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Review Article

Management of iron deficiency in chronic heart failure: Practical considerations for clinical use and future directions

Maria Nikolaou[a,*], Christina Chrysohoou[b], Theodosis Anastasios Georgilas[c], Gregory Giamouzis[d], George Giannakoulas[e], Apostolos Karavidas[f], Christodoulos Papadopoulos[g], Sotirios Patsilinakos[h], Dimitrios Tziakas[i], John Parissis[j], for the Hellenic Iron Consensus Group

[a] Cardiology Department, General Hospital "Sismanogleio-Amalia Fleming", Athens, Greece
[b] Heart Failure Unit, 1st Cardiology Clinic, University of Athens, "Hippokratio" Hospital, Athens, Greece
[c] Cardiology Department, General Hospital "Tzaneio", Piraeus, Greece
[d] Department of Cardiology, University of Thessaly, Larissa, Greece
[e] Cardiology Department, AHEPA University Hospital, Aristotle University of Thessaloniki, Greece
[f] Cardiology Department, General Hospital "G. Gennimatas", Athens, Greece
[g] Cardiology Department, "Hippokratio "Hospital, Thessaloniki, Greece
[h] Cardiology Department, "Konstantopouleio" General Hospital, Athens, Greece
[i] Cardiology Department, University Hospital of Alexandroupolis, Alexandroupolis, Greece
[j] Heart Failure Unit, Second Cardiology Department, University of Athens, Attikon Hospital, Athens, Greece

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ABSTRACT

Heart Failure (HF) is a global pandemic with rapidly increasing prevalence. In an attempt to maintain patients well being, the therapeutic interest has expanded to the vicious cycles that confer to HF mortality and morbidity and a number of comorbidities have been targeted. Iron deficiency represents a common comorbid condition that affects outcomes in HF. The treatment of iron deficiency is strongly supported by the cardiologic societies all over the world. Intravenous iron, primarily ferric carboxymaltose, has shown clinical benefit in this setting, irrespective of the anemia status. Practical recommendations though are lacking. In this document, we have tried to cover the practical gap and provide useful details for intravenous iron use.

1. Introduction

Heart Failure (HF) is a global pandemic which is attributed to the ageing of the population, the comorbidities and the elongation of HF survival. Even if recent advances in the management of the syndrome have improved mortality and morbidity, the natural course of the disease along with its increased prevalence have raised dramatically the absolute indices of morbidity. HF represents the first cause of hospitalization and early readmissions, accounting for more than one fifth of all hospitalizations in patients > 65 years old, resulting in a huge psychosocial burden on patients' quality of life and a huge financial cost on health expenditures [1,2].

In an attempt to improve patients well being, the therapeutic interest has expanded to the vicious cycles that contribute to HF mortality and morbidity and a number of comorbidities have been targeted. Iron deficiency (ID), irrespective of the presence or absence of anemia, has lately emerged as an independent comorbid condition, which needs screening, diagnosis and treatment in chronic heart failure (CHF) patients.

2. Definition and epidemiology

2.1. Definition

ID has for a long time been considered as a major cause of anemia or less often as a nutritional disorder. In both cases, ID was not perceived as a medical condition of itself. Not until recently, ID was defined as a health-related condition in which iron availability is insufficient to meet the body's needs and which can be present with or without anemia [3].

The traditional gold standard method for detecting ID is based on bone marrow staining. Bone marrow staining assesses directly iron stores by the amount of iron in the extracellular space and secondarily the functional capacity of iron for erythropoiesis by the percentage of

* Corresponding author.
E-mail address: marianikolaou1974@yahoo.com (M. Nikolaou).

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Table 1
Terminology of proteins/markers involved into the pathophysiology of iron deficiency.

Ferritin: intracellular iron-storage protein secreted by iron-storing tissues (e.g. liver and reticuloendothelial system). Serum ferritin concentrations are a surrogate marker of stored iron quantity.
Ferroportin (FP): transmembrane protein that transports iron from intracellular to extracellular space.
Transferrin (TF): plasma glycoprotein that binds iron tightly but reversibly, depending on pH. Each transferrin molecule has the ability to carry two iron ions in the ferric form (Fe3+). When a transferrin protein loaded with iron encounters a transferrin receptor (TfR) on the surface of a cell, it binds to it and is transported into the cell releasing its iron ions.
Soluble transferrin receptor (sTfR): cleaved extracellular portion of transferrin receptor 1 that is released into serum.
TIBC (total iron-binding capacity): measures the total amount of iron that can be bound by proteins in the blood. Since transferrin is the primary iron-binding protein, the TIBC test is a good indirect measurement of transferrin availability—the amount of transferrin that is available to bind to iron.
Transferrin saturation (TSAT): calculation that estimates how many of transferrin iron-binding sites are occupied. Under normal conditions, transferrin is typically one-third saturated with iron and about two-thirds of its capacity is held in reserve. TSAT reflects the percentage of iron binding transferrin to the total amount of transferrin. It is calculated by dividing the iron concentration by the TIBC or less commonly, the iron concentration may be divided by the transferrin concentration, not the TIBC. This similar estimate is usually called the transferrin index.
Hepcidin: liver protein that binds to ferroportin and induces its internalization and degradation, serving as the “master regulator” of ferroportin expression and iron absorption and mobilization. Chronic inflammation increase the production of hepcidin and along with the decreased clearance due to CHF, hepcidin levels are high. Hepcidin internalize and degrade ferroportin on the lateral membrane of duodenal enterocytes and spleen macrophages. Consequently iron remains trapped in enterocytes and reticulo-endothelial system (RES).

iron containing erythroblasts [4]. Since bone marrow aspirate is quite an invasive procedure, several serum biomarkers are used to estimate iron stores. The most clinically applicable is serum ferritin (Table 1). The World Health Organization, defines ID as serum ferritin < 15 μg/L in a general adult population. However, serum ferritin levels are subjected to increase in chronic inflammatory conditions, as an acute phase protein and the cut-off values are almost arbitrarily set in a higher level. Thus, the use of transferrin saturation (TSAT) is also recommended [5,6].

Ferritin is an intracellular iron-storage protein secreted by iron-storing tissues (e.g. liver and cells in the reticuloendothelial system). Serum ferritin concentrations are a surrogate marker of stored iron quantity. TSAT (defined as % of transferrin that has iron bound to it) is used as a marker of the availability of circulating iron to supply metabolizing cells (Table 1). TSAT value is calculated by dividing the serum iron concentration by the total iron-binding capacity (TIBC) [7]. According to the recommendation for chronic inflammatory conditions such as chronic heart failure, chronic renal failure and inflammatory bowel disease, the diagnosis of absolute ID in the presence or absence of anemia, is based on ferritin levels < 100 μg/l or TSAT < 20%. If ferritin ranges from 100 to 300 μg/l, TSAT < 20% is necessary to define functional ID [3].

The necessity of detecting iron status, independent of anemia, in CHF patients has been clearly stated in the current ESC HF guidelines 2016 (class I, level of evidence C) [8]. The proposed diagnostic levels are compatible with the widely accepted ones, as above mentioned, as well as with those proposed by the American College of Cardiology/ American Heart Association/ Heart Failure Society of America, by the Canadian Cardiovascular Society and by the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand (ferritin < 100 μg/l or ferritin 100–299 μg/land TSAT < 20%) [9–11].

2.2. Markers of ID

The diagnostic accuracy of many serum markers of ID were recently validated against the gold standard bone marrow aspirate in heart failure patients with reduced ejection fraction (HFrEF) undergoing coronary artery bypass surgery (CABG). The widely accepted and used definition of ID showed a sensitivity of 82% and a specificity of 72% [12]. Surprisingly, a definition solely based on TSAT ≤19,8% had a sensitivity of 94% and specificity of 84%, while serum iron ≤13 μmol/L also showed an excellent diagnostic accuracy (ROC AUC 0.911). As iron levels vary widely, even from hour to hour, it is recommended that serum iron levels should not be used for the assessment of ID [13]. Novel markers of ID such as soluble transferrin receptor (STfR) and hepcidin have also been previously described as markers which correlate very well with iron status, even in the acute HF setting [14]. Despite exhibiting higher sensitivity, with less specificity compared to serum ferritin, those tests are not widely available nor used.

On the other hand, commonly measurable markers such as mean corpuscular volume, mean corpuscular Hb (MCH) and MCH concentration (MCHC) have been found to be unreliable markers of iron deficiency status [15]. Even in non-anemic patients with normal indices, the prevalence of ID reached 36%. Red blood cell distribution width (RDW) is quite specific but not sensitive enough. Consequently, measuring their levels is not recommended for screening of iron deficiency in patients with HF.

It is important to state that ID can be present even without anemia, so haemoglobin levels alone cannot be used as a guide for screening ID. Ferritin and TSAT should be measured in all CHF patients at least once a year. In case of anemia, special advice should be sought, in order to detect occult blood loss, or other pathology causing the anemia.

2.3. Epidemiology

ID is a very common comorbid condition in HF affecting about one out of two patients [16,17]. The reported prevalence varies largely from 35% to 83%, depending on the population screened. The severity of clinical status (NYHA class, natriuretic peptide levels), the acute HF setting, the presence of anemia and female sex represent the subgroups where ID is more frequent, exceeding 50% [18,19]. Notably, in the majority of cases, absolute ID is detected [18].

Although ID is not well studied in HFpEF, small trials and registries report similar or even higher prevalence compared to HFrEF, exceeding 55% [20,21].

3. Pathophysiology

The etiology of ID in HF patients is multifactorial and associated with: a. poor iron intake due to malnutrition, b. decreased iron absorption due to gastrointestinal edema, or proton pump inhibitors use, c. increased blood loss mostly by the gastrointestinal system, that may occur because of antiplatelet or anticoagulant use, d. chronic inflammation [22] (Fig. 1). All these factors may result in absolute ID, while chronic inflammation may result in functional ID, through hepcidin increase. It is well known that inflammatory cytokines, and especially interleukin-6, induces the production of liver hepcidin, which consequently degrades ferroportin and traps iron into duodenal enterocytes and spleen macrophages by preventing its exit to the extracellular space (Table 1, Fig. 1) [23].

It should be stated though that as CHF advances, hepcidin levels decrease despite inflammation exacerbation, potentially implying the dominance of the profound ID in this setting [24]. The clinical impact of ID extends beyond erythropoesis, since iron is a key element in enzymes involved in cellular respiration, oxidative phosphorylation, citric acid cycle, nitric oxide generation, oxygen radical production etc. Cells that are metabolically active, such as myocardial or skeletal muscle cells, depend on iron for their functional and structural integrity. Therefore, ID leads to depletion of iron stores in myoglobin and causes mitochondrial dysfunction and impaired energetics (Table 2) [25,26].

Myocardial iron deficiency (MID) in HF has been studied in

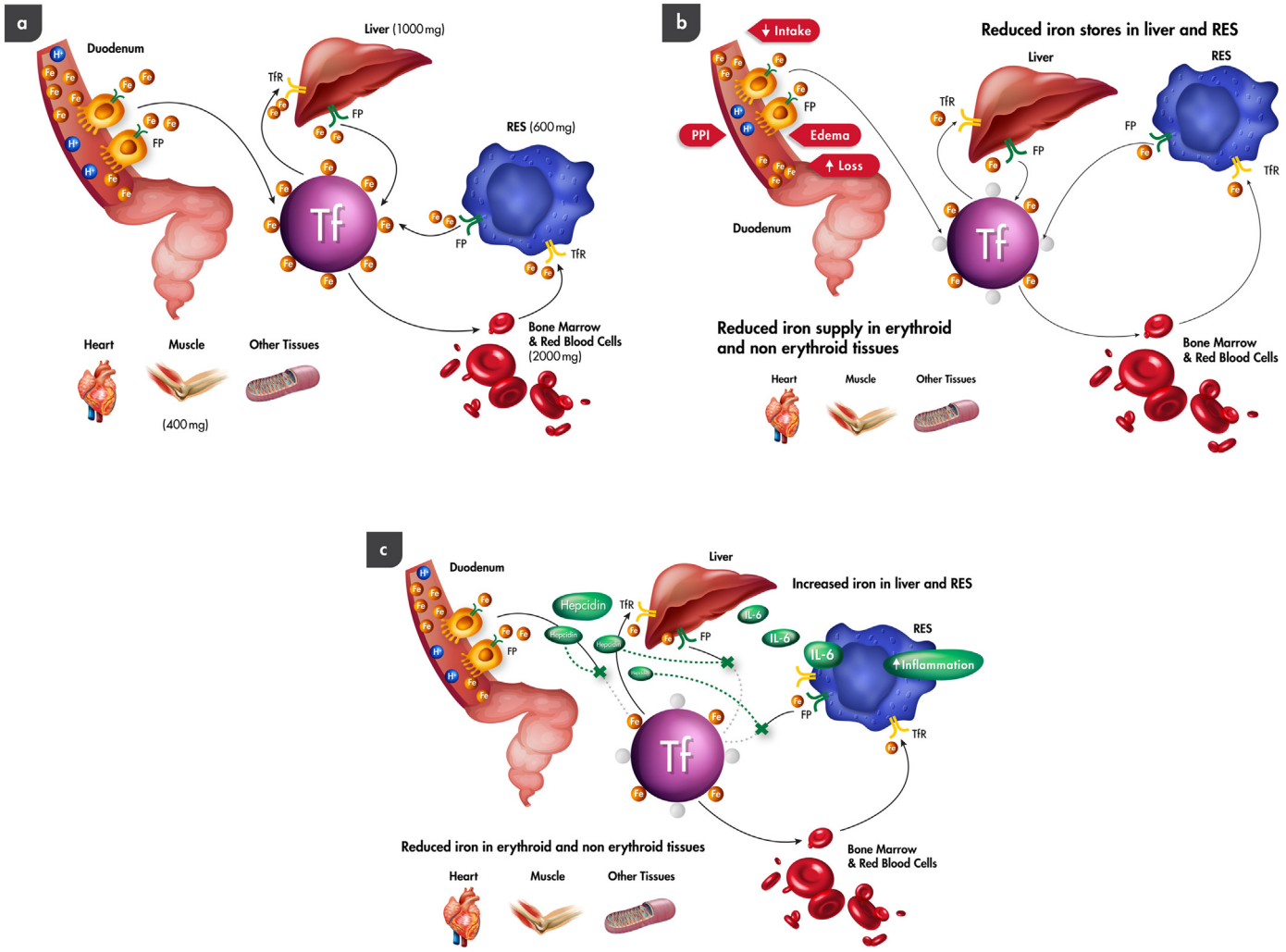

Fig. 1. Iron homeostasis.
a. in normal conditions. In normal conditions, ions of Fe^{3+} are transferred through ferroportin receptors from duodenal cells to transferrin. Transferrin carries Fe^{3+} towards liver and RES where iron is trapped through transferrin receptor (TfR) and stored (about 1000 mg is stored in the liver and 600 mg is stored in RES). Transferrin also carries Fe^{3+} towards bone marrow cells and other tissues. Almost 2400 mg represent the functional iron storage.
b. in absolute iron deficiency. In cases of absolute iron deficiency, the amount of absorbed iron is decreased and both stores (absolute and functional) are depleted.
c. in functional iron deficiency. In cases of functional iron deficiency, inflammation through IL-6 mostly, promotes increased levels of hepatic hepcidin, which disrupts normal iron mobilization. Hepcidin prohibits the ferroportin pathways and reduces partly iron absorption but mostly reduces the release of iron from liver and RES. Consequently, iron may be increased in absolute stores, while is depleted in functional stores.
RES: reticulo-endothelial system, FP: ferroportin, TfR: transferrin receptor, Tf: transferrin, PPI: proton pump inhibitors, IL-6: interleukin 6.

experimental models which showed that MID contributes to worsening of mitochondrial dysfunction, already present in HF (reduced activity of Krebs cycle, ROS protective enzymes) and promotes the metabolic shift (from fatty acids to glucose use). Consequently, severe MID can cause progressive left ventricular (LV) remodeling and lethal cardiomyopathy in mice [4,27]. Interestingly, patients with MID experience difficulty in initiating and up-titrating beta blockers [28].

Concerning peripheral and respiratory muscles, the decrease of the iron containing myoglobin, along with the impaired mitochondrial energetics leading to metabolic alterations are the main mechanisms related to muscle atrophy, weakness, reduced exercise capacity, exertional dyspnoea and fatigue (Table 2).

4. Prognosis

The impact of ID, irrespective of the presence or absence of anemia, has been documented in HFrEF patients during recent years. In terms of hard endpoints, ID has been independently associated with increased long term mortality. The reported hazard ratios range from 1,26 (for absolute ID) to 1,71 (for anemic patients) [15,18,19]. Increased hospitalizations and readmission rates have also been reported [17,21].

Furthermore, ID has been associated with a number of softer endpoints such as impaired exercise capacity (measured by 6 min walk test [6MWT] and peak VO2max) and poor quality of life (QoL), estimated by various self administered questionnaires (Kansas City Cardiomyopathy Questionnaire, Minnesota Living with Heart Failure Questionnaire, EuroQoL 5 Dimensions Questionnaire, Patient Global Assessment) [16].

Concerning the prognosis in patients with ID and HFpEF, data are scarce. Not until recently, Bekfani et al. showed that ID is associated with worse exercise capacity and QoL in these patients [20]. Very limited data exist also in acute HF (AHF). It seems that absolute ID, irrespective of anemia or LVEF, is associated with increased mortality and HF hospitalization within one year after index hospitalization with a relative risk of 1,50 [29].

Table 2
Central and peripheral tissue-consequences of iron deficiency.

	Molecular level	Cell & tissue level	Clinical expression
Central (myocardium)	• ↓activity of citric acid cycle enzymes • ↓ ROS protecting enzymes • ↓ mitochondrial oxygen consumption	• Glucose utilization (instead of fatty acids) • ↓ cell viability / ↑ apoptosis • Myocardial remodeling	• LV dysfunction • Lower BB use
Peripheral			
Bone marrow	• ↓ heme synthesis	• ↓ RBC production	• Anemia
Red blood cells	• ↑ oxidative stress	• ↑ RBC membrane stiffness • ↓life span of RBC	• Anemia
Skeletal muscle	• mitochondrial inefficiency • ↓ myoglobin • ↑ expression of glucose transporters • ↑ expression of lipogenic genes	• Oxidative–glycolytic shift • Alterations in carbohydrate and fat metabolism (↑ lactate, ↑ lipid accumulation) • Skeletal atrophy	• ↓ performance • ↓exercise capacity • Fatigue • Metabolic adaptations (hyperinsulinaemia, hyperglycaemia, hypertriglyceridaemia) • Cachexia
Respiratory muscle			• Exertional dyspnoea • Inspiratory weakness • Impaired physical fitness

ROS: reactive oxygen species, RBC: red blood cells, BB: beta blocker.

5. Evidence for ID management

5.1. Intravenous iron replacement

Since ID is associated with worse prognosis in HFrEF, the rational hypothesis that correcting ID may be associated with better outcomes, was tested in several randomized clinical trials. In all trials, the widely accepted definition of ID (ferritin < 100 μg/l or ferritin 100–300 μg/l and TSAT < 20%) was used, while the iron preparations and the protocols conducted differed. A correction phase (until iron stores were replenished) and a maintenance phase were common in all protocols, though.

The first encouraging results were derived from small clinical trials that randomized a few patients with iron deficiency anemia (IDA) to iron sucrose or placebo (Table 3) [30]. Iron deficit was calculated by the Ganzoni formula [iron deficit = BWx2,4 x (15-Hb) + 500], which takes into account body weight and current Hb. Iron sucrose 200 mg was infused IV every week until correction of ID. A total dose of 1000–2000 mg appeared to be efficient.

The first large multicenter randomized double-blind study was Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF) [31]. For the first time, ferric carboxymaltose (FCM) was administered in patients irrespective of anemia status (Hb < 13,5 g/dl). By 24 weeks, significant improvement in Patient Global Assessment (PGA), NYHA class, exercise capacity (as assessed by 6MWT) and quality of life (as assessed by ED5D and KCCQ) were observed in the FCM arm. Interestingly, the benefit was consistent in patients with or without anemia. Even if this trial was not designed to address mortality or morbidity end-points, there was a trend for lower rate of hospitalization for cardiovascular cause in the treatment (FCM) arm.

The CONFIRM-HF (A Study to Compare the Use of Ferric Carboxymaltose With Placebo in Patients With Chronic Heart Failure and Iron Deficiency) strengthened these findings using higher single iron doses (up to 1000 mg), extending the observed benefits to 52 weeks and including patients with haemoglobin < 15 g/dl [32]. Regardless of anemia, patients in the FCM arm showed significant improvement in exercise capacity and symptomatology, but also in hospitalizations due to HF worsening. Even if the last was not a prespecified end-point, the result was noteworthy.

The third large trial assessing FCM was conducted in order to assess more objective measures of exercise capacity and disease severity. In EFFECT-HF (Effect of Ferric Carboxymaltose on Exercise Capacity in Patients with Chronic Heart Failure and Iron Deficiency) 172 patients were enrolled [33]. The primary end-point was change in pVO2 and the secondary endpoints were clinical status and biochemical measurements of hematinic indices and natriuretic peptides. Patients in the placebo arm showed significantly worse pVO2values in w24, but this result derived after imputation of missing data regarding drop-outs due to death with the value of zero.

The effect of FCM on “harder” end-points, such as mortality and hospitalizations was studied in a recently published meta-analysis, including data from 4 double blind randomized trials (FAIR-HF, CONFIRM-HF and two small unpublished trials FER-CARS-01 and EFFICACY-HF) [34]. In total, 839 patients were included (504 had received FCM). Compared with those taking placebo, patients on FCM had lower rates of recurrent CV hospitalizations and CV mortality [rate ratio 0,59, 95% confidence interval (CI) 0,40–0,88; $P = 0,009$]. Treatment with FCM also reduced recurrent HF hospitalizations and CV mortality (rate ratio 0,53, 95% CI 0,33–0,86; P = 0,011) and recurrent CV hospitalizations and all-cause mortality (rate ratio 0,60, 95% CI 0,41–0,88; P = 0,009). The administration of IV FCM was not associated with an increased risk for adverse events.

Randomized trials designed to address the impact of IV iron on mortality and morbidity are currently ongoing (FAIR-HF2, HEART-FID, IRON-MAN).

Very recently, a mechanistic study of iron isomaltoside infusion in patients with ID irrespective of anemia status, was published, showing evidence that iron replenishment improves muscle energetics as estimated by phosphocreatinine recovery times [35].

5.2. Oral Iron replacement

Oral iron replacement is widely used to correct ID in the general population, due to low cost. However it is related to poor adherence because of gastrointestinal side-effects and slow correction of iron stores. In CHF, oral iron treatment has been tested in a phase II double blind placebo controlled trial. The Iron Repletion effects On Oxygen Up-Take in Heart Failure (IRONOUT-HF) randomized 225 patients to oral iron polysaccharide ($n = 111$) or placebo ($n = 114$), 150 mg twice daily for 16 weeks [36]. The primary endpoint was a change in pVO2, from baseline to 16 weeks. Secondary endpoints included changes in six minute walk distance (6MWT), plasma NT-pro BNP levels and health status as assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ). High dose oral iron did not improve any of the study endpoints (Table 3). The results of the IRONOUT HF study do not support

Table 3
Randomized trials of iron deficiency correction in chronic heart failure.

Trial	N	Major inclusion criteria (HF)	Major inclusion criteria (ID)	Major inclusion criteria (Hb)	Arms	Calculation of deficiency	Correction phase	Maintenance phase	duration	Primary end-points/ secondary end-points	Results for IV arm
FERRIC-HF (2008)	35	NYHA II/III LVEF < 45% pVO2 < 18 ml/ kg/min	Ferritin < 100 µg/l, or Ferritin 100–300 µg/l and TSAT < 20%	< 12,5 mg/dl (anemic) 12,5–14,5 mg/dl (non-anemic)	2 (IV iron sucrose) :1 (control)	Ganzoni formula	200 mg weekly until ferritin > 500 µg/l	200 mg (w4, w8, w12, w16)	18 w	pVO2 (w18)/NYHA, MLHF, PGA, fatigue score	Improved adjusted pVO2. NYHA, PGA, fatigue, MLHF (p = .07)
FAIR-HF (2009)	459	LVEF < 45%, NYHA III LVEF < 40%, NYHA II	Ferritin < 100 µg/l, or Ferritin 100–299 µg/l and TSAT < 20%	9,5–13,5 mg/dl	2 (IV FCM): 1 (PL)	Ganzoni formula	200 mg weekly until iron repletion	200 mg q4 w (starting w8 or w12)	24w	PGA, NYHA (w24)/PGA, NYHA (w4,w12), 6MWT, QoL (EQ5D, KCCQ) (w4,w12, w24)	Improved PGA, NYHA. Improved PGA, NYHA (w4, w12) Improved 6MWT, QoL (w4, w12, w24).
CONFIRM-HF (2015)	304	NYHA II/III LVEF < 45% Elevated NPs	Ferritin < 100 µg/l, or Ferritin 100–300 µg/l and TSAT < 20%	< 15 mg/dl	1 (IV FCM): 1 (PL)	According to BW, Hb	500-2000 mg in 2 doses (d0, w6)	500 mg w12, s24, w36 if ID still present	52 w	6MWT (w24)/NYHA, PGA, 6MWT, fatigue score, QoL (KCCQ, EQ5D) in w6,12,24,36,52, Death or hospitalization	Improved 6MWT (w24). Improved PGA (from w12), NYHA class (from w24), fatigue (from w12), QoL (from w12). Improved hospitalizations due to HF worsening
EFFECT-HF (2017)	172	NYHA II/III LVEF < 45% Elevated NPs pVO2 10-20 ml/ kg/min	Ferritin < 100 µg/l, or Ferritin 100–300 µg/l and TSAT < 20%	< 15 mg/dl	1 (IV FCM): 1 (PL)	According to BW, Hb	500-2000 mg in 2 doses (d0, w6)	500 mg w12 if ID still present	24 w	Change in pVO2/Hematinic markers, NYHA, NPs, PGA	Improved pVO2 with imputation of deaths Improved NYHA, PGA.
IRONOUT-HF (2017)	225	NYHA II-IV LVEF < 40%	Ferritin 15–100 µg/l, or Ferritin 100–300 µg/l and TSAT < 20%	9–15 mg/dl (male) 9–13,5 mg/dl (female)	1 (oral iron polysaccharide):1 (PL)	NR	150 mg bid		16 w	Change in pVO2/6MWT, NTproBNP, KCCQ.	No significant differences

HF: Heart failure, LVEF: left ventricular ejection fraction, pVO2: peak oxygen consumption, TSAT: tranferin saturation, ID: iron deficiency, NYHA: New York Heart Association, Hb: haemoglobin, FCM ferric carboxymaltose, PL: placebo, MLHF: Minnesota Living with Heart Failure questionnaire, KCCQ: Kansas City Cardiomyopahty Questionnaire, PGA: Patient Global Assessment, 6MWT: 6 min walking test, NTproBNP: N-terminal pro-brain natriuretic peptide, NPs: natriuretic peptides, QoL: quality of life.

the use of oral iron therapy for the correction of iron deficiency in patients with HFrEF. In contrast to previous studies with intravenous iron repletion, oral iron therapy produced minimal improvement in iron stores, implicating the route of administration rather than the strategy of iron repletion led to lack of clinical benefit. The significant relationship between higher baseline hepcidin levels and lack of iron repletion provides mechanistic insight into this study's observed findings. The trial has also been criticized for limited true iron deficiency based on only minor decrease of median baseline TSAT value of the population.

5.3. Guidelines recommendations for ID

Based on the above mentioned data, the current 2016 ESC HF guidelines recommend the use of IV FCM for the treatment of iron deficiency in CHF in order to alleviate HF symptoms, and improve exercise capacity and quality of life (class of recommendation IIa, level of evidence A) [8]. Of note, the negative trial of oral iron and the meta-analysis on mortality and morbidity had not been published at that time and their results had not been incorporated in the ESC guidelines.

In the same direction, but with a more strict class of recommendation, the ACC/AHA/HFSA 2017 guidelines have recently included the use of intravenous iron replacement to improve functional status and quality of life (class of recommendation IIb, level of evidence B) [9].

Furthermore, the Canadian Cardiovascular Society (CCS) and the National Heart Foundation of Australia also support the use of intravenous iron to improve symptoms and quality of life (strong class of recommendation, moderate quality of evidence) [11,19]. The CCS, based on a previous meta-analysis, gives the same recommendation for reducing HF hospitalizations as well. It remains to be seen if the more recent meta-analysis and the results of ongoing trials will add the indication of hospitalization reduction in other society guidelines in Europe and US. The guidelines recommendations are summarized in Table 4.

6. Practical considerations for intravenous iron treatment with FCM

Despite the universal agreement on the recommendation of using intravenous iron in iron depleted CHF patients, HF physicians are still not very familiarized with all practical.

issues, concerning an entirely non cardiovascular drug. However, they are responsible for screening, diagnosing and treating ID. The first practical guidance based on the ESC HF 2016 guidelines has just been published, addressing the approach of patients with ID in a stepwise manner [37].The use of FCM, which is the only IV iron formulation to date to have been studied in this setting, should become more convenient, but always within a scientific setting.

6.1. Patients' profile

According to the ESC HF 2016 guidelines, ID should be screened for the initial evaluation of a HF patient (class I, LOE C) [8]. Obviously, ID can appear during the course of HF, so it should be re-evaluated, as a routine screening at least once a year, or more often if the patient complains of exercise intolerance and fatigue. Based on the inclusion criteria of the published trials using FCM, patients with chronic HF and LVEF < 45%, who remain symptomatic (NYHA II/III) despite optimal medical treatment, or device implantation if applicable (mostly cardiac resynchronization.

therapy), for at least 3 months should be screened for ID. It is noteworthy that in some cases, beta blockers (BB) are not up-titrated due to exercise intolerance and fatigue, symptoms that can be related to ID as well. Correcting ID in this setting may facilitate BB up-titration. The proposed screening and treatment algorithm is depicted in Fig. 2.

Table 4
Recommendations for iron substitution in chronic heart failure.

	Recommendation	Class	Level	Ref
ESC HF 2016	Intravenous FCM should be considered in symptomatic patients with HFrEF and ID[a] in order to alleviate HF symptoms, and improve exercise capacity and Quality of life.	IIa	A	8
ACC/AHA/HFA 2017	In patients with NYHA class II and III HF and intravenous iron replacement might be reasonable to improve functional status and QoL	IIb	B	9
CCS 2017	IV iron therapy be considered for patients with HFrEF and iron deficiency[a], in view of improving exercise tolerance, quality of life, and reducing HF hospitalizations	Strong	Moderate	10
National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand 2018	In patients with HFrEF associated with persistent symptoms despite optimized therapy, iron studies should be performed and, if the patient is iron deficient[b] intravenous iron should be considered, to improve symptoms and quality of life.	Strong	Moderate	11

[a] It is defined as ferritin < 100 μg/l, or ferritin levels between 100-299 μg/l and TSAT < 20%
[b] It is defined as ferritin < 100 μg/l, or ferritin levels between 100-300 μg/l and TSAT < 20%

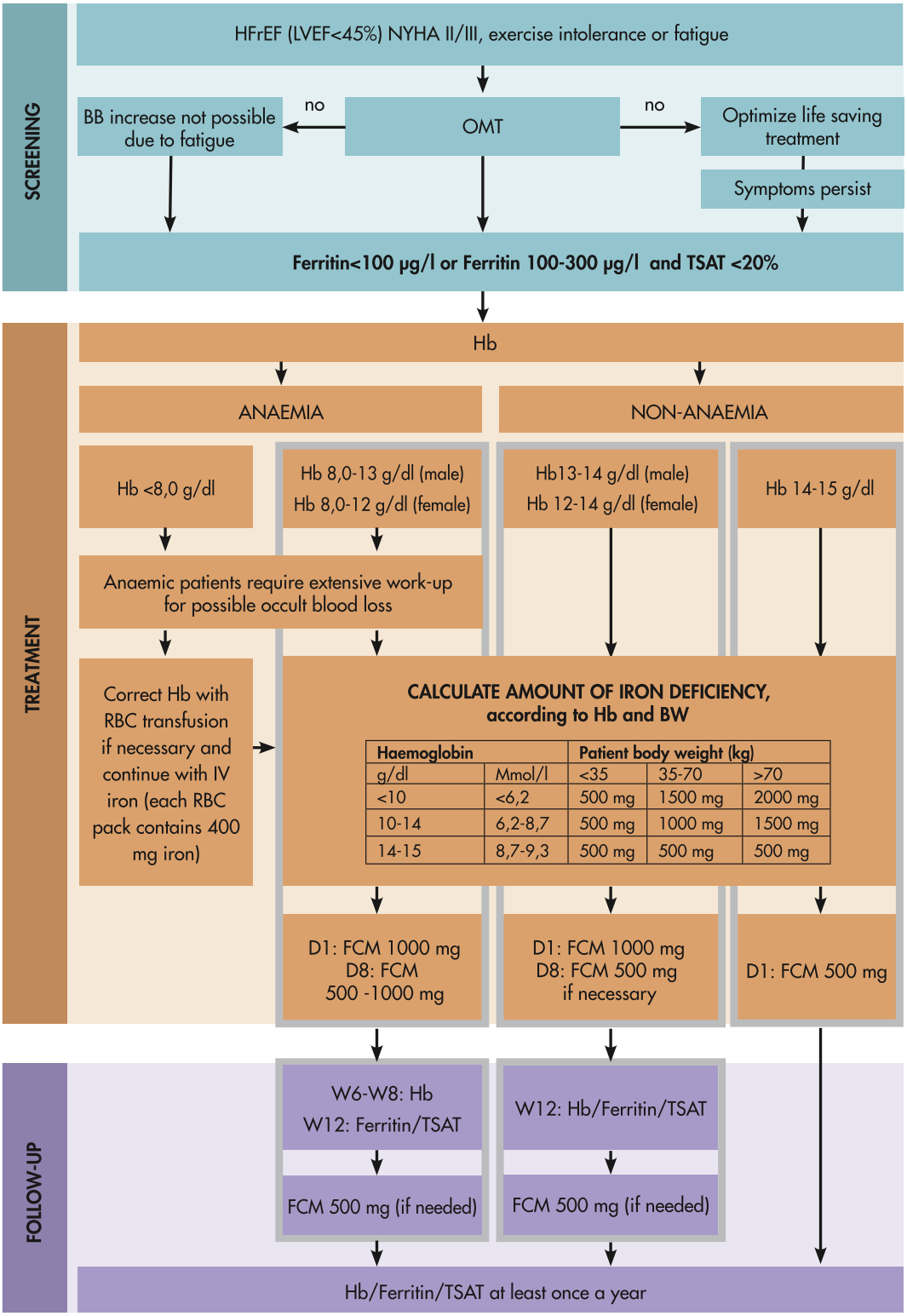

Fig. 2. Proposed algorithm for the management of ID in HF.
HFrEF: Heart failure with reduced ejection fraction, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, OMT: optimal medical treatment, Hb: haemoglobin, BB: beta blocker, BW: body weight, RBC: red blood cells, FCM: ferric carboxymaltose.

6.2. Screening markers

ID in all clinical trials and society guidelines is defined as ferritin < 100 µg/l or ferritin 100–299 µg/l and TSAT < 20%. For the time being, these are the two markers that we ought to use, for screening and treating ID. Whether TSAT alone can better direct ID treatment, since it is better correlated with iron stores, remains to be determined.

6.3. How do we proceed

It is very important to screen all patients for ID irrespective of

haemoglobin levels, or other indices from the blood count. Hb levels determine the following work-up and management. In FAIR-HF, patients enrolled had Hb levels between 9,5 g/dl and 13,5 g/dl. In CONFIRM-HF though, there was an extended range of Hb levels allowed (no lower limit except if requirement of transfusion, upper limit of 15 g/dl).

Our working group supports ID correction according to CONFIRM-HF inclusion and exclusion criteria and splits the population according to the anemia status. In case of severe anemia, red blood cell (RBC) transfusions may be necessary especially in life threatening conditions. After correction of severe anemia, or in case of iron deficient anemia (IDA), an extensive work-up for occult causes of blood loss or other causes of anemia should be performed, before or in parallel with ID correction.

In case of ID without anemia we should proceed with ID correction. If Hb > 15 mg/dl no data support iron supplementation.

The total amount of iron deficit can be calculated based on body weight (BW) and Hb levels [37]. The calculated deficit can be administered in one or two doses, one week apart. FCM can be administered either as slow bolus injection or as an infusion (≥ 15 min). The maximum single dose is 1000 mg/week (15 mg/kg for bolus, 20 mg/kg for infusion). The drug should not be overdiluted, since this affects drug stability (500 mg should be diluted in a maximum of 100 ml sodium chloride 0.9%). Patients should be monitored for potential side effects for 30 min post infusion. The most common side effects are dizziness, headache, hypertension, hypophosphataemia, injection-site reactions, and nausea. The risk of hypersensitivity reactions with IV FCM is low, with a frequency (events/patients treated) of ≥0,1% to < 1,0% observed during clinical trials and post-marketing surveillance, in contrary to traditional iron formulations which reported increased risk of anaphylaxis.

FCM is contraindicated in cases of known hypersensitivity to the substance or to other iron formulations, in cases of anemia not due to iron depletion and in cases of iron overload.

6.4. Follow-up

In anemic patients, reassessment of Hb levels should be performed within 1–2 months and not earlier, since erythropoiesis normally begins 2–3 weeks after iron supplementation. In case of a non-responding patient, physicians should check ferritin again and re-evaluate the cause of anemia.

In non-anemic patient, reassessment of ferritin and/or TSAT should be performed not earlier than 3 months. If performed earlier, ferritin may be falsely high due to an inflammatory status (being an acute phase protein)c and not related to true iron stores. If ID is present, re-administer 500 mg FCM.

7. Conclusion

ID represents a HF comorbidity that requires screening and special intervention, as IV iron replenishment in the form of FCM has been shown to improve exercise capacity, QoL and possibly hospitalization rates. All CHF patients, irrespective of Hb levels, should be checked for ID based on ferritin and/or TSAT values. ID should be treated with IV iron, while per os formulations have not shown efficacy in HF patients. The experience gained derives mostly from trials using Ferric Carboxymaltose, which is the proposed drug in ESC HF 2016 guidelines.

There are still no data concerning the screening and treatment of ID in the acute HF setting (awaiting results of the ongoing AFFIRM-AHF trial) and in populations with HFpEF (awaiting results the FAIR-HFpEF study). Trials designed to address the impact of IV iron on mortality and morbidity are also currently ongoing (FAIR-HF2, HEART-FID, IRONMAN).

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CC: received honoraria for lectures and advisory boards from Novartis, Servier, Roche diagnostics and Genesis Pharma.
TAG: received honoraria from Genesis Pharma
GrGi: received honoraria from Genesis Pharma
GeGi: received lecture honoraria and/or advisory boards from Genesis Pharma, Novartis, Servier, ELPEN Pharmaceuticals, Roche, Pfizer
AK: received honoraria for lectures and advisory boards from Novartis, Servier, Roche diagnostics and Genesis Pharma
CP: received honoraria from Genesis Pharma
SP: received honoraria for lectures from Novartis
DT: received honoraria from advisory board from Genesis Pharma
JP: received honoraria for lectures and advisory boards from Novartis, Servier, Roche diagnostics and Genesis Pharma.

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