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REVIEW ARTICLE

Iron Therapy in Patients with Heart Failure and Iron Deficiency: Review of Iron Preparations for Practitioners

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Abstract In patients with heart failure (HF), iron deficiency (ID) correlates with decreased exercise capacity and poor health-related quality of life, and predicts worse outcomes. Both absolute (depleted iron stores) and functional (where iron is unavailable for dedicated tissues) ID can be easily evaluated in patients with HF using standard laboratory tests (assessment of serum ferritin and transferrin saturation). Intravenous iron therapy in iron-deficient patients with HF and reduced ejection fraction has been shown to alleviate HF symptoms and improve exercise capacity and quality of life. In this paper, we provide information on how to diagnose ID in HF. Further we discuss pros and cons of different iron preparations and discuss the results of major trials implementing iron supplementation in HF patients, in order to provide practical guidance for clinicians on how to manage ID in patients with HF.

Key Points

Iron deficiency, regardless of haemoglobin level, is an indication for supplementation in symptomatic patients with heart failure with reduced ejection fraction.

Only intravenous carboxymaltose has been demonstrated to be safe and effective for iron repletion in these patients. Oral iron supplementation is not effective in iron deficient patients with heart failure.

Morbidity-mortality trials have been launched to verify whether iron repletion improves outcomes in patients with heart failure.

1 Introduction

Iron deficiency (ID) constitutes the most common form of malnutrition worldwide, affecting more than 2 billion people globally [1, 2]. The prevalence of ID in different populations varies according to host factors including age, gender, some physiological, pathological, and environmental factors, and socioeconomic conditions [2–6]. The burden of ID remains significant in both developing and developed countries, for example, in the USA, it affects 2 and 9% of adult males and females, respectively [7, 8].

It needs to be emphasized that ID can occur without decreased haemoglobin. Beyond the traditional view of ID as the cause of anaemia, the spectrum of negative health and economic consequences related to ID is wide,

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including poor pregnancy outcomes, impaired school performance, and decreased productivity, to name a few [2]. Importantly, although the prevalence of ID is linked with various chronic diseases and conditions, the majority of randomized control trials (RCTs) investigated ID and iron repletion in patients with chronic kidney disease (CKD) [9–11]. Nevertheless, in recent years, ID has also been extensively studied in patients with other chronic diseases, such as heart failure (HF) [12, 13].

Being involved in cellular metabolism (as a component of respiratory chain proteins in mitochondria and other enzymes crucial for energy generation), iron is indispensable for every living cell [14, 15]. Of note, this microelement is particularly important for tissues either with high energy demand (e.g. myocardial tissue, skeletal muscles) or high mitogenic activity (e.g. haematopoietic cells). The presence of ID is also associated with deranged haematopoiesis (erythroid, lymphoid and thrombocyte cell lines) [16–18]. Studies, performed in patients with HF, have proven decreased overall exercise capacity and more severe HF symptoms such as fatigue and exertional dyspnoea [15]. Clinical benefits of iron therapy in iron-deficient patients with HF are therefore expected to result not only from the increase in haemoglobin concentration, but also from an improvement in the functioning of non-haematopoietic tissues, such as skeletal muscles.

For metabolic purposes, it is important that we replete iron body stores. The pharmaceutical preparation is important in terms of the amount of iron we are able to successfully deliver to the body, taking into account the safety profile of particular preparations. For therapeutic purposes, iron can be administered through enteral or parenteral routes.

2 Mechanisms of Iron Deficiency (ID) in Heart Failure (HF)

The pathophysiology of ID in HF is presumably multifactorial, and potential mechanisms include reduced intake and increased loss of iron, and re-distribution of this microelement to tissue compartments where it is not available for metabolic processes (for example, entrapment in the reticuloendothelial system), to name a few. It needs to be acknowledged that iron is not actively excreted from the body; however, a certain amount of iron is lost through shedding epidermal skin cells and intestinal lining cells.

It is considered that ID in HF partially results from inadequate iron intake in the diet [19, 20], low bioavailability of iron in the diet (more frequent in developing countries), and handicapped gastrointestinal absorption. The latter results from intestinal interstitial oedema, the use of medications increasing gastric pH (such as proton pump

inhibitors or H_2 receptor antagonists), and the ingestion of food reducing iron absorption (calcium, tannins, oxalates, phytate, phosphates, antacids) [21, 22]. Increased iron loss is associated with several gastrointestinal disorders (peptic ulceration, esophagitis, gastritis, duodenitis), menstrual blood loss, and also frequent blood sampling. Importantly, there is no correlation between the prevalence of ID and the use of anticoagulants or antiplatelet drugs in patients with HF [23, 24].

Although the inflammatory state characterizing several chronic diseases (including HF) is considered responsible for impaired iron absorption, recycling and release from body stores [16, 26–29], in two studies, one recruiting patients with stable HF, the second performed among acute HF patients, ID was found in both anaemic and non-anaemic subjects, without the major involvement of measured inflammatory biomarkers [16, 26–29]. Moreover, we would like to emphasise that although postulated, circulating hepcidin has been shown to be low (but not high) in patients with HF. First of all, in patients with chronic stable heart failure with reduced ejection fraction (HFrEF), we have demonstrated that patients with ID have low hepcidin [25]. Even more worthy of note is that 46% of patients with acute HF have very low hepcidin, not high, and low hepcidin predicted the worse outcome in these patients [25, 26].

3 Assessment of ID

Bone marrow aspiration is the most accurate method to assess iron status [27–31], but this examination is invasive, not widely available, and unsuitable for assessing ID in daily clinical practice. Laboratory blood tests are therefore the preferred method to diagnose and monitor ID.

Circulating ferritin is a reliable indicator of iron stores. The primary tissues where iron is physiologically stored are reticuloendothelial cells within bone marrow, liver and spleen. A ferritin level of <100 μg/L is considered to reflect an absolute ID in HF. Lower values of ferritin correlate with more depleted iron stores. In the general population, the cut-off of serum ferritin to diagnose absolute ID is usually 30 μg/L [31, 32], although lower values (i.e. 12–15 μg/L) have also been applied [33, 34]. Importantly, ferritin is an acute phase reactant, and its level is increased in the state of inflammation [35–41]. Therefore, in chronic disease accompanied by inflammation (e.g. HF), when diagnosing ID, higher cut-off values of ferritin should be used (100 μg/L) [15, 30, 42].

The second type of ID is functional ID (or relative ID), in the course of which the availability of iron for metabolic processes is restricted despite preserved iron stores. Functional ID is characterized by low transferrin saturation (TSAT). TSAT reflects the percentage of transferrin with

in-bound iron and is calculated as the ratio of serum iron and total iron-binding capacity by transferrin (TIBC), and direct transferrin measurement is not necessary [15]. Transferrin may be elevated in the setting of inflammation, which indicates lower TSAT if circulating iron is constant. On the other hand, low circulating transferrin (accompanying malnutrition in the course of chronic inflammatory disease) can result in an artificially increased TSAT.

The accepted criteria for detecting ID in patients with HF are serum ferritin <100 μg/L defined as absolute ID, or serum ferritin 100–300 μg/L in combination with a TSAT of <20% defined as functional ID [13, 15, 43]. This definition was previously applied in CKD [42] and further adapted in HF studies [12, 13]. Importantly, neither serum iron nor serum transferrin alone should be analysed as biomarkers of iron status. It needs to be acknowledged that there are attempts to develop more precise definitions of ID based on experimental biomarkers, e.g. the combined assessment of serum hepcidin (correlates with iron stores more precisely than ferritin) and soluble transferrin receptor (sTfR) (facilitates intracellular import of iron; ID induces the expression and release of the transferrin receptor to the circulation) [32, 37, 44].

In patients with iron deficiency anaemia (IDA), we need to exclude other causes than ID before initiation of iron therapy. The physician should include the following in the anamnesis and diagnostic process: dietary history, to identify poor iron intake; history of blood donations; use of NSAIDs; inherited disorders of iron absorption (i.e. coeliac disease); haematological disorders; impaired renal and liver function; and bleeding (e.g. digestive). The diagnosis of ID in patients without anaemia usually does not require further investigation, and iron therapy can be initiated immediately.

4 Prevalence of ID in HF

ID constitutes a frequent co-morbidity in patients with HF, and its prevalence varies according to the clinical characteristics of the studied cohort and the applied definition of ID. Based on laboratory tests (the only study investigating ID in HF based on bone marrow aspirates is presented in Table 1), the prevalence of ID in HF ranges from 33 to 74% [14, 23, 24, 26, 45–53], with higher rates in anaemics versus non-anaemics [14, 23, 24, 26, 45, 48, 49] and decompensated [26, 52, 54, 55] versus stable HF [14, 23, 24, 45–51, 53, 56–58] (Table 1).

The majority of data on the prevalence of ID in HF comes from European HFrEF cohorts [14, 24, 48, 50, 56]; however, the limited data on patients with both reduced and preserved left ventricle ejection fraction (HFpEF) show similar percentages of iron-deficient enrolees [23, 46]. Importantly, in

one study involving a multi-ethnic Southeast Asian population of patients with HF, the prevalence of ID was higher than in European cohorts [23, 26, 49, 55]. The gender differentiation has been shown in one study with patients with decompensation of chronic HF [55], where the prevalence of ID was 69% in men and 75% in women, and in one study in chronic stable HF where the prevalence of ID was 32% in men and 54% in women [24]. Besides anaemia [23, 24], the higher prevalence of ID in patients with HF correlates with female sex [23, 24], more advanced HF symptoms [higher New York Heart Association functional classification (NYHA) class] [23, 24], neurohormonal activation [higher N-terminal pro-brain natriuretic peptide (NT-proBNP)] [23, 24], and inflammation (higher high-sensitivity C-reactive protein) [24].

5 Clinical Consequences of ID in HF

In patients with HFrEF, ID is associated with impaired aerobic performance, as reflected by lower peak oxygen consumption (VO$_2$), higher ventilatory response to exercise (VE-VCO$_2$ slope) [14, 51, 59], and lower 6-min walk test (6MWT) distance [51]. Importantly, in patients with HFrEF, the impact of ID on both peak VO$_2$ and VE-VCO$_2$ slope is independent of and much stronger than the effect of anaemia alone [59]. Similar associations were observed in studies on HFpEF. Núñez et al. have shown that in these patients, low TSAT and ferritin correlate with impaired functional capacity as assessed by cardiopulmonary exercise test [52]. Importantly, in one study including both HFrEF and HFpEF patients, the 6MWT distance was also decreased in subjects with versus without ID [53]. The presence of ID is also associated with decreased health-related quality of life (HRQoL), as assessed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) [46, 60]. Further, in both HFrEF and HFpEF, concomitant ID predicts increased long-term all-cause mortality independently of the presence of anaemia [14, 23, 24, 26] or ethnicity [49]. In patients hospitalized for acute HF, ID increases the risk for re-hospitalization within 30 days after discharge [61], combined all-cause death or non-fatal cardiovascular event (hospitalization for congestive HF, acute coronary syndrome, severe arrhythmia or stroke) [48], and combined death or heart transplantation [24].

6 Oral Iron Supplementation

In healthy persons, an overall iron absorption depends on several factors, such as consumed form of iron, iron absorption enhancers or inhibitors, and the degree of iron

Table 1 Prevalence of ID in studied HF patients

Study	Main HF population criteria	Include HFrEF	Include HFpEF	Applied ID definition	Anaemia definition (HGB, g/dL)	Prevalence of ID (%)		
						All patients	Anaemic patients	Non-anaemic patients
Nanas et al. 2006 [54]	Acute HF hospitalization	+	−	ID in bone marrow smear	<12.0 men, <11.5 women	–	73	–
Cohen-Solal et al. 2014 [55]	Acute HF hospitalization	Not stated	Not stated	Ferritin <100 µg/L or ferritin 100–299 µg/L and TSAT <20%	<13.0 men, <12.0 women	69 in men 75 in women	–	57 in men 79 in women
Jankowska et al. 2014 [26]	Acute HF hospitalization	Not stated	Not stated	Ferritin <100 µg/L or ferritin 100–299 µg/L and TSAT <20%	–	65	–	–
de Silva et al. 2006 [56]	Chronic HF	+ (≤45%)	−	Serum iron <34 µmol/L and/or serum ferritin <30 µg/L	<13.0 men, <12.0 women	24	43	15
Jankowska et al. 2010 [24]	Chronic HF	+ (≤45%)	−	Ferritin <100 µg/L or ferritin 100–299 µg/L and TSAT <20%	<13.0 men, <12.0 women	37	57	32
Parikh et al. 2011 [45]	Self-reported congestive HF (survey)	Not stated	Not stated	Ferritin <100 µg/L or ferritin 100–299 µg/L and TSAT <20%	<13.0 men, <12.0 women	61	73	56
Okonko et al. 2011 [14]	Chronic HF	+ (≤45%)	−	Ferritin <100 µg/L or ferritin 100–300 µg/L and TSAT <20%	<13.0 men, <12.0 women	65	78	65
Klip et al. 2013 [23]	Chronic HF	+	+	Ferritin <100 µg/L or ferritin 100–299 µg/L and TSAT <20%	<13.0 men, <12.0 women	50	61	46
Comín-Collet et al. 2013 [46]	Chronic HF	+	+	Ferritin <100 µg/L or ferritin <800 µg/L and TSAT <20%	–	63	–	–
Kasner et al. 2013 [47]	Chronic HF	Not stated	Not stated	Ferritin <100 µg/L or ferritin 100–299 µg/L and TSAT <20%	–	58	–	–
Rangel et al. 2014 [48]	Chronic HF	+ (≤45%)	−	Ferritin <100 µg/L or ferritin 100–299 µg/L and TSAT <20%	<13.0 men, <12.0 women	36	43	34
Yeo et al. 2014 [49]	HF inpatients at discharge and stable HF outpatients	+ (≤50)	+ (>50)	Ferritin <100 µg/L or ferritin 100–300 µg/L and TSAT <20%	<13.0 men, <12.0 women	61	65	–
				TSAT <20%	–	61 in HFpEF, 64 in HFrEF	–	–
Schou et al. 2015 [50]	Patients referred to an outpatients HF clinic	+ (≤45%)	−	Ferritin <100 µg/L or ferritin 100–300 µg/L and TSAT <20%	–	45	–	–
Ebner et al. 2016 [51]	Chronic HF	+	+	Ferritin <100 µg/L or ferritin 100–299 µg/L and TSAT <20%	–	45	–	–
Vega et al. 2015 [57]	Chronic HF (retrospective study)	Not stated	Not stated	Ferritin <100 µg/L or ferritin 100–300 µg/L and TSAT <20%	–	51	–	–

Table 1 continued

Study	Main HF population criteria	Include HFrEF	Include HFpEF	Applied ID definition	Anaemia definition (HGB, g/dL)	Prevalence of ID (%)		
						All patients	Anaemic patients	Non-anaemic patients
Przybylowski et al. 2016 [58]	After first orthotopic heart transplantation	Not stated	Not stated	Ferritin <100 μg/L or ferritin 100–300 μg/L and TSAT <20%	–	30 absolute ID, 17 functional ID	–	–
	Chronic HF, admitted for PCI	Not stated	Not stated		–	15 as absolute ID, 18 as functional ID	–	–
Núñez et al. 2016 [52]	Acute HF hospitalization (patients with ACS excluded)	+	+	Ferritin <100 μg/L or ferritin 100–299 μg/L and TSAT <20%	–	74; 48 absolute ID, 26 functional ID	–	–
Enjuanes et al. 2016 [53]	Chronic HF	+	+	Ferritin <100 μg/L or ferritin <800 μg/L and TSAT <20%	–	61	–	–

ACS acute coronary syndrome, *HF* heart failure, *HFrEF* heart failure with reduced ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HGB* haemoglobin, *ID* iron deficiency, *PCI* percutaneous coronary intervention, *TSAT* transferrin saturation

depletion. Greater overall amount of consumed iron and a diet rich in iron compounds with better bioavailability increase total iron absorption. Haem iron is more easily absorbed than non-haem iron, and, for example, ascorbic acid promotes iron absorption [21].

Iron absorption increases when body iron stores are low and decreases when they are sufficient [62]. An average absorption of iron from the whole diet is approximately 12–16%, but it varies between 1 and 50% (in the vast majority of studies analysed in the meta-analysis of Collings et al. [63], the mean absorption was below 10 mg/day) [63].

In the general population, oral iron supplementation is usually "the first choice therapy" for ID, but frequently the response to the treatment is suboptimal. It is a reasonable option for healthy subjects without absorption disorders, in whom ID is usually mild and rapid replenishment is not necessary. The tolerance of iron differs depending on the used oral iron formulation. There are two forms of absorbable iron: ferrous (Fe^{2+}) and ferric (Fe^{3+}). Due to lower solubility, ferric iron is less bioavailable than ferrous iron [64]. Ferrous fumarate, ferrous sulphate, and ferrous gluconate are the major types of ferrous iron supplements, with comparable bioavailability [65–67]. The estimated absorption rate of the ferrous salts was found to be 10–15%, without significant differences among the three major formulations, in a small RCT [68]. The recommended therapeutic dosage ranges from 150 to 180 mg/day of elemental iron delivered in divided doses two to three times a day [69]. Importantly, the therapy with oral iron

supplements can be complicated by gastrointestinal side effects, such as abdominal discomfort, nausea, vomiting, and constipation, to name a few. Enteric-coated iron supplements have fewer side effects [70]. The newest formulation of iron is a delayed-release polysaccharide iron complex (PIC). This is a combination of ferric iron and a low-molecular weight polysaccharide, which contains 150 mg of elemental iron. Its structure closely resembles endogenous carriers of iron. PIC has been designed to minimize gastrointestinal upset by delaying iron release in the intestines [71–73]. On the other hand, in Taiwanese populations, delayed release of iron from PIC results in slower treatment of IDA (improvement in ferritin and haemoglobin) as compared with an equivalent daily dose of ferrous fumarate [74].

Iron supplements at doses of 60 mg or higher of elemental iron as ferrous sulphate increase serum hepcidin for up to 24 h and are associated with lower iron absorption on the following day. In iron-depleted (defined as plasma ferritin ≤20 μg/L), non-anaemic women, the fractional absorption is highest at low iron doses (40–80 mg) and consecutive-day dosing results in decreased iron bioavailability compared with every other day dosing. For total iron absorption, a twice-daily iron supplementation seems to have limited additional effect compared with a daily administration. The sTfR/ferritin ratio and hepcidin are equivalent predictors of iron absorption from supplements [75]. It is worth noting that in elderly patients over 80 years of age, low-dose iron supplementation (15 mg of elemental iron daily) appears to be a reasonable option for

the treatment of IDA, as it significantly reduces adverse effects of the therapy [76].

The majority of studies regarding oral iron supplementation and its effectiveness recruited subjects with IDA or patients with CKD. In patients with IDA and non-dialysis CKD in seven randomized studies, the superiority of intravenous (IV) iron over oral iron as a faster and more efficient support for erythropoiesis has been demonstrated [77–83].

It needs to be acknowledged that available clinical evidence on the effectiveness of oral iron therapy in patients with HF and ID is very limited. In a retrospective study, regarding iron-deficient patients with HFrEF, oral iron supplementation over 180 days resulted in an increase in ferritin, TSAT, serum iron, and haemoglobin concentration. The authors suggested that oral iron supplementation could be an alternative for IV iron, but it is worth noting that after 5 months of the therapy, the level of ferritin was still far below the threshold for an absolute ID in HF (ferritin <100 μg/L). Moreover this study did not reveal any clinical benefits beyond improvement in serum iron indices and haemoglobin; particularly, there was no difference regarding re-hospitalization rates [84]. In another study in HF patients with anaemia, the use of oral iron for 1 year was not associated with any clinical benefits in the context of any improvement in NYHA status, measured exercise endurance, oxygen use during exercise, renal function and plasma B-type natriuretic peptide levels, and the need for hospitalization [85]. Additionally, in the recently presented prospective, randomized clinical trial (IRON-OUT), PIC (150 mg twice daily for 16 weeks) had little effect in replacing iron stores and did not improve peak VO$_2$, 6-min walking distance, oxygen kinetics, ventilatory efficiency, and HRQoL score in anaemic HFrEF patients [86, 87].

7 Parenteral Iron Supplementation

Historically, in the general population with anaemia, the first parenteral iron preparations were administered as an iron oxyhydroxide complex [88, 89], which resulted in large amounts of non-transferrin-bound iron and therefore increased oxidative stress [90]. This resulted in several side effects, such as hypotension, nausea, vomiting, and peripheral oedema, to name a few [91]. This problem has been solved with the introduction of compounds containing iron in a core surrounded by a carbohydrate shell, which influences molecular size, pharmacokinetics and adverse reaction profiles [92].

There are at least ten parenteral (IV or intramuscular) iron formulations approved for therapeutic use: ferric sorbitol, iron dextrans (high- and low-molecular weight dextran), iron polymaltose, iron sucrose (ISC), ferric gluconate, ferric carboxymaltose (FCM), iron isomaltoside 1000, and ferumoxytol (Table 2). Five of them were formally investigated in patients with HF [12, 13, 93–104]. ISC was administered in seven studies (yielding a total of 136 patients) [94–100], and FCM was administered in two multicentre, randomized, placebo-controlled, double-blind trials (a total of 454 patients) [12, 13]. Iron dextran, iron isomaltoside 1000, and ferric gluconate were investigated only in a small single-centre study.

FCM, iron isomaltoside 1000, and ferumoxytol are considered more stable iron compounds, and are characterized by slower degradation. These formulations make it possible to administer high single doses of iron. Iron dextran can also be administered in a large single dose, but its safety profile in comparison to FCM, iron isomaltoside 1000, and ferumoxytol is worse as it can more often cause severe immunological reactions, including life-threatening anaphylaxis, and delayed hypersensitivity-like reactions [105, 106].

8 Iron Formulations Administered in Patients with HF

8.1 Ferric Carboxymaltose

FCM [Ferinject® or Injectafer®, Vifor (International) Inc., Zurich, Switzerland] is useful for rapid and high-dose replenishment of depleted iron stores [78, 107–109]. It has been observed that serum iron concentration increases rapidly after administration of a single dose of IV FCM equivalent to 100–1000 mg of iron [110]. FCM is rapidly distributed from plasma not only to bone marrow, but also liver and spleen [111]. Rapid iron uptake by the bone marrow occurs in the first 10 min following FCM administration, with subsequent uptake occurring at a slower but steady rate. In patients receiving a single dose of FCM equivalent to 100–1000 mg of iron, the half-life of elimination of FCM from the plasma is 7–12 h [110]. Renal elimination of iron is negligible [111]. Weekly administration of FCM (up to two infusions of 1000 mg of iron and four infusions of 500 mg of iron) does not result in accumulation of iron in the serum [62]. Being dextran-free, FCM does not react with anti-dextran antibodies and a test dose is not required [110].

In the FAIR-HF study [13, 43], the Ganzoni formula [112] was applied to calculate the required total FCM dose. In the CONFIRM-HF study, FCM was administered according to a fixed scheme (Table 3) based on the subject's weight and haemoglobin concentration at screening. The latter dosage scheme is convergent with a total iron dose administered to patients in the FAIR-HF study [113],

Table 2 All intravenous iron formulations

	High-molecular weight iron dextran [105]	Low-molecular weight iron dextran [115]	Ferric carboxymaltose[a]	Iron sucrose[b]	Ferric gluconate [135]	Iron isomaltoside 1000 [136]	Ferumoxytol[c]	Iron polymaltose [125]
Trade name	DexFerrum	INFeD	Ferinject, injectafer	Venofer	Ferrlecit	Monofer	Feraheme	Ferrosig
Carbohydrate shell	Complex branched glucan	Complex branched glucan	Carboxymaltose (branched polysaccharide)	Sucrose (disaccharide)	Gluconate (monosaccharide)	Linear chemical structure of average 5.2 glucose units	Polyglucose sorbitol carboxymethyl ether	Dextrin
Molecular weight by manufacturer, Dalton × 10^3	265	<165	150	34–60	289–444	150	750	462
Dosage used for the PK characteristics, mg Fe	Not stated	500–2000	100/1000[a]	100[b]	125	100/200	316[c]	100
Terminal half-life, h	9.4–87.4, average 58.9	5.20	7.4/9.4	5.3	1.42	20.8–23.5	14.7	22.4
Test dose required	Yes	Yes	No	No	No	No	No	No

PK pharmacodynamic

[a] Geisser et al. 2010 [135]: study in volunteers with mild iron deficiency anaemia

[b] Danielson et al. 1996 [119]: study in healthy volunteers

[c] Landry et al. 2005 [136]: study in normal subjects and haemodialysis patients

Table 3 Treatment dosing scheme used in the CONFIRM-HF study

Haemoglobin (g/dL)	Weight (kg)	Dose of ferric carboxymaltose depending on visit		
		Week 0 (mg)	Week 6	Week 12, 24, 36 (mg)
<10	<70	1000	500 mg	500[a]
<10	≥70	1000	1000 mg	500[a]
10–14	<70	1000	No dose	500[a]
10–14	≥70	1000	500 mg	500[a]
≥14, <15	All	500	No dose	500[a]

[a] Dose to be administered if serum ferritin <100 mg/mL or serum ferritin 100–300 ng/mL with transferrin saturation <20%

in which the median total iron dose during the correction phase was 1000 mg plus an additional 1000 mg in the maintenance phase [113]. Additional doses of FCM can be administered at weeks 12, 24, and 36 if the patient remains iron deficient. It is worth noting that more than 75% of treated patients required a maximum of two injections of FCM [12].

8.2 Iron Sucrose

ISC (Venofer, Vifor Pharma Ltd.) contains iron(III)-hydroxide sucrose complex. In healthy volunteers, a single dose of ISC equivalent to 100 mg of elemental iron is quickly cleared from serum, with a half-life of 5 ± 2 h [63]. Renal elimination is negligible (on average <5%). Serum ferritin level increases significantly after 8–10 h and doubles after 24 h. In anaemic patients, a single-dose administration of radiolabelled ISC equivalent to 100 mg of elemental iron is followed by rapid uptake of this microelement by the liver, spleen, and bone marrow, reaching maximum rates at 10, 20 and 100 min after an administration, respectively [64]. Up to 97% of administered iron is utilized for erythropoiesis, and both ferritin and TSAT return to baseline levels within 3–4 weeks. The extensive safety and tolerability record of ISC (including a low prevalence of hypersensitivity reactions) supports the recommendations of the European Medicines Agency (2013) that a test dose need no longer be applied prior to ISC administration. Special caution is recommended with every dose of IV iron instead, even in patients who responded well previously. The total dose of ISC should be determined individually, based on the calculated total iron deficit according to Ganzoni's formula (depending on the target level of haemoglobin; the frequently applied concentration is 15 g/dL). A common dosing scheme of ISC in HF includes the drip infusion of 200 mg of ISC (in 0.9% sodium chloride solution) weekly for 3 or 5 weeks, depending on the total required dose [13]. A slow IV bolus infusion is also allowed. Doses and dosing schemes in clinical trials with HF are listed in Table 4.

8.3 Iron Isomaltoside 1000

Iron isomaltoside 1000 (Monofer®, Pharmacosmos, Copenhagen, Denmark) consists of iron tightly bound in a carbohydrate matrix structure that guarantees a slow release of iron. The plasma half-life is 5 h for unbound circulating iron and 20 h for total iron (bound and circulating) [114]. Due to the low anaphylactic potential, a test dose is not required, and this formulation can be administered in high doses (up to 20 mg/kg within 30–60 min) [114]. To date, only one small study with iron isomaltoside 1000 has been performed in HF patients [103].

8.4 Iron Dextran

There are two formulations of iron dextran: low-molecular-weight iron dextran (INFeD, Watson Pharmaceuticals) [115] and (CosmoFer, Pharmacosmos) [116], and high-molecular weight iron dextan (DexFerrum, Watson Pharmaceuticals) [105]). The molecular weight of INFeD and CosmoFer is lower than that for DexFerrum, and reduces the risk of anaphylaxis [106]. These products still require the test dose, and their parenteral use is associated with increased risk of anaphylactic reactions as compared with ISC and ferric gluconate [117]. CosmoFer can be administered in a maximal single dose of 20 mg/kg of body weight, but in a very slow IV infusion (over 4–6 h). The maximum daily dose of INFeD and DexFerrum should not exceed 2.0 mL (100 mg of iron).

8.5 Ferric Gluconate

Ferric gluconate (Ferrlecit) is a labile weak complex of iron and requires multiple IV injections with a maximal single dose of 125–250 mg [118–120]. The test dose is suggested only in patients who have had an iron allergy or other drug allergies. An intensive IV dosing scheme (250 mg in 2 h infusions twice daily) improves haematological parameters and is well tolerated in hospitalized patients with advanced HF [104].

Table 4 Overview of critical inclusion criteria, haematological status, intravenous iron formulations, doses, and dosing schemes in prospective clinical trials with iron replenishment without erythropoiesis stimulating agents in patients with HF and ID (sorted by iron formulations and date of study)

Study	Study design	Major HF cardiac inclusion criteria	HGB (g/dL)	ID criteria (ferritin in ng/dL)	Dosing scheme	Single iron dose (mg)	Total iron dose (mg)	Number of injections	Administration method	Patients in treated/placebo group
FCM										
Anker et al. 2009 FAIR-HF [13]	Multi-centre, randomized, placebo-controlled, double-blind	LVEF ≤40% and NYHA II or LVEF ≤45% and NYHA III	9.5–13.5	Ferritin <100 or ferritin 100–299 and TSAT <20	Ganzoni's formula with target HGB 15 g/dL[c, d], 200 mg weekly in correction phase then every 4 weeks until 24 weeks since randomization[e]	100 or 200	Mean 1850; mean in correction phase 1000 and maintain phase 1000	Median 6 (3–7) in correction phase, NS in maintenance phase	Bolus injection	304/155
Ponikowski et al. 2015 CONFIRM-HF [12]	Multi-centre, randomized, placebo-controlled, double-blind	LVEF ≤45%, NYHA II–III, BNP >100 pg/mL or NT-proBNP >400 pg/mL	<15.0	Ferritin <100 or ferritin 100–300 and TSAT <20%	Doses fixed—based on weight and HGB[a] 500–2000 mg (on W00 and W06); 0–1500 mg on W12, W24, W36	500 or 1000	Median 1500 (500–3500)	Over 75% of treated patients required max. of 2 injections	Bolus injection over at least 1 min.	150/151
Robles-Mezcua et al. 2016 [93]	Single-centre, retrospective cohort study	LVEF ≤40%, NYHA II–III	NS	Ferritin <100 or ferritin 100–299 and TSAT <20%	Simplified Ganzoni's formula	NS	Max. 1000	1 or 2	NS	70/–
ISC										
Bolger et al. 2006 [94]	Single-centre, non-comparative	HFrEF (LVEF not specified)	≤12.0	Ferritin <400	600–1000 mg; (200 mg on days 1, 3, 5), if ferritin ≤400 on day 12, further 200 mg on days 15 and 17	200	Mean 950 ± 137	Mean 9.5	Injection of undiluted ISC over 10 min	16/–

Table 4 continued

Study	Study design	Major HF cardiac inclusion criteria	HGB (g/dL)	ID criteria (ferritin in ng/dL)	Dosing scheme	Single iron dose (mg)	Total iron dose (mg)	Number of injections	Administration method	Patients in treated/placebo group
Toblli et al. 2007 [95]	Single-centre, randomized, placebo-controlled, double-blind	LVEF ≤35%, NYHA II–IV	<12.5 men, <11.5 women	Ferritin <100 or TSAT <20%	200 mg weekly for 5 weeks	200	1000	5	Injection of ISC in 200 mL normal saline over 60 min	20/20
Okonko et al. 2008 FERRIC-HF [96]	Double-centre, randomized, placebo-controlled, observer-blind	LVEF ≤45%, NYHA II–III, peak VO₂ ≤18 mL/min/kg	≤12.5 (anaemic group), 12.5–14.5 (non-anaemic group)	Ferritin <100 or ferritin 100–300 with TSAT <20	Ganzoni's formula with target HGB 15 g/dL[c] 200 mg weekly[f]	200	1433 ± 365; anaemic group: 1583 ± 366; non-anaemic group: 1269 ± 297	–	Injection of ISC in 50 mL normal saline over 30 min; patients observation for up to 1 h after injection; a test infusion (10 mL over 10 min) before the first treatment	24/11
Usmanov et al. 2008 [97]	Single-centre, open-label, comparative	LVEF ≤45%, NYHA II–III	<11.0	NA	100 mg 3 times weekly for 3 weeks, then once weekly for 23 weeks	100	3200	32	Injection of ISC in 150 mL saline over 30 min	22/32
Terrovitis et al. 2012 [98]	Single-centre, randomized, open-label	Recently hospitalized for HF decompensation (LVEF not specified)	<12.0 men, <11.5 women	ID identified in bone marrow biopsy	300 mg once weekly for 6 weeks	300	1800	6	Injection of ISC in 100 mL normal saline over 3 h; a test dose of 25 mg ISC diluted in saline was infused before the first full dose	14/–[b]
Beck-da-Silva et al. 2013 IRON-HF [99]	Multi-centre, randomized, placebo-controlled, double-blind	LVEF ≤40%, NYHA II–IV	9.0–12.0	Ferritin <100 or TSAT <20%	200 mg weekly for 5 weeks	200	1000	5	30-min infusions	10/6[g]
Toblli et al. 2015 [100]	Single-centre, randomized, placebo-controlled, double-blind	LVEF ≤35%, NYHA II–IV, CrCl ≤90 mL/min	<12.5 men, <11.5 women	Ferritin <100 or TSAT <20%	200 mg weekly for 5 weeks	200	1000	5	Injection of ISC in 200 mL normal saline over 60 min	30/30

Iron dextran (exact formulation not specified)

Table 4 continued

Study	Study design	Major HF cardiac inclusion criteria	HGB (g/dL)	ID criteria (ferritin in ng/dL)	Dosing scheme	Single iron dose (mg)	Total iron dose (mg)	Number of injections	Administration method	Patients in treated/placebo group
Gaber et al. 2012 [101]	Single-centre, non-comparative	LVEF ≤40%	>12.0	Ferritin <100 and TSAT <20%	Ganzoni's formula with target HGB 15 g/dL^c; 200 mg weekly	200	NS	–	Injection of iron dextran in 200 mL normal saline over 2 h; patients observation for up to 2 h after injection	40/–
Iron dextran and ISC										
Kaminsky et al. 2016 [102]	Single-centre, retrospective cohort study	Hospitalization due to acute HF	<13.0	TSAT <20%	Dose was calculated based on iron dextran (INFeD) labelling using a target HGB of 12 g/dL		Mean dose of 1057 (± 336) of iron; min. 25, max. 1925	1	4–6-h infusion after the tolerance of a test dose	44/128
Iron isomaltoside 1000										
Hildebrandt et al. 2010 [103]	Multi-centre, non-comparative	chronic HF (diagnosis established by the attending physician)	<12.5 men, <11.5 women	Ferritin <800	Ganzoni's formula with target HGB 13 g/dL^c; single dose	650–1000	Mean 868	1	Bolus injection	20/–

Table 4 continued

Study	Study design	Major HF cardiac inclusion criteria	HGB (g/dL)	ID criteria (ferritin in ng/dL)	Dosing scheme	Single iron dose (mg)	Total iron dose (mg)	Number of injections	Administration method	Patients in treated/placebo group
Ferric gluconate										
Reed et al. 2015 [104]	Single-centre, non-comparative, open-label	hospitalized, LVEF ≤40%, NYHA III–IV	≤12.0	Ferritin <100 or ferritin 100–300 with TSAT <20	Ganzoni's formula with target HGB 15 g/dL[c, d]; 250 mg twice daily until the ID was corrected or until discharge	250	Mean 1269 ± 207	–	Injection of ferric gluconate 250 in 100 mL normal saline over 2 h twice/day; patient observation for up to 2 h after injection	13/–

BNP brain natriuretic peptide, *CrCl* creatinine clearance, *FCM* ferric carboxymaltose, *HF* heart failure, *HFrEF* heart failure with reduced ejection fraction, *HGB* haemoglobin, *ID* iron deficiency, *ISC* iron sucrose, *LVEF* left ventricular ejection fraction, *NA* not applicable, *NYHA* New York Heart Association classification, *NS* not stated, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *TSAT* transferrin saturation, *VO₂* oxygen consumption, *W00* randomization visit, *Wxx* week xx visit

 See Table 3 — [a] See Table 3

[b] In this study, there was the third parallel group of 16 patients treated with both ISC and darbepoetin alfa

[c] The total dose of iron was estimated as body weight (kg) × 2.4 × (target HGB [g/dL] − patient HGB [g/dL]) + 500 mg; adjusted body weight was used for patients with a body mass index of >25 kg/m²

[d] Normalized weights were used in Ganzoni's formula (kg); normalized weight (kg) = 25 × height (m) × height (m)

[e] In the FAIR-HF study, therapy was withheld if ferritin >800 or 500–800 μg/L with TSAT >50%, or HGB >16 g/dL; could be restarted if ferritin <400 μg/L, TSAT <45%, HGB <16 mg/dL

[f] In FERRIC-HF, on visits W04, W08, W12, and W16, therapy was withheld if ferritin ≥500 ng/mL or HGB ≥16.0 g/dL or TSAT ≥45% at any stage and reinstituted 2 weeks later if ferritin <500 ng/mL, HGB <16.0 g/dL, and TSAT <45%

[g] There was also a third treatment arm with oral ferrous sulphate 200 mg 3 times a day

9 Iron Formulations Not Used in HF

9.1 Ferumoxytol

A novel therapeutic option for HF patients is ferumoxytol (Feraheme®/Rienso®, AMAG Pharmaceuticals, Inc., Lexington, MA, USA/Takeda Pharmaceutical Company Limited, Tokyo, Japan). It is a non-stoichiometric magnetite (superparamagnetic iron oxide) coated with polyglucose sorbitol carboxymethyl ether [121]. The efficacy of this formulation in patients with CKD and IDA (irrespective of the dialysis dependence) appears to be non-inferior to ISC [82]. In addition, the safety profile of ferumoxytol is similar to placebo in anaemic patients with CKD [122]. Since only small amounts of free iron are present in the preparation, doses of 510 mg have been administered safely during an infusion of less than 30 s. In patients receiving a single dose of ferumoxytol equivalent to 316 mg of elemental iron, the mean serum terminal elimination half-life is 15 h [123]. In short-term studies [82, 122, 124], IV ferumoxytol was safe and more effective than oral iron therapy in the correction of anaemia in anaemic patients with CKD.

9.2 Iron Polymaltose (Iron Dextrin)

This active substance is available in an oral, intramuscular, and IV form, and contains an iron(III)-hydroxide polymaltose complex with non-ionic iron. It has not been tested in HF patients. After an IV administration of 100 mg of iron polymaltose, the mean terminal half-life is 22 h. The maximal intramuscular dose for adults is 200 mg (this dose may be repeated every second day), and for IV, the maximal dose is up to 2500 mg in a slow infusion lasting over 5 h [30]. Initial test doses are not obligatory [125]. Although a parenteral formulation has been registered for more than 50 years, the evidence on the safety of this formulation is limited. Self-limiting side effects that occur up to 2 days after an IV infusion affect 26% of patients and include headache, fever, and arthralgia [126].

9.3 Iron Sorbitol

Iron sorbitol is administered intramuscularly only (maximal daily dose of 100 mg), and has not been tested in HF patients [127].

10 Is It Worthwhile to Treat ID in HF?

The benefits of iron replenishment have been tested in a few studies. Most of these studies have been performed in small subgroups, and the value of this data is limited.

Taking into consideration all the evidence, the therapeutic effect of iron supplementation involves an improvement in (a) exercise capacity {increase in 6MWT distance [12, 13, 93–95, 101] and higher peak VO_2 in cardiopulmonary exercise testing (only anaemic patients have been tested) [96]}, (b) HF symptoms (NYHA class [12, 13, 95–97, 101], fatigue score [12, 96]), and (c) HRQoL {as assessed using different questionnaires: Kansas City Cardiomyopathy Questionnaire (KCCQ) score and EuroQol five dimensions questionnaire (EQ-5D) health state score [12, 13], MLHFQ score [94–97], linear analogue scale assessment (LASA) [103], and self-reported patient global assessment (PGA) [12, 13, 96]} (Table 5).

In small samples (treated groups: $n = 16$, $n = 20$, $n = 24$, $n = 22$, $n = 30$), an improvement in echocardiographic parameters has been observed, but only in anaemic patients (Table 5) [94–97, 101]. Currently, it is being verified in patients with ID and HF (NYHA II–III) with left ventricular ejection fraction (LVEF) of ≤45% whether treatment with FCM improves LVEF as determined by cardiac magnetic resonance imaging from baseline to week 12 (http://www.clinicaltrial.gov: iCHF, NCT01837082).

The results of smaller studies are consistent with the results of two large, multicentre, randomized, double-blind, placebo-controlled trials, in which iron therapy improved primary outcomes: NYHA class and self-reported PGA in the FAIR-HF trial [13] and 6MWT distance in the CONFIRM-HF trial [12]. In the FAIR-HF trial, 304 ambulatory symptomatic HF patients [LVEF ≤40% (NYHA II) or ≤45% (NYHA III)] with ID (serum ferritin <100 ng/mL or ferritin 100–300 ng/mL with TSAT <20%) and haemoglobin 9.5–13.5 g/dL were randomized in a 2:1 ratio to receive 200 mg FCM IV or saline IV weekly until iron repletion (the correction phase), then monthly until week 24 (the maintenance phase). Primary endpoints were self-reported PGA at week 24 and NYHA class at week 24, adjusted for baseline NYHA class [43]. Among patients receiving IV iron, 50% were reported as being much or moderately improved, as compared with 28% of subjects receiving placebo, according to the self-reported PGA. Among patients assigned to FCM, 47% had an NYHA functional class of I or II at week 24, as compared with 30% of study participants assigned to placebo. Significant improvements were also seen with the iron arm in 6MWT distance and quality of life. The results were similar in patients with and without anaemia, and it is worth noting that iron therapy improved HF symptoms even without a significant change in haemoglobin concentration from baseline. The rates of death, adverse events, and serious adverse events were similar in two study arms [13].

In the CONFIRM-HF trial, ambulatory patients with HF [NYHA class II/III, LVEF ≤45%, brain natriuretic peptide

Table 5 Benefits of iron replenishment in patients with iron deficiency and HF

Benefits	Evidence in interventional studies		
	Total population	Anaemic patients	Non-anaemic patients
Exercise tolerance			
6MWT distance ↑	Anker 2009, Ponikowski 2015	Bolger 2006, Toblli 2007, Ponikowski 2015	Gaber 2012, Ponikowski 2015
Peak VO$_2$ in CPET ↑		Okonko 2008	
NYHA ↓	Okonko 2008, Anker 2009, Ponikowski 2015	Toblli 2007, Okonko 2008, Usmanov 2008, Anker 2009	Anker 2009, Gaber 2012
Echocardiographic parameters			
LVEF ↑		Toblli 2007, Usmanov 2008 (NYHA III)	
LVESD ↓, LVEDD ↓, LVPWD ↓		Usmanov 2008, Toblli 2015	
LVESV ↓, LVEDV ↓, LVMI ↓		Usmanov 2008	
IVS thickness ↓		Toblli 2015[@]	
Improvement of S', E', decline in E/E', reduced peak systolic strain rate			Gaber 2012
Quality of life ↑			
PGA	Okonko 2008, Anker 2009, Ponikowski 2015	Anker 2009	Anker 2009
Fatigue score	Okonko 2008, Ponikowski 2015		
KCCQ score	Anker 2009, Ponikowski 2015		
EQ-5D health state score	Anker 2009, Ponikowski 2015[&]		
MLHFQ	Okonko 2008 Usmanov 2008	Bogler 2006, Toblli 2007	
LASA		Hildebrandt 2010	
Haematological and biochemical blood parameters			
HGB ↑	Anker 2009, Ponikowski 2015	Bogler 2006, Toblli 2007, Anker 2009, Usmanov 2008, Terrovitis 2012, Beck-da-Silva 2013, Toblli 2015	Gaber 2012
Serum iron ↑		Bogler 2006, Usmanov 2008	
Serum ferritin ↑	Okonko 2008, Anker 2009, Ponikowski 2015	Bogler 2006, Toblli 2007, Okonko 2008, Usmanov 2008, Toblli 2015	Okonko 2008, Anker 2009, Gaber 2012
TSAT ↑	Okonko 2008, Anker 2009, Ponikowski 2015	Bogler 2006, Toblli 2007, Okonko 2008, Usmanov 2008, Beck-da-Silva 2013, Toblli 2015	Okonko 2008, Anker 2009, Gaber 2012
MCV ↑	Anker 2009	Anker 2009	
sTfR ↓	Okonko 2008		
Creatinine clearance ↑		Toblli 2007	
NT-proBNP ↓, CRP ↓		Toblli 2007	
Reduction in the number of first hospitalizations due to worsening HF or all-cause death	Ponikowski 2015, Anker 2009 trend		

Table 5 continued

Benefits	Evidence in interventional studies		
	Total population	Anaemic patients	Non-anaemic patients
Reduction in the number of hospitalizations due to worsening HF	Ponikowski 2015	Toblli 2007	

6MWT 6-min walk test, *BNP* brain natriuretic peptide, *CPET* cardiopulmonary exercise test, *CRP* C-reactive protein, *EQ-5D* EuroQol five dimensions questionnaire, *HGB* haemoglobin, *IVS* interventricular septal thickness, *KCCQ* Kansas City Cardiomyopathy Questionnaire, *LASA* linear analogue scale assessment, *LVEDD* left ventricular end diastolic diameter, *LVEDV* left ventricular end diastolic volume, *LVEF* left ventricular ejection fraction, *LVESD* left ventricular end systolic diameter, *LVESV* left ventricular end systolic volume, *LVMI* left ventricle mass index, *LVPWD* left ventricle posterior wall diameter, *MCV* red blood cell mean corpuscular volume, *MLHFQ* Minnesota Living with Heart Failure Questionnaire, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *NYHA* New York Heart Association functional classification, *PGA* patient global assessment, *sTfR* soluble transferrin receptor, *TSAT* transferrin saturation, *VO₂* peak oxygen consumption

[&] Significant only on week 36

[@] Change in treated group clinically relevant, but not statistically significant

(BNP) >100 pg/mL or NT-proBNP >400 pg/mL], ID (definition analogous to the FAIR-HF trial) [12], and haemoglobin below 15 g/dL were randomized 1:1 to treatment with FCM or placebo for 52 weeks. The dosing scheme is presented in Table 3. Study medication was administered in single doses as undiluted bolus injection of up to 1000 mg of iron or normal saline at day 0 and week 6 up to iron repletion. Further doses of FCM were administered at weeks 12, 24, and 36—if predefined ID was still present [128]. The primary endpoint was a change from baseline in 6MWT distance at week 24. Secondary endpoints were change in PGA, NYHA class, fatigue score, and HRQoL. Treatment with FCM significantly improved 6MWT distance at week 24, with the treatment effect consistent in all study subgroups and present up to week 52. Throughout the study, an improvement in NYHA class, PGA, HRQoL, and fatigue score in patients treated with FCM was detected, with statistical significance observed from week 24 onwards. The number of deaths (FCM 12, placebo 14) and the incidence of adverse events were comparable between the two study groups (iron vs. placebo) [12]. Importantly, in post hoc sensitivity analyses, the treatment with FCM reduced the combined risk of first hospitalization for worsening HF or all-cause death.

There are a few meta-analysis regarding iron therapy in patients with HF and ID [129–133]. The most recent report analysed the results of five trials regarding HF patients with LVEF of ≤45% (509 patients received IV iron therapy, and were compared with 342 controls), with at least a single-blind randomization, and without a concomitant therapy with erythropoiesis-stimulating agents [133]. It has been shown that IV iron therapy reduced the risk of unplanned HF hospitalization, the risk of the combined endpoint of all-cause death or cardiovascular hospitalization, and the risk of combined cardiovascular death or hospitalization for worsening HF, but without the impact on either all-

cause or cardiovascular mortality (which may be due to a low number of reported events and relatively short follow-up) [133]. Additionally, iron therapy resulted in an improvement in exercise capacity, an alleviation of HF symptoms, and an improvement in HRQoL as assessed using questionnaires either specific for HF or those reflecting patients' general medical condition [133].

At present, a new RCT is being conducted on a relatively large group of subjects and aims to verify the effect of FCM on exercise capacity (as a change in peak VO₂ from baseline to week 24) in anaemic and non-anaemic iron deficient subjects with stable chronic HF (NYHA II–III) on optimal background therapy for heart failure with reduced exercise capacity and reduced LVEF (http://www.clinicaltrial.gov: EFFECT-HF, NCT01394562).

We would like to emphasize the fact that the IV iron administration differed in two major clinical trials in HF. In FAIR-HF, during the correction phase, patients received FCM IV infusion weekly. The total dose needed to correct ID was calculated according to Ganzoni's formula [112] and was provided over a period of between 3 and 7 weeks (a median of six injections). In CONRFIM-FH, the FCM was administered in large doses (500 mg or 1000 mg) based on subject weight and haemoglobin value at screening, according to the scheduled dosing scheme (Table 3). Over 75% of the patients required a maximum of two injections of FCM (with a 6-week interval) to correct and maintain the iron repletion. Based on the pharmacological characteristics of the drug, this treatment scheme is actually recommended.

It is also worthy of note that beneficial effects of IV iron treatment are encountered as early as 4 weeks after commencement of supplementation [12, 13].

Moreover, it has been shown that the treatment of ID with FCM in patients with chronic HF is equally

efficacious across different clinical subgroups (NYHA class, 6MWT, PGA, KCCQ score and EQ-5D health state score) and shows a similar favourable safety profile, irrespective of the concomitance of anaemia [113].

Based on aforementioned evidence, the 2016 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic HF emphasize the clinical relevance of predefined ID in HF patients regardless of haemoglobin level (and the presence of anaemia) [134] and recommend consideration of IV iron therapy in symptomatic patients with HFrEF and absolute or functional ID (serum ferritin <100 μg/L, or ferritin between 100–299 μg/L and TSAT <20%) in order to alleviate HF symptoms and improve exercise capacity and quality of life [134] (class of recommendations IIa, level of evidence A).

11 Conclusions

Despite normal access to elemental iron in the diet, the majority of HF patients in developed countries develop ID, and the origin of disordered iron homeostasis in these subjects appears complex and remains not fully understood. Oral iron therapy did not lead to iron repletion and was not translated into any clinical benefits. ID is associated with reduced survival. So far it has been demonstrated that IV iron therapy in ID patients with HFrEF mainly improves exercise capacity, quality of life, and alleviates HF symptoms. The hypothesis of whether IV iron therapy reduces mortality has not been verified yet and further large-scale mortality-morbidity trials have been initiated in acute (http://www.clinicaltrial.gov: AFFIRM-AHF, NCT02937454) and in chronic HF (http://www.clinicaltrial.gov: IRONMEN, NCT02642562).

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