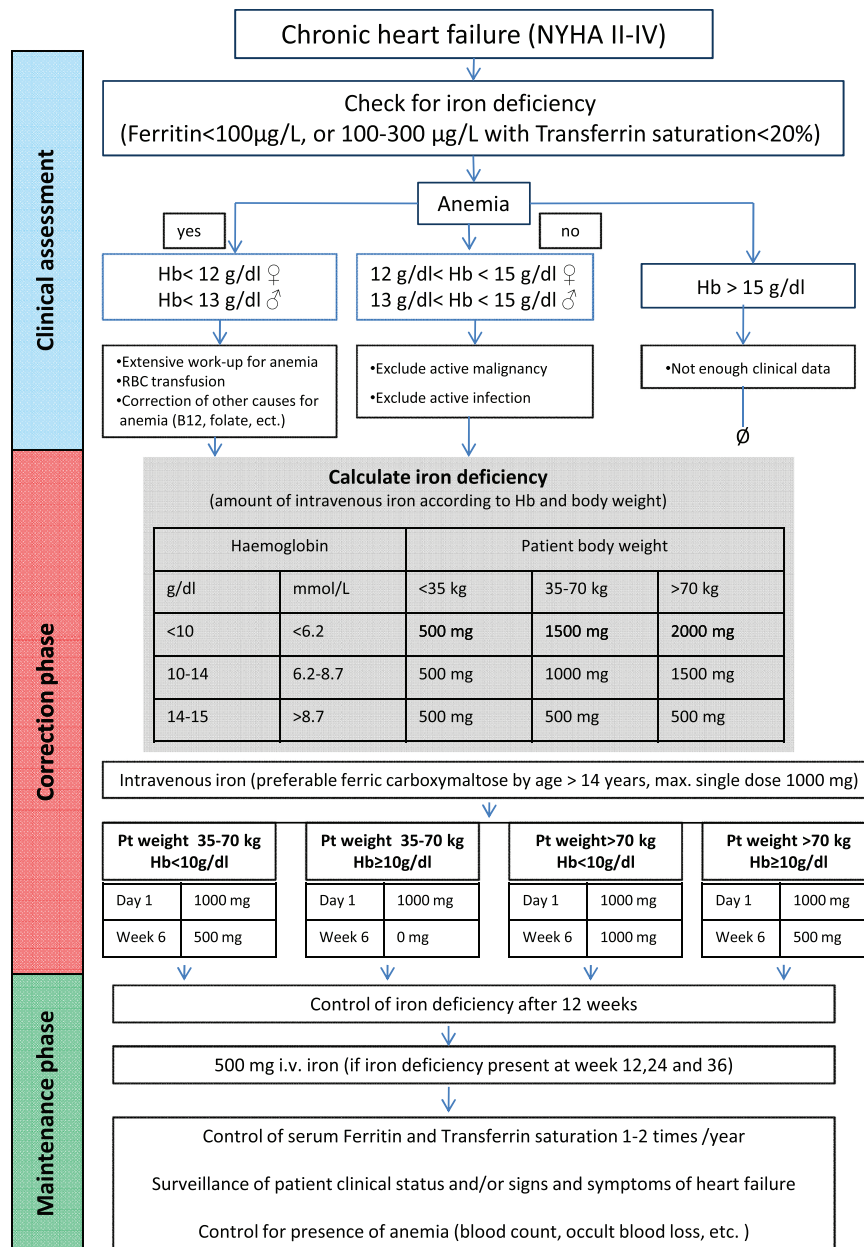
As such, ferritin is one of the most commonly used laboratory measures of iron status worldwide.<sup>49</sup> There is a linear relationship between serum ferritin and ferritin expression in iron storage tissues, what enables usage of serum ferritin as surrogate marker of stored iron quantity and means that low circulating ferritin reflects depleted body iron stores.<sup>50</sup> However, serum ferritin levels are subjected to increase in chronic and inflammatory diseases, such as HF and chronic kidney disease. It is way cut-off values for the diagnosis of ID in HF are arbitrarily set at a higher level (e.g. 100 mg/L).<sup>51</sup> It is worth mentioning that previous studies did not establish

strong correlation between bone marrow iron and blood parameters of ID in HF. Nanas *et al.* found in 27 from 37 evaluated patients, hospitalized for decompensated HF, signs of ID in bone marrow biopsy despite normal levels of ferritin and erythropoietin in the serum.<sup>52</sup>

Transferrin saturation (TSAT), representing the per cent of transferrin that has iron bound to it, is used as a marker of the availability of circulating iron to supply metabolizing cells.<sup>43</sup> Definition of ID solely based on TSAT < 20% in 42 patients with HF and a reduced left ventricular ejection fraction (LVEF ≤ 45%) undergoing median sternotomy for coronary artery bypass grafting showed compared with iron quantification in bone marrow aspirate a sensitivity of 94% and a specificity of 84%.<sup>53</sup> In HF, absolute ID is typically diagnosed with cut-off ferritin values < 100 mg/L and, distinguished from functional ID, diagnosed with normal serum ferritin (100–300 mg/L) and low TSAT (< 20%).<sup>48</sup>

Newly, soluble transferrin receptor (sTfR) and hepcidin were proposed as novel serum markers for ID in HF. The sTfR indicates reduced intracellular iron availability for metabolic needs and is a reliable diagnostic tool for confirmation of ID anaemia.<sup>54</sup> Importantly, the effect of chronic inflammation on circulating sTfR is minor, making sTfR a promising candidate for ID detection in chronic inflammatory states.<sup>55</sup> Jankowska *et al.* postulated a novel definition of ID based on

**Figure 2** Proposed algorithm for the management of iron deficiency in heart failure. Algorithm adapted from McDonagh *et al.*<sup>47</sup> Hb, haemoglobin; i.v., intravenous; NYHA, New York Heart Association Functional Classification; Pt, patient.



the combined measurement of low circulation hepcidin (<14.5 ng/mL, the fifth percentile in healthy peers) and high circulation sTfR (≥1.59 mg/L, the 95th percentile in healthy peers). In multivariable analysis, this definition was strongly predictive of all-cause mortality at 12 months.<sup>39</sup> Nevertheless, due to difficult and non-standardized assessment of its circulating levels, hepcidin is currently used exclusively in research settings and mandates additional effort in overcoming specific methodological difficulties prior to its implementation in clinical routine.

Of note, mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration have been found to be unreliable markers of ID status. Therefore, measuring these levels is not recommended for assessment of ID in patients with HF.<sup>56</sup> At the same time, serum transferrin alone does not represent iron storage or functional ID and should not be used in diagnostic work-up in HF patients.

Serum iron levels ≤13 µmol/L showed an excellent diagnostic accuracy of 91% for ID compared with bone marrow biopsy.<sup>53</sup> However, as iron serum levels exhibit circadian

variations, it cannot be used as reliable diagnostic tool for assessment of ID.

Since the 1970s, the iron deficit in chronically ill patients was calculated using Ganzoni's formula [iron deficit = body weight  $\times$  2.4  $\times$  (15 – haemoglobin in g/dL) + 500 mg], assuming that ideal haemoglobin concentration amounts 15.0 g/dL (or 13.0 g/dL by body weight <35 kg) and that additional 500 mg of iron is needed for replenishment of iron stores, Ganzoni's formula usually calculates iron deficit at 1000 mg or higher and was used for determination of iron deficit in the majority of randomized trials.<sup>57,58</sup>

Important place in diagnostic work-up of iron deficiency should be given to exclusion of treatable and reversible causes of iron depletion in HF patients. It is important to mention that depleted iron stores could be also a sign of undiagnosed malignancies, consequence of treatment with anticoagulants, or recurrent gastrointestinal bleedings.<sup>59</sup> It is why even decent lowering of haemoglobin values with concomitant laboratory signs of iron deficiency should trigger thorough medical evaluation of HF patients.

## Oral iron therapy

*Table 1* summarizes randomized clinical trials on ID in HF. Because of wide availability and low costs, oral iron replacement was considered as a promising strategy in ID management. Unfortunately, poor adherence, plethora of gastrointestinal side effects, and low intestinal absorption of iron additionally challenged investigation of feasibility of oral iron supplementation. Additionally, oral iron absorption test, which should evaluate plausibility and applicability of oral iron supplementation, identifying patients who are suitable for oral iron administration, finds rarely its place in clinical routine. Accordingly, so far, only two clinical randomized trials using oral iron preparation were conducted in patients with chronic HF.<sup>61,64,68–70</sup>

In IRON-HF study, suitable patients (LVEF < 40%, NYHA Class II–IV, haemoglobin 9–12 g/dL, TSAT < 20%, and ferritin <500  $\mu$ g/L) were randomized in a double-blind fashion to ferrous sulfate per os or intravenous therapy with iron sucrose combined with placebo.<sup>50</sup> The oral treatment arm of the study encompassed only seven patients, where 10 patients were assigned to intravenous iron supplementation. Three months after treatment, intravenous unlike oral iron therapy led to higher peak oxygen consumption. Compared with oral iron treatment group, intravenous supplementation resulted in numerically higher TSAT and ferritin increase. Although results and design of IRON-HF study were an important step in research efforts towards better understanding of ID, because of highly limited number of patients (in total 23 patients included in the study), conclusions derived from this study should be interpreted with caution.

In the second trial (IRONOUT HF—Oral Iron Repletion Effects On Oxygen Uptake in Heart Failure), patients underwent treatment with oral iron polysaccharide, 150 mg twice daily over 16 weeks, in a double-blind, randomized, placebo-controlled fashion. The primary endpoint was a change in peak oxygen uptake from baseline to 16 weeks. Secondary endpoints included changes in 6 min walk distance, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, and health status measured through Kansas City Cardiomyopathy Questionnaire. Oral iron therapy did not significantly improve any of the study endpoints and minimally influenced iron storages, implicating that route of administration, more than the dose regimen or treatment strategy, is essential for clinical benefit.<sup>65</sup>

In conclusion, available evidence does not justify oral iron supplementation for ID in patients with chronic HF and due to unnecessary polypharmacy and possible side effects should be avoided.

## Intravenous iron therapy

Over the past 20 years, we witnessed enormous development of parenteral iron preparations.<sup>71,72</sup> Currently, there are five different formulations available in the USA and Europe, suitable for intravenous iron supplementation (*Table 2*). All studies in patients with chronic HF have used either iron sucrose or ferric carboxymaltose (*Figure 3*). Intravenous iron proved to be safe in patients with HF and allows rapid correction of iron indices, particularly in instances in which intestinal absorption is compromised. The usually described side effects of intravenous iron therapy (such as hypotension, electrolyte imbalance, skin reactions, and musculoskeletal side effects) did not represent safety concern in published trials.<sup>62,73,74</sup>

FAIR-HF (Ferinject Assessment in patients with IRon deficiency and chronic Heart Failure) was the first large multicentre trial of treatment with ferric carboxymaltose in patients with chronic HF. Patients with NYHA Class II and LVEF  $\leq$  40% or NYHA Class III and LVEF  $\leq$  45 were randomized in a 2:1 fashion to receive intravenous ferric carboxymaltose or placebo. Iron deficit was defined as serum ferritin of <100 mg/L or ferritin ranging from 100 to 300 mg/L, with TSAT of <20%. The presence of anaemia was not relevant for study inclusion, so that patients with haemoglobin concentration varying from 9.5 to 13.5 g/dL were eligible for study participation. Intravenous supplementation was conducted in two phases: first, correction phase with weekly intravenous administration of 200 mg of ferric carboxymaltose, followed with maintenance phase and monthly administration of 200 mg intravenous iron formulation according to individually calculated iron deficit. At follow-up after 24 months, patients in the ferric carboxymaltose group reported improved self-reported patient global assessment, NYHA functional

**Table 1** Summary of studies evaluating iron supplementation in patients with heart failure

Author	Study design	Sample size	Inclusion criteria	Iron deficiency/Hb	Iron supplementation	Duration	Primary endpoint	Major results in intervention arm
Silverberg <i>et al.</i> <sup>60</sup>	Single-centre, uncontrolled, and open-label	26	LVEF < 35% and NYHA class >III	Hb < 12 g/dL	Erythropoietin Iron sucrose i.v.	15–60 weeks	Respective/observational: no primary endpoint Peak VO <sub>2</sub> (from baseline to Week 16)	NYHA class ↓, LVEF ↑, diuretic dose ↓, and hospitalization ↓ No change in peak VO <sub>2</sub>
Lewis <i>et al.</i> <sup>61</sup> (IRONOUT HF)	1:1 randomized and double-blind	225	NYHA class II–IV and LVEF ≤ 40%	Ferritin < 100 ng/mL or serum ferritin 100–299 ng/mL with TSAT < 20% TSAT < 20%, ferritin < 100 µg/mL, and Hb < 12.5 g/dL	150 mg iron polysaccharide 2 x a day p.o.	16 weeks	NT-proBNP; inflammatory status ↓	QoL ↑, NYHA class ↓, and hospitalization rate ↓
Toblli <i>et al.</i> <sup>62</sup>	1:1 randomized, double-blind, and placebo-controlled	40	NYHA class II–IV and LVEF < 35%	Ferritin < 100 µg/mL or serum ferritin < 100 µg/mL, and Hb < 12.5 g/dL	Iron sucrose 200 mg weekly for 5 weeks	25 weeks	Self-reported PGA; NYHA class from baseline to Week 24	PGA ↑, NYHA class ↓, and 6MWD ↑
Anker <i>et al.</i> <sup>63</sup> (FAIR-HF)	2:1 randomized, double-blind, and placebo-controlled	459	NYHA class II and LVEF < 40%; NYHA Class III and LVEF < 45%	100–299 µg/mL with TSAT < 20% and Hb 9.5–13.5 g/dL	200 mg ferric carboxymaltose until ferritin < 500 µg/L, then 200 mg monthly	24 weeks	Peak VO <sub>2</sub> from baseline to Week 12	Peak VO <sub>2</sub> —no significant ↑ in the i.v. iron group, ferritin ↑, and TSAT ↑ (in treated groups)
Beck-da-Silva <i>et al.</i> <sup>64</sup> (IRON-HF)	1:1:1 randomized, double-blind, and placebo-controlled	23	NYHA class II and LVEF < 40%	Ferritin 500 µg/mL with TSAT < 20% and Hb 9–12 g/dL	200 mg ferrous sulfate p.o. for 8 weeks 200 mg/week iron sucrose i.v.	5–22 weeks	Change in 6MWD from baseline to Week 24	Peak VO <sub>2</sub> ↑ (with imputation of deaths), NYHA class ↓, and PGA ↑
Ponikowski <i>et al.</i> <sup>65</sup> (CONFIRM-HF)	1:1 randomized, double-blind, and placebo-controlled	304	NYHA class II–III and LVEF < 40%, BNP > 100 pg/mL, and NT-pro-BNP > 400 pg/mL	Ferritin < 100 ng/mL or serum ferritin 100–299 ng/mL with TSAT < 20% and Hb < 15 g/dL	500–2000 mg ferric carboxymaltose at baseline and Week 6, then by persistent ID every 12 weeks	52 weeks	Change in peak VO <sub>2</sub> from baseline to Week 24	Peak VO <sub>2</sub> ↑ (with imputation of deaths), NYHA class ↓, and PGA ↑
Van Veldhuisen <i>et al.</i> <sup>66</sup> (EFFECT-HF)	1:1 randomized, double-blind, and placebo-controlled	174	NYHA class II–III LVEF < 40%, BNP > 100 pg/mL, and NT-pro-BNP > 400 pg/mL	Ferritin < 100 ng/mL or serum ferritin 100–299 ng/mL with TSAT < 20% and Hb < 15 g/dL Peak VO <sub>2</sub> 10–20 mL/kg/min	500 mg ferric carboxymaltose at baseline, 6 weeks, and 12 weeks if ID persistent	24 weeks	Change in peak VO <sub>2</sub> from baseline to Week 24	Peak VO <sub>2</sub> ↑ (with imputation of deaths), NYHA class ↓, and PGA ↑

(Continues)

Table 1 (continued)

Author	Study design	Sample size	Inclusion criteria	Iron deficiency/Hb	Iron supplementation	Duration	Primary endpoint	Major results in intervention arm
Jankowska <i>et al.</i> <sup>67</sup>	Meta-analysis	509	NYHA class II–III LVEF < 45%	Ferritin < 100 ng/mL or serum ferritin 100–299 ng/mL with TSAT < 20% and Hb < 13 g/dL	Total iron dose: 1000–2000 mg i.v. (3 trials) iron sucrose and 2 trials ferric carboxymaltose)	5–36 weeks	All-cause/cardiовascular death, cardiovascular hospitalization, NYHA class ↓, quality of life (EQ-5D, KCCQ, MLHFQ, and PGA), NYHA class, 6MWD, and LVEF	All-cause death ↓, cardiovascular death and hospitalization ↓, NYHA class ↓, 6MWD ↑, and EQ-5D, KCCQ, MLHFQ, and PGA ↑

6MWD, 6 min walk distance; BNP, brain natriuretic peptide; EQ-5D, European Quality of Life-5 Dimensions Questionnaire; ID, iron deficiency; Hb, haemoglobin; i.v., intravenous; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA class, New York Heart Association Functional Classification; p.o., per os; peak VO<sub>2</sub>, peak oxygen consumption; PGA, patient global assessment; QoL, quality of life; TSAT, transferrin saturation.  
This table summarizes clinical trials of ID correction in chronic heart failure.

class, 6 min walk distance, and quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire.<sup>63</sup> Furthermore, the substudy of FAIR-HF trial showed that intravenous ferric carboxymaltose was associated with early reductions in calculated plasma volume status and weight, implying that decongestion might be one mechanism via which iron repletion aids chronic HF patients.<sup>75</sup>

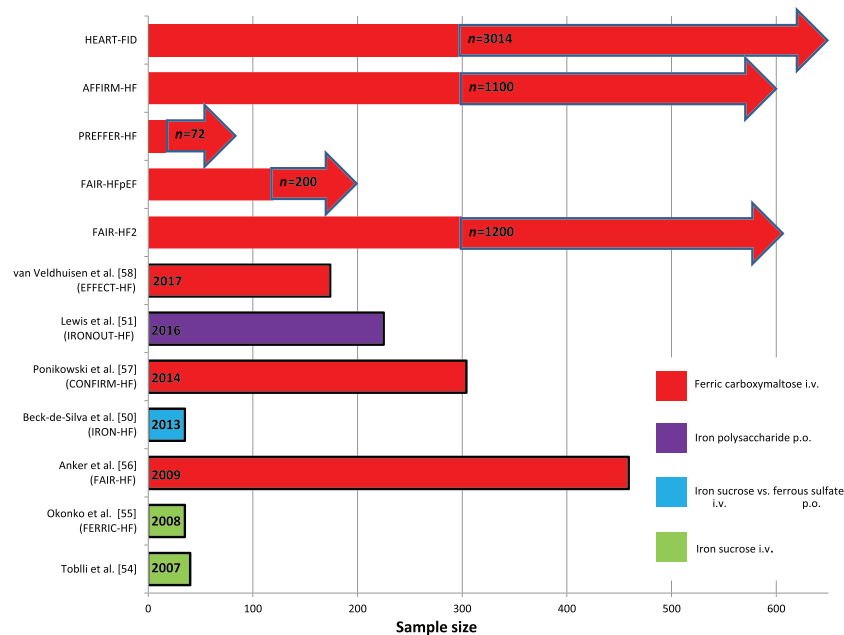
Importance of iron treatment in setting of chronic HF with reduced LVEF found further affirmation in results of CONFIRM-HF trial. In comparison with FAIR-HF, in the CONFIRM-HF trial, 6 min walk distance, as a more robust and objective method in assessment of the clinical status of HF patients, was used as primary endpoint over longer period of follow-up from 52 weeks. Of note, the study protocol offered simplified dosing regimen for ferric carboxymaltose proposed by Evstatiev *et al.*<sup>76</sup> based on weight and haemoglobin levels, easily applicable in clinical routine compared with the traditional used Ganzoni formula. Patients with symptomatic HF (NYHA Class II or III, LVEF of ≤45%, and elevated level of either NT-proBNP or BNP) were randomized in 1:1 manner to receive between 500 and 2000 mg of ferric carboxymaltose or placebo within the first 6 months following treatment with ferric carboxymaltose by persistent ID according to ferritin or TSAT at visits at 12, 24, and 36 weeks. Intravenous iron therapy with ferric carboxymaltose in patients with symptomatic HF and ID resulted in sustainable improvement in 6 min walk distance at follow-up after 24 months.<sup>65</sup> One of the possible mechanisms, by which iron substitution induces improvement of cardiopulmonary exercise, could be its effect on cardiac remodelling.<sup>77</sup> Lacour *et al.* proved negative predictive value of iron deficiency on reverse cardiac remodelling after CRT therapy in patients with symptomatic HF and reduced LVEF.<sup>78</sup> Furthermore, Núñez *et al.* found that replenishment of iron myocardial amount in patients with chronic symptomatic HF with reduced ejection fraction (NYHA II–III) is strongly correlated with increase of LVEF at follow-up.<sup>79</sup>

Improvement of exercise capacity of HF patients under intravenous iron supplementation was additionally confirmed through results of EFFECT-HF study. In this open-label prospective study, a total of 174 patients were randomized to intravenous ferric carboxymaltose or no intervention. After 24 months, ferric carboxymaltose significantly increased serum ferritin and TSAT. Additionally, treatment with intravenous iron prevented decline in peak oxygen consumption, which was observed in non-treated control group (−0.16 ± 0.375 vs. −0.63 ± 0.375 mL/min/kg; *P* = 0.23).<sup>66</sup>

Current body of knowledge points out that ID can be frequently encountered in patients with acute decompensated HF. In the substudy of BIostat-CHF trial, which included patients either hospitalized for HF or presenting with worsening HF in the outpatient setting (LVEF ≤ 40% or, alternatively, BNP or NT-proBNP levels of >400 or >2000 ng/L, respectively), ID

**Table 2** Most important clinical features and side effects of available intravenous iron preparations

Iron preparation	Brand name	Maximal single dose (mg)	Plasma half-life (h)	Side effects	Tested in heart failure
Sodium ferric gluconate	Ferrlicit <sup>®</sup>	125	1	Hypersensitivity, nausea, hypotension, cramps, hypertension, dizziness, and chest pain	No
Ferric carboxymaltose	Ferinject <sup>®</sup> / Injectafer <sup>®</sup>	15 mg/kg (max 1000 mg in one infusion)	16	Hypersensitivity, hypertension, nausea, flushing, hypophosphatemia, and dizziness	Yes <sup>56–58</sup>
Iron sucrose	Venofer <sup>®</sup>	200–300	6	Hypersensitivity, hypotension, iron overload, diarrhoea, nausea, vomiting, headache, dizziness, hypotension, pruritus, and leg/back cramps	Yes <sup>50,54,55,65</sup>
Iron dextran	Dexferrum <sup>®</sup>	20 mg/kg	60	Fatal and serious hypersensitivity–anaphylaxis, diarrhoea, nausea, vomiting, headache, and dizziness	No
Ferumoxytol	FeraHeme <sup>®</sup>	510	15	Fatal and serious hypersensitivity–anaphylaxis, diarrhoea, nausea, dizziness, hypotension, and constipation	No

**Figure 3** Overview of major publications and ongoing trials evaluating effects of treatment of iron deficiency in chronic heart failure. Ongoing trials are marked with an arrow. i.v., intravenous; p.o., per os.

was identified in 61.6% of patients, with highest prevalence in female (71.1% vs. 58.3%;  $P < 0.001$ ). The presence of ID was significantly associated with lower estimated protein intake, chronic kidney disease, lower haemoglobin, higher C-reactive protein levels, lower serum albumin levels, and P2Y12 inhibitor use (all  $P < 0.05$ ), representing independent predictors of worse outcome in multivariable Cox proportional hazard regression analyses. These results imply that the aetiology of ID in worsening HF is complex and multifactorial and seems to consist of a combination of reduced iron uptake (malnutrition and fluid overload), impaired iron storage (inflammation and chronic kidney disease), and iron loss (anti-platelets).<sup>80</sup>

Upcoming results from AFFIRM-AHF trial (ClinicalTrials.gov identifier: NCT02937454) will provide valuable insights concerning disease-modifying potential of intravenous iron replenishment in patients hospitalized primary due to acute decompensated HF. In total, 1100 patients with NYHA II–III, LVEF  $< 50\%$ , and clinical signs of volume overload or lung congestion have been enrolled in the study from April 2017 to 31 July 2019 and assigned to be treated with either 500–1500 mg of ferric carboxymaltose or placebo. The primary outcome of Affirm-AHF trial presents the composite of recurrent HF hospitalizations and cardiovascular mortality. The main secondary outcomes include the composite of recurrent cardiovascular hospitalizations and cardiovascular



mortality, recurrent HF hospitalizations, and safety-related outcomes.<sup>81</sup> Each individual patient will be followed over a period of 52 weeks, so that first results are expected in 2021.

Heart failure with preserved ejection fraction (HFpEF) is increasingly the predominant form of HF in the developed world and tends to reach epidemic proportions.<sup>48</sup> ID negatively affects exercise tolerance and quality of life in HFpEF patients.<sup>82,83</sup> In stratified comparison of patients with reduced, mid-range, and preserved LVEF in one prospective database of HF patients, ID was highly prevalent in all patient subgroups (64% in HFpEF cohort) and associated with decreased peak oxygen consumption. Furthermore, in HFpEF patients, baseline presence of ID led to worse clinical outcome,<sup>10</sup> although these results appear to be inconsistent across published systematic reviews and meta-analyses.<sup>84</sup> These findings are suggestive of an important role of ID in HFpEF, indicating that it has a similar impact to that in HF with reduced ejection fraction. However, in the absence of randomized clinical trials of iron supplementation in HFpEF setting, we should focus on upcoming trials such as FAIR-HFpEF (ClinicalTrials.gov identifier: NCT03074591) and PREFER-HF (ClinicalTrials.gov identifier: NCT03833336), in order to fully comprehend the necessity and clinical effects of iron replenishment in HFpEF patients.

At the moment, we encounter gaps in evidence concerning effects of treatment of ID in HF concerning hard cardiovascular endpoints, such as mortality and hospitalization rates. Based on this, the results of FAIR-HF2 trial (Intravenous Iron in Patients with Systolic Heart Failure and Iron Deficiency to Improve Morbidity and Mortality, ClinicalTrials.gov identifier: NCT03036462) are eagerly awaited. This trial aims at 1:1 double-blind randomization of 1200 HF patients (NYHA II–III and LVEF  $\leq$  45%) with ID to ferric carboxymaltose or placebo. The primary endpoint includes a combined rate of recurrent hospitalizations for HF and cardiovascular death. The end on recruitment is planned for December 2021, while follow-up will be event driven and should last for minimal 12 months. Focusing on patients with more severe HF (NYHA III–IV and LVEF 35%), HEART-FID trial (ClinicalTrials.gov identifier: NCT03037931) aims at enrolling 3014 patients with ID. Effects of treatment with ferric carboxymaltose (1:1 randomization to placebo) will be tested on 12 month rate of death, hospitalization for worsening of HF, and 6 month change in 6 min walk test performance (primary endpoint). Only patients on maximally tolerated guideline-recommended medical therapy of HF at least 2 weeks prior to randomization are included.

Available meta-analyses and results from retrospective studies give us reason to believe that ID correction in HF patients improves clinical course of HF and reduces cardiovascular mortality. A meta-analysis including patients with chronic HF included in four randomized trials of ID treatment (FER-CARS-01, FAIR-HF, EFFICACY-HF, and CONFIRM-HF) suggested that treatment with intravenous ferric carboxymaltose reduces rates of recurrent cardiovascular hospitalizations and

cardiovascular mortality [odds ratio (OR): 0.59, 95% (CI) 0.40–0.88;  $P = 0.009$ ] as well as recurrent HF hospitalizations and cardiovascular mortality (OR: 0.53, 95% CI 0.33–0.86;  $P = 0.011$ ).<sup>58</sup> In another meta-analysis, Jankowska *et al.* found that intravenous iron therapy reduced the risk of the combined endpoint of all-cause death or cardiovascular hospitalization [OR: 0.44, 95% CI 0.30–0.64,  $P < 0.0001$ ], and the combined endpoint of cardiovascular death or hospitalization for worsening HF (OR 0.39, 95% CI 0.24–0.63,  $P = 0.0001$ ) in iron-deficient patients with systolic HF.<sup>67</sup>

Management of ID in HF with combined treatment modalities did not prove to be clinically efficient and useful in HF patients. Silverberg *et al.* were among the first to treat anaemic HF patients with erythropoietin and intravenous ferric sucrose. After 6 months, treated patients reported improvements in mean haemoglobin concentration, LVEF, and NYHA functional class.<sup>60</sup> These results evoked high hopes and induced several clinical trials focusing on anaemia correction in HF. Unfortunately, long-acting erythropoietin derivative alone did not show prognostic benefit in patients with HF. In the RED-HF-Trial (Reduction of Events by Darbepoetin Alfa in Heart Failure), anaemic patients with systolic HF treated with darbepoetin alfa did not show improvement concerning the primary endpoint in compared with non-treated counterparts. Even more, darbepoetin alfa administration led to increase rate of thrombo-embolic events (13.5% vs. 10.0%, respectively;  $P = 0.009$ ) and an increased risk of ischaemic stroke (4.5% vs. 2.8%, respectively;  $P = 0.03$ ), proving to be potentially harmful for treated patients.<sup>85</sup>

## Conclusions

In the last two decades, emerging importance of ID in symptomatic HF resulted in numerous very important clinical trials, which were able to underline necessity for iron supplementation and verify its impact on patient's quality of life.

In spite of certain inconsistency related to the cut-off values for ID conformation across conducted clinical trials, ferritin of  $<100$  mg/L or ferritin 100–300 mg/L when TSAT is  $<20\%$  should be regarded as diagnostic for the presence of ID in HF patients.

Randomized clinical trials demonstrated that in HF patients with ID, intravenous iron repletion was well tolerated, safe, and associated with improvement in functional status and exercise capacity.

Although meta-analyses and results from retrospective studies suggest beneficial effects of iron supplementation concerning hospitalization and cardiovascular mortality, definitive relationship of iron supplementation with mortality and morbidity in HF patients needs further validation in ongoing and future large-scale, randomized prospective trials.

## Acknowledgement

We would like to thank all authors for support and effort.

## Conflict of interest

None declared.

## Funding

M.L. was funded by the Slovenian Research Agency (grant no. J3-9292, Burden of cachexia and sarcopenia in patients with chronic diseases: epidemiology, pathophysiology and outcomes, and grant no. J3-9284, Epidemiology, pathophysiology and clinical relevance of anemia in chronic cardiopulmonary patients). G.L. was funded by Serbian Ministry of Science (grant no. 175033).

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