Chronic Heart Failure: Clinical Implications of Iron Homeostasis Disturbances Revisited

Leonardo P. Suciadi 1, Joshua Henrina 2, Iwan Cahyo Santosa Putra 3, Irvan Cahyadi 1, Hoo Felicia Hadi Gunawan 3

1. Cardiology, Siloam Hospitals Kebon Jeruk/Siloam Institute, Jakarta, IDN 2. Family Medicine, Balaraja Public Health Center, Tangerang, IDN 3. Research, Siloam Heart Institute, Jakarta, IDN

Abstract
Iron deficiency is prevalent in chronic heart failure (CHF) patients. Nonetheless, the diagnosis is often overlooked and, often, the treatment is commenced just when overt anemia has ensued. Therefore, a better appreciation of this disease is needed, and all seasoned cardiologists should know how to approach CHF patients with iron deficiency correctly, as mandated by clinical practice guidelines. In this comprehensive review, we describe iron homeostasis, the pathophysiologic changes of iron homeostasis, and the clinical implications of iron deficiency on CHF patients. In addition, we delineate the evolution of clinical trials, ranging from the inception to the ongoing clinical trials of iron deficiency treatment in CHF patients. Iron deficiency contributes to the worse clinical outcome of the patients. Numerous studies have reported the clinical benefit of iron supplementation, particularly in intravenous preparation, in heart failure patients regarding symptoms, functional capacity, and quality of life (QoL) improvement. Therefore, the current guidelines recommend routine screening of iron status in all newly diagnosed heart failure patients. Eventually, intravenous iron replacement is recommended for symptomatic heart failure patients with iron deficiency, irrespective of anemia.

Introduction And Background
Heart failure is one of the most important cardiovascular diseases owing to its significant impact on mortality, morbidity, hospitalization rates, and quality of life (QoL) [1]. Despite advancements regarding therapy in the fields of cardiovascular medicine in the past decade, the mortality and morbidity due to heart failure remain high. Generally, the prognosis of chronic heart failure (CHF) patients is dismal, and in comparison to other diseases, such as colorectal, breast, and prostatic cancer, its mortality is higher [2]. According to the Atherosclerosis Risk in Communities Cohort Study, mortality rates attributed to heart failure at 30 days, one year, and five years post-hospitalization were 10.4%, 22%, and 42.3%, respectively [3]. Heart failure is a clinical syndrome caused by structural abnormality and/or ventricles systolic or diastolic dysfunction, which renders the inability of heart tissues to meet and maintain metabolic demands due to inadequate systemic and peripheral oxygenation [4]. Presently, it is known that heart failure is a progressive disease caused by complex systemic mechanisms that include substrate abnormality of the myocardium, maladaptive compensation, and amplification [2,5]. Furthermore, sympathetic nerve activation and catecholamine release, renin-angiotensin-aldosterone system (RAAS), and inflammatory cytokines also play essential roles in the heart failure mechanisms [5-6]. Consequently, other than causing myocardial damage and injury, these maladaptive systemic responses inflict damage and disturbances to the vascular endothelium, kidney, skeletal muscles, bone marrow, lungs, and liver. These systemic pathomechanisms will manifest clinically as heart failure syndromes with their respective potential comorbidities in the course of illness. Various comorbidities and complications that accompany CHF will ultimately influence the progressivity, clinical symptoms, and prognosis of heart failure [4,7].

Iron deficiency is one of the comorbidities worthy of recognition in CHF patients and holds a promising and potential treatment target [8]. However, its diagnosis is often overlooked because of nonspecific findings on clinical examination and only to be explored once it culminates with anemia. Therefore, laboratory workup is needed to assess several parameters of body iron status to establish the diagnosis of iron deficiency [9]. Routine screening for iron deficiency in CHF patients is endorsed in major clinical practice guidelines for cardiologists [4,10].

Iron homeostasis derangement is a common event in chronic diseases, especially CHF [11]. Several pieces of research have shown that iron deficiency is prevalent in this disease, even without overt anemia. A cohort involving 1506 CHF subjects reported that the prevalence of iron deficiency is 50%, and, astoundingly,
45.6% of them are not anemic [12]. The predisposing factors and major predictors of iron deficiency in CHF patients are not fully elucidated, particularly in the non-anemic population. This issue is compounded by the scarcity of clinical research data or studies that included only a small number of subjects that show the correlation of several iron deficiency parameters and CHF [8].

Another controversy is whether low serum iron is a consequence of protracted CHF or a comorbid factor that influences CHF’s progressivity. Moreover, the diagnostic utility of serum iron monitoring in non-anemic CHF populations is not extensively studied and rarely checked in clinical practice.

**Review**

**Cardiomyocyte’s metabolism and energetics in chronic heart failure**

The process of energy metabolism in cardiomyocytes proceeds in three stages, i.e., substrate uptake and utilization, energy generation through oxidative phosphorylation, and energy transfer through creatinine kinase. Any derangement of these steps will ultimately cause contractility dysfunction. In CHF, several principal components needed for cardiomyocytes’ energy metabolism are downregulated [13]. A study of cardiomyocyte energetics in advanced heart failure patients showed that the total concentrations of adenosine triphosphate (ATP)/adenosine diphosphate (ADP)/adenosine monophosphate (AMP), creatinine kinase activity, creatine phosphate, creatine phosphokinase, and creatine phosphate/ATP ratio were decreased [14]. Nevertheless, these alterations are not clearly distinguished whether they were biomarkers or the cause of progressivity of left ventricular dysfunction in heart failure.

In a physiologic condition, the primary substrate for cardiomyocyte’s energy metabolism is the oxidation of fatty acids in the mitochondria [15]. The involved gene in this energy utilization pathway is regulated primarily by fatty acid-activated peroxisome proliferator-activated receptors (PPARs) and the PPAR-gamma coactivator-1α (PGD-1α). In an experimental animal model of heart failure, energy utilization via fatty acid oxidation was decreased due to the downregulation of genes that regulates fatty acid metabolism. Thus, in heart failure, there is a shift in substrate utilization by cardiomyocytes to glucose and energy generations via glycolysis, which decreases ATP production [13-14]. Therefore, modulation of intracellular energy metabolism is a novel and promising target in the treatment of heart failure [16].

Other causes of diminished cardiomyocyte ATP production are the abnormality of mitochondrial structures and functions. Evidence points out that in dilated cardiomyopathy, hibernating myocardium, and advanced heart failure, the mitochondria were smaller and fragmented. Furthermore, mitochondria in failing heart cardiomyocytes experienced an imbalance in dynamics between mitochondrial fusion and division [17]. The reduction of mitochondrial fusion will lead to reduced oxygen consumption and impairment of energy metabolism in the cardiomyocytes of a failing heart. In addition, it also contributes to cell death via apoptosis and/or mitophagy [17-18].

Several studies have shown that mitochondrial dysfunction played a prominent role in the progressivity of heart failure [19]. Therefore, a novel approach of mitochondrial biogenesis stimulation to increase intracellular mitochondrial concentration and the elimination or inhibition of reactive oxygen species (ROS) and to maintain mitochondrial iron homeostasis is a promising and potential therapeutic for CHF. Hopefully, it will improve cellular energy metabolism and augment myocardial contractility performance [19].

**Iron metabolism and regulation**

Iron is an essential micronutrient and plays a multitude of functions in all of the human cells, which are metabolic and cellular proliferation, hemoglobin synthesis, DNA synthesis, oxygen transport and reserve, a cofactor of oxidative reaction, and cellular electron transfer. Moreover, iron plays a crucial part in a myriad of cellular enzymes, including the cytochrome system in mitochondria [20]. On the other hand, unbound iron is poisonous and harmful for human tissues because it can precipitate a chemical reaction that produces reactive oxygen species such as singlet oxygen and hydroxyl radical (OH-) [21]. Fortunately, the human body is equipped with a strict iron homeostasis regulatory mechanism that simultaneously assists cellular physiology and prevents unnecessary toxicities [22].

The total iron in the human body is approximately 3-4 grams, and it varies between genders and ages. Erythrocytes and turnover products from erythrocytes destruction constitute two-thirds of the total body iron, and the rest is stored in the form of ferritin/hemosiderin. Therefore, erythrocytes dominate the total human body iron in the form of hemoglobin (Table 1) [23]. Approximately, only 1-2 mg of absorbed iron from the gastrointestinal tract entered the circulation [11,23]. Excessive or insufficient amounts of iron in the human body will interfere with the normal functions of the human organs.
Iron content (mg) adult man, 80 kg

| Source: [13] |
|-------------|

| Iron distribution in the human body |
|------------------------------------|
| Source: [13] |

Mg = Milligrams, Kg = Kilograms

| TABLE 1: Iron content (mg) adult Woman, 60 kg |
|----------------------------------------------|

| Iron content (mg) adult Woman, 60 kg |
|-------------------------------------|
It has been previously mentioned that the circulating iron binds with a glycoprotein called transferrin. The majority of iron-transferrin complexes will get into the bone marrow and will be utilized for erythropoiesis [31]. The turnover rates of these complexes depend on the plasma iron level and the bone marrow erythropoiesis activity. The average clearance half-life of these complexes was 60–90 minutes, although the half-life will be shortened with an increased erythropoiesis rate and in the setting of iron deficiency [31].

Moreover, circulating iron-transferrin complexes will interact with specific transferrin receptors [24,32]. To date, two types of transferrin receptors have been discovered, which are transferrin receptor 1 (TFR1) and TFR2. These receptors are ubiquitously found in the human cells, including cardiomyocytes and hepatocytes, but the majority are found on the surface of erythroblasts in the bone marrow. TFR1 is a functional transferrin receptor in erythroblasts and is involved in erythropoiesis, whereas the TFR2 is abundant on hepatocyte surfaces with unknown iron uptake functions [33].

The interaction between iron-transferrin complexes and their corresponding receptors will cause endocytosis and internalization of the complexes within endosomes. In erythroblasts, the iron component will subsequently be utilized for heme synthesis, whereas transferrin will be returned into the circulation [24,33]. Afterward, the synthesized iron in the form of hemoglobin will be returned into the circulation as erythrocytes. The excess iron not needed for erythropoiesis will bind with apoferritin, forming ferritin, which is in charge of cellular iron storage, and some of the iron integrate as an enzyme component responsible for cellular metabolism [24-27]. The liver is the primary organ of iron storage, and excess iron is stored in the form of ferritin and hemosiderin [24].

Hepcidin, a peptide that regulates systemic iron metabolism, is a negative regulator that restricts gastrointestinal iron absorption and prevents its release from the reticuloendothelial system [23-24,28-29]. In a state of iron excess, hepcidin synthesis will be increased, and because it is an acute-phase protein, its level will rise in an inflammatory state. On the other hand, the genetic and expression abnormality of hepcidin is attributed to iron deposition in the tissues or hemochromatosis in the state of excess iron [34].

The role of myoglobin in cellular energy metabolism

Myoglobin is a cytoplasmic hemoprotein consisting of a single polypeptide of 154 amino acids. It is structurally and functionally similar to hemoglobin. The concentration of myoglobin varies among species and tissue. Myoglobin, as a cellular component in the human body, is abundantly found within the cardiomyocyte and oxidative skeletal muscle fiber [35].

Myoglobin has an essential role in cardiac and skeletal muscle physiological function. It plays an important role at the cellular level, especially in oxidative metabolism and to bind, transport, and store oxygen intracellularly [36]. Heme residue, which consists of a complex of porphyrin ring and iron ion, is a vital component of myoglobin [37]. Thus, iron is a necessary component for myoglobin function. Furthermore, the intracellular concentration of myoglobin correlates with oxidative enzyme activity, capillary density, and mitochondrial density [35]. The concentration of intracellular myoglobin can increase along with the increase of physiologic demand and ischemic conditions.

Myoglobin is the most critical protein component of muscle to keep oxygen storage (oxymyoglobin/MbO2). Myoglobin also plays a role as intracellular partial oxygen pressure (PO2) through its capacity as an oxygen reservoir and transport in tissue. This buffer function allows intracellular concentration to remain reasonably constant and homogeneous despite an increase in muscle activity, permitting an optimal oxidative metabolism within mitochondria [37]. The myoglobin function of the PO2 buffer is achieved through a mechanism of PO2 gradient regulation and oxygen transport from the sarcolemma to the mitochondria.

Myoglobin participates in facilitating oxygen diffusion to mitochondria, thus increasing oxygen influx to mitochondria, other than through a simple diffusion process [35-36]. The outer membrane of mitochondria has an unusually low resistance towards oxygen flow. Therefore, only a low pressure of oxygen is necessary for oxygen to flow towards mitochondria. Oxygen pressure around the outer membrane of mitochondria and the aid of myoglobin in oxygen diffusion ensure the availability of oxygen to oxidase cytochrome in normal cardiac conditions [38].

Another study reported the function of myoglobin as a cellular antioxidant through its ability to bind to nitric oxide (NO), a molecule with both an advantageous and a disadvantageous cellular effect [39]. NO can inhibit cytochrome C oxidase, disrupting mitochondrial respiration. It has a vasodilatory effect in cardiac blood vessels and a depressant effect in myocardial contractility. Myoglobin binds to NO through two different reactions, a direct interaction of MbO2 with NO, which then forms methemoglobinemia, and a nitrosylation of myoglobin deoxygenase (Mb), which then forms an intermediate compound of MbNO before reacting farther with oxygen [40]. This clearance mechanism of NO will attenuate the bioactivity of intracellular NO, particularly in the myocardium. Myoglobin also has a peroxidase activity, supporting the role of myoglobin as an antioxidant [37].
A study on mice found a shift of myocardial metabolism from fatty acid to glucose in myoglobin-deficient mice. This shift in metabolism happens as a compensatory mechanism, as myoglobin plays a part in the binding and facilitation of fatty acid diffusion through sarcoplasm [35]. Other animal studies found significant myocardial dysfunction in a low cellular MbO2 concentration [35-36]. In myoglobin deficient mice, even when sarcomere structure and mitochondrial content are normal, there were lower cellular and molecular adaptive response towards relative hypoxia. Consequently, this condition inevitably leads to myocardial contractility dysfunction with subsequent left ventricular failure [41].

**Pathomechanism of iron homeostasis in chronic heart failure**

Disruption of iron homeostasis is often found in various chronic diseases with systemic manifestation, such as connective tissue disease, inflammatory bowel disease, chronic kidney disease, including CHF [42]. Furthermore, the cause is multifactorial and causes both absolute and functional iron deficiency. Mesenteric congestion and hypoperfusion are common manifestations of heart failure, resulting in anoxia and low nutritional intake, edema, and intestinal cell dysfunction. These cause an exaggerated intestinal villi degeneration that culminates with loss of iron through the gastrointestinal tract [32,43]. This condition ultimately ends with an absolute iron deficiency in heart failure patients, marked by a decrease in circulating and reserved iron [43]. Moreover, the increased pro-inflammatory cytokines in CHF patients disturb iron regulation and homeostasis, resulting in functional iron deficiency [37].

In an exaggerated inflammatory state, the concentrations of hepcidin will rise. This acute-phase protein is solely responsible for functional iron deficiency by reducing ferroportin expression, limiting gastrointestinal tract iron absorption, iron redistribution from circulation to tissue iron reservoir, and iron retention within the reticuloendothelial system [33]. Numerous inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), and other acute-phase reactants also play a part in an iron regulation disturbance in chronic inflammation [44].

In the early stage of CHF, circulating iron decreased by 15%-30%. In comparison, the tissue iron reservoir or ferritin can increase by 24% [43]. This situation reflects on iron dysregulation and functional iron deficiency in CHF. Moreover, as heart failure progressed, the iron reserve will concurrently decrease, signifying absolute iron deficiency [45].

A low circulating iron level consequently disrupts active erythropoiesis in bone marrow, causing anemia. Moreover, iron deficiency exclusively can also cause organ dysfunction without full-blown anemia. A previous study found that cardiomyocyte’s iron content is decreased in CHF patients because of neurohormonal activation, which reduces mRNA expression, downregulates Tfr1, and ultimately prevents iron uptake [46]. Low cardiomyocyte iron levels result in lower myoglobin concentration, which functions as a tissue iron reservoir and a facilitator in cellular energy metabolism [46]. This condition has the potential to further cause dysfunction in mitochondria and cellular energy metabolism.

Dysfunctional cardiomyocyte’s cellular metabolism relating to iron deficiency can potentially cause cardiomyocyte contractility dysfunction [46]. The decreased cardiomyocytes’ myoglobin content, hence, reduced cellular antioxidant capacity, is one factor contributing to cardiac fibrosis and myocardial depression [37]. Long-standing iron deficiency positively correlates with myocardial fibrosis’s progressivity, left ventricular systolic dysfunction, and the clinical course of heart failure [47]. The pathomechanisms of iron deficiency in heart failure patients are summarized in Figure 1.
Clinical implication of iron deficiency in chronic heart failure

Studies in the past decade have found that iron deficiency is important comorbidity often found in CHF [48]. However, proper evaluation and management of iron deficiency in CHF are frequently disregarded when not accompanied by anemia. Furthermore, iron deficiency without anemia symptoms is unspecific, causing it to be easily overlooked. Therefore, a systematic evaluation of various laboratory indicators is necessary to diagnose iron deficiency [49].

The prevalence of iron deficiency in CHF regardless of anemia is relatively high, around 30-50% [12,48,50]. A cohort of 1506 systolic heart failure patients reported that iron deficiency is more commonly found in patients with anemia (61.2%) while the prevalence is also high in patients without anemia (45.6%). Other predictors of iron deficiency in CHF include female gender, higher New York Heart Association (NYHA) functional classification, higher N-terminal pro-brain-type natriuretic peptide (NT-proBNP) level, and lower erythrocyte mean corpuscular volume [12]. Another study also showed that iron deficiency is more commonly found in patients with higher high-sensitivity C-reactive protein (hs-CRP) levels [48]. Meanwhile, there was no significant correlation between antiplatelet and anticoagulant use with the incidence of iron deficiency in CHF patients [43].

Iron deficiency is also thought to contribute to the progressivity of structural dysfunction and remodeling in CHF. In an experimental animal model of iron deficiency studied for 12 weeks, it was found that there were left ventricular dilatation, mitochondrial macro-structure abnormalities, sarcomere structure irregularities, and an increase in oxidative stress response, including an increase in mitochondrial Cyt c and reactive nitrogen species (RNS) [51].

Several studies in the last few years reported the link between iron deficiency and worse clinical outcomes in CHF patients. Univariate and multivariate analysis in 546 systolic heart failure patients, ranging from mild to severe delineated iron deficiency as a strong independent predictor towards mortality and heart transplant [12,48]. Another study in 157 patients with CHF also supported the data finding iron deficiency to increase mortality rate, independent of anemia [43]. Furthermore, iron deficiency in CHF also contributes to poorer QoL. It impacts aerobic capacity, endurance, physical activity, and work performance [27,43]. It is also attributed to cognitive, behavioral, and emotional dysfunction [52]. Lastly, CHF patients with iron deficiency have been reported to have a tendency for psychological and emotional disorders [52].
Owing to the significant impact of CHF on mortality, morbidity, and QoL, the issue of iron deficiency should not be underestimated, and adequate therapy with proven clinical efficacy and safety needs to be known by all cardiologists. Thus, we summarized the relevant evidence from randomized clinical trials and systematic reviews/meta-analyses. Numerous studies have demonstrated the clinical benefit of intravenous iron administration in CHF patients. A randomized clinical, prospective, double-blind study by Toblli et al. reported that the intravenously administered iron sucrose (5 doses, 200 mg each week) lowers NT-proBNP and CRP levels significantly compared with placebo [53]. The subjects were 40 systolic heart failure patients (ejection fraction <35%) with anemia, iron deficiency (serum ferritin <100 µg/L and/or transferrin saturation <20%), and mild renal dysfunction. The duration of observation was six months. The iron sucrose group also exhibited a substantial improvement in their NYHA functional class, Minnesota Living with Heart Failure (MLHF) score, 6-minute walk test (6MWT) distance, and ejection fraction.

The Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF) study, a large scale clinical trial of intravenous iron administration in chronic heart failure study, compared intravenous FCM preparation administration from placebo in a prospective, randomized, double-blind, multicenter trial of 459 heart failure patients with the NYHA functional class of II–III [54]. Iron deficiency is defined as a ferritin level of <100 µg/L or ferritin level between 100-299 µg/L with transferrin saturation of <20%. Subjects consist of patients with or without anemia, with a hemoglobin level between 9.5 and 13.5 g/dL. The correction phase of 200 mg of intravenous FCM administration weekly occurs for eight to 12 weeks. Then it is followed by a maintenance phase of 200 mg intravenous FCM administration every four weeks. At the end of the 24-week monitoring, the group with intravenous iron had a significant increase in hemoglobin and serum ferritin levels. This increase in iron level is also accompanied by clinical improvement in heart failure patients, including improvement in symptoms, improvement in functional capacity (50% in the iron group and 28% in the placebo group; p<0.001), QoL in relation to personal health, and 6MWT distance [54]. This clinical improvement is found in patients with or without anemia, even though hemoglobin levels did not change after intravenous iron administration in the non-anemic subgroup.

Then, after four years of hiatus regarding iron therapy clinical trials in CHF patients, several studies started to emerge. The IRON-HF study in 2013 was a multicenter, randomized, double-blind, placebo-controlled trial that aimed to compare the effects of intravenous iron versus oral iron supplements in anemic heart failure patients [55]. The interventions given were intravenous iron sucrose 200 mg once a week for five weeks, oral ferrous sulfate 200 m, three times daily for eight weeks, or placebo. It was found that intravenous iron seems to be superior in improving the functional capacity of heart failure patients with an increment of 3.5 ml/kg/min in peak oxygen consumption in the intravenous iron group and no increment in peak oxygen consumption in the oral iron group.

Ferric Carboxymaltose (FCM) Evaluation on Performance in Patients with Iron Deficiency in Combination with Chronic Heart Failure (CONFIRM-HF) in 2015 was a multicenter, double-blind, double-blind, placebo-controlled trial that enrolled 304 symptomatic, iron-deficient HF patients to assess the potential long-term impact of intravenous iron therapy [56]. Patients were randomized to treatment with intravenous iron of FCM or placebo over one year. Treatment of symptomatic, iron-deficient HF patients with FCM over one year resulted in sustainable improvement in functional capacity, symptoms, and QoL as assessed by an improvement in NYHA class, patient’s global assessment, QoL score, and fatigue score. In addition, treatment may also be associated with a risk reduction of hospitalization for worsening heart failure.

A study in CHF patients with chronic kidney disease and iron deficiency anemia as comorbid conditions demonstrated the benefit of 200 mg/week intravenous iron administration for five weeks to improve cardiac structure and function, aside from clinical improvement [57]. By the end of the six months evaluation period, subjects with iron therapy displayed significant progress in heart failure symptoms, NYHA functional class, NT-pro-BNP level, hemoglobin level, transferrin saturation, and ferritin level. Iron therapy also improved on left ventricular function and structure, which were demonstrated by echocardiography parameter changes, including a decrease in left ventricular diastolic diameter (LVD), left ventricular systolic diameter (LVXd), left posterior ventricular wall (LVPW), and left ventricular ejection fraction. A decline in inflammatory status was assessed by CRP levels, reflecting the positive response towards iron therapy. Thus, this study supports the hypothesis that cardiac function improvement has a parallel relationship with iron status in CHF patients.

The Effect of FCM on Exercise Capacity in Patients with Iron Deficiency and Chronic Heart Failure (EFFECT-CHF) [58] study in 2017 was a prospective randomized controlled, multicenter, open-label trial with blinded endpoint evaluation. They aimed to examine the effect of treatment with intravenous FCM compared with standard care, on exercise capacity in patients with symptomatic CHF and iron deficiency in 172 patients with systolic heart failure (left ventricular ejection fraction <45%) and mild to moderate symptoms despite optimal heart failure medication. After 24 weeks of FCM administration, it was found that the peak oxygen consumption had significantly decreased in the control group compared with the FCM group. The patients’ global assessment and NYHA functional class improved in the FCM group.

The European Society of Cardiology in 2016 recommended that iron status should be evaluated as part of the initial work-up of all newly diagnosed heart failure patients [4]. Ferritin and transferrin saturation are
blood markers that can be used for the diagnosis of iron deficiency. Iron deficiency is treated based on a serum ferritin level of <100μg/L or 100–299μg/L when transferrin saturation is <20%. Ferritin and transferrin saturation testing should be performed simultaneously and evaluated together. Current treatment options to correct iron deficiency in the general population are intravenous or oral iron. In symptomatic patients with systolic heart failure (LVEF >40%), iron deficiency is treated with intravenous FCM. Similarly, the American Heart Association in 2017 also recommended that in heart failure patients with NYHA class II and III, and iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation is <20%), intravenous iron replacement might be reasonable to improve functional status and QoL [59].

The iron preparation recommended for CHF patients is in the form of intravenous iron [8]. The use of oral iron preparation has limitations such as limited effectiveness, limited absorption, gastrointestinal side effects, and the potential for interaction with heart failure medications. In the functional iron deficiency setting, intravenous iron has better effectiveness than the oral counterpart [60]. The Ganzoni formula has been used to calculate the amount of iron deficiency and the total dose of iron supplementation needed [61]. Total iron dose (mg) = weight (kg) x [15 - actual hemoglobin (g/dL)] x 2.4 + 500.

Table 2 and Table 3 summarize other completed and ongoing clinical trials, respectively.

| Title | First Author | Type | Diagnosis | Operational Definition | Number of patients | Randomization group | Dosage | Duration | Outcome |
|-------|--------------|------|-----------|------------------------|--------------------|---------------------|--------|----------|---------|
| Beneficial Effects of Long-Term Intravenous Iron Therapy with Ferric Carboxymaltose in Patients with Symptomatic Heart Failure and Iron Deficiency | Porto Piconelli, 2015 | Multi-centre, double-blind, placebo-controlled trial | HF patients | HF patients: 1) Stable ambulatory HF patients with NYHA II or III, with LVEF ≤45%, and elevated iron deficiency: a) Serum ferritin level <100 ng/mL or between 100 and 300 ng/mL if TSAT <20% (2) 212224. DOI 10.7759/cureus.21224 Intravenous FCM 200 mg weekly 364 152-152 (FCM vs Placebo) | 364 | 152-152 (FCM vs Placebo) | Intravenous FCM 200 mg weekly | 52 weeks | PE 1. Improved 6MWT distance significantly at week 24 SE 1. Improved NYHA class 2. Improved PGA 3. Improved QoL 4. Improved Fatigue Score |
| Changes in Echocardiographic Parameters of Iron Deficiency Patients with Heart Failure and Chronic Kidney Disease Treated with Intravenous Iron | Jorge E Toblii, 2015 | Double-blind, randomized, placebo-controlled study | HF, CKD, and iron deficiency anemia | HF/EF: 1) LVEF < 30% 2) NYHA IV/III 3) Receiving optimal treatment for HF CKD 4) GPOD = 90 mL/min iron deficiency anemia 1) Hb < 12g/dL (men) and Hb < 11.5g/dL (female) 2) Serum ferritin = 100 ng/mL and TSAT = 20% | 60 | 1:1 (IS vs Placebo) | IV iron sucrose (IS) treatment 200 mg/200 mL weekly | 25 weeks | ↓ 1. LVEF (p=0.01) 2. Improved in NYHA functional class (p=0.01) 3. LVEF and LVGT (p<0.01) 4. Not significantly change in LVPW (p=0.027) 5. Not significantly change in LVFS (p=0.09) 6. ↓Hb, ferritin and TSAT (p=0.017) 7. ↑ Inflammatory marker (p=0.017) 8. ↓ BMI (p=0.015) |
| Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Chronic Heart Failure and Iron Deficiency | Dirk J. von Veldhuisen, 2017 | Prospective randomized controlled, multicenter, open-label trial with blinded endpoint evaluation | HF, CKD and iron deficiency anemia | HF/EF: 1) LVEF ≤45% and had to be performed in ≥3 months of screening 2) LVEF ≤45% and ≥3 months after failure to eligible β-blocker therapy or device implantation 3) BNP > 100 ng/mL or NT-proBNP > 450pg/mL 4) NYHA class III–IV iron deficiency anemia: a) Serum ferritin = 0 – 300 ng/mL 2) TSAT ≤20% | 172 | 1:1 (FCM vs Placebo) | Day 0 1) Hb ≤14 g/dL → 1000 mg FCM (30 mL), whereas patients 2) Hb >14 g/dL → 500 mg FCM (10 mL) Week 8 1) Hb <10 g/dL , +70 g/kg → second dose of 500 mg FCM, 70 g/kg → second dose of 500 mg FCM Week 12 2) Hb >14 g/dL → second dose of 500 mg FCM 3) Hb <14 g/dL → no additional dose Week 12 serum ferritin was <100 ng/mL or ferritin was 100 to 300 ng/mL with TSAT ≥20% → first dose of 500 mg FCM | 24 weeks | PE: not significantly change in peak VO2 (P=0.12) SE: 1. LVEF (p=0.12) did not significantly change 2. Improved NYHA functional class (p=0.01) 3. Hb, ferritin and TSAT (p=0.03) 4. Patient’s global assessment (p=0.03) |
| Effect of Oral Iron Replacement on Exercise Capacity in Patients with Heart Failure With Reduced Ejection | Gregory D. First, 2017 | Prospective randomized controlled study | HF, CKD and iron deficiency anemia | HF/EF: 1) LVEF ≤45% and had to be performed in ≥3 months of screening 2) LVEF ≤45% and ≥3 months after failure to eligible β-blocker therapy or device implantation 3) BNP > 100 ng/mL or NT-proBNP > 450pg/mL 4) NYHA class III–IV iron deficiency anemia: a) Serum ferritin = 0 – 300 ng/mL 2) TSAT ≤20% | 225 | 111-114 (Oral iron vs Placebo) | Oral iron polysaccharide 150 mg twice daily | 16 weeks | PE: not significantly change in peak VO2 (P = 0.46) SE: not significant changes in 6-minute walk distance, NT-proBNP |

Table 2 and Table 3 summarize other completed and ongoing clinical trials, respectively.
TABLE 2: Summary of Completed Clinical Trials

| Study | Principal Investigator Start date | Estimated study completion date | Study design | Subjects | Intervention | Control | Duration of observation/Intervention | Primary Outcomes | Secondary outcomes |
|-------|-----------------------------------|---------------------------------|-------------|----------|-------------|---------|-----------------------------------|-----------------|-------------------|
| HF    | Julio Nunez, 2020                 |                                  | Investigator-initiated, multicenter, double-blind, randomized clinical trial | HF/EF: functional class II–IV 50% (Stage 1) | iv FCM (Placebo) | 24–28 days | iv FCM 1000 mg before discharge | PE: not significantly change in LVEF (P = 0.40) | iv FCM 1000 mg before discharge |
| HF    | Dr. O.B. Ambrose, 2010            |                                  | Randomized, double-blind, placebo-controlled study | HF/EF: class II–IV with LVEF ≥ 40% | iv FCM (Placebo) | 21–28 days | iv FCM 1000 mg before discharge | PE: not significantly change in LVEF (P = 0.40) | iv FCM 1000 mg before discharge |
| HF    | Dr. O.B. Ambrose, 2010            |                                  | Randomized, double-blind, placebo-controlled study | HF/EF: class II–IV with LVEF ≥ 40% | iv FCM (Placebo) | 21–28 days | iv FCM 1000 mg before discharge | PE: not significantly change in LVEF (P = 0.40) | iv FCM 1000 mg before discharge |
| HF    | Dr. O.B. Ambrose, 2010            |                                  | Randomized, double-blind, placebo-controlled study | HF/EF: class II–IV with LVEF ≥ 40% | iv FCM (Placebo) | 21–28 days | iv FCM 1000 mg before discharge | PE: not significantly change in LVEF (P = 0.40) | iv FCM 1000 mg before discharge |
| HF    | Dr. O.B. Ambrose, 2010            |                                  | Randomized, double-blind, placebo-controlled study | HF/EF: class II–IV with LVEF ≥ 40% | iv FCM (Placebo) | 21–28 days | iv FCM 1000 mg before discharge | PE: not significantly change in LVEF (P = 0.40) | iv FCM 1000 mg before discharge |
| HF    | Dr. O.B. Ambrose, 2010            |                                  | Randomized, double-blind, placebo-controlled study | HF/EF: class II–IV with LVEF ≥ 40% | iv FCM (Placebo) | 21–28 days | iv FCM 1000 mg before discharge | PE: not significantly change in LVEF (P = 0.40) | iv FCM 1000 mg before discharge |
| HF    | Dr. O.B. Ambrose, 2010            |                                  | Randomized, double-blind, placebo-controlled study | HF/EF: class II–IV with LVEF ≥ 40% | iv FCM (Placebo) | 21–28 days | iv FCM 1000 mg before discharge | PE: not significantly change in LVEF (P = 0.40) | iv FCM 1000 mg before discharge |
| HF    | Dr. O.B. Ambrose, 2010            |                                  | Randomized, double-blind, placebo-controlled study | HF/EF: class II–IV with LVEF ≥ 40% | iv FCM (Placebo) | 21–28 days | iv FCM 1000 mg before discharge | PE: not significantly change in LVEF (P = 0.40) | iv FCM 1000 mg before discharge |
| HF    | Dr. O.B. Ambrose, 2010            |                                  | Randomized, double-blind, placebo-controlled study | HF/EF: class II–IV with LVEF ≥ 40% | iv FCM (Placebo) | 21–28 days | iv FCM 1000 mg before discharge | PE: not significantly change in LVEF (P = 0.40) | iv FCM 1000 mg before discharge |
| HF    | Dr. O.B. Ambrose, 2010            |                                  | Randomized, double-blind, placebo-controlled study | HF/EF: class II–IV with LVEF ≥ 40% | iv FCM (Placebo) | 21–28 days | iv FCM 1000 mg before discharge | PE: not significantly change in LVEF (P = 0.40) | iv FCM 1000 mg before discharge |
| HF    | Dr. O.B. Ambrose, 2010            |                                  | Randomized, double-blind, placebo-controlled study | HF/EF: class II–IV with LVEF ≥ 40% | iv FCM (Placebo) | 21–28 days | iv FCM 1000 mg before discharge | PE: not significantly change in LVEF (P = 0.40) | iv FCM 1000 mg before discharge |

HF = Heart Failure; HHEF = Heart Failure Reduced Ejection Fraction; NYHA = New York Heart Association; LVEF = Left Ventricular Ejection Fraction; ADHF = Acute Decompensated Heart Failure; TSAT = Transferrin Saturation; Hb = Hemoglobin; 6MWT = 6 Minute Walk Test; PE = Primary Endpoint; SE = Secondary Endpoint; NT-proBNP = N Terminal-pro Brain Natriuretic Peptide; BNP = Brain Natriuretic Peptide; BMI = Body Mass Index; KCCQ = Kansas City Cardiomyopathy Questionnaire; QoL = Quality of Life; PGA = Patient Global Assessment; RR = Respiratory Rate; ADP = Adenosine Diphosphate; VAS = Visual Analog Scale; VO2 = Rate of Oxygen; LVDD = Left Ventricular Diastolic Dysfunction; LVSD = Left Ventricular Systolic Dysfunction
| Trial ID | Stage | Principal Investigator | Start Date | End Date | Intervention Details | Primary Outcome Measures |
|----------|-------|-----------------------|------------|----------|----------------------|--------------------------|
| FAIR-HF2 | [7]   | Maler, Kaseke, MD     | February 7, 2017 | December 2021 | Double-blind, parallel-group, randomized, controlled, interventional trial | FCM 1000 mg IV, followed by an optional administration of SBE-1050 mg within the first 4 weeks, followed by administration of 500 mg FCM at every 4 months, except when hemoglobin is > 16.0 g/dL or ferritin is > 800 μg/L. | 1) Combined rate of recurrent hospitalizations for any reason and of cardiovascular death 2) Combined rate of recurrent hospitalizations for any reason and of cardiovascular death 3) Rate of recurrent carboxymaltose ferric iron deficiencies 4) Rate of recurrent HF hospitalizations 5) Rate of recurrent hospitalizations of any kind 6) All-cause mortality 7) Cardiovascular mortality 8) Changes in NYHA functional class 9) Changes in 6-minute walk test 10) Changes in EQ-SD 11) Changes in Patient Global Assessment (PGA) of wellbeing 12) Changes in renal laboratory parameters 13) Changes in cardiovascular laboratory parameters 14) Changes in inflammatory laboratory parameters 15) Changes in metabolic laboratory parameters |
| HEART-FID | [69] | Stuart Katz, PhD, Rull, MD, Morales José Luis Prof, Doehner, Wolfram MD, Ponikowski, Piotr MD, Hernandez, Karaks, MD | March 15, 2017 | August 23, 2017 | Double-blind, parallel-group, randomized, placebo-controlled study | FCM 2x15mg/kg IV (max individual dose: 750mg) 7 days apart, repeated every 4 months as indicated by iron indices | 1) Incidence of Death (Time Frame: 1 year) 2) Incidence of hospitalization for heart failure (Time Frame: 1 year) 3) Change in 6MWT distance (Time Frame: 6 months) |
| Affirm-AHF | [68] | Plok Poutkounakis, MD | April 3, 2020 | June 2020 | Randomized, parallel-group, placebo-controlled trial | HFE & Deficiency | 1) HF hospitalizations and CV death up to 52 weeks after randomization 2) HF hospitalizations or CV death 3) CV mortality 4) The composite of HF hospitalizations or CV death 5) Days lost due to HF hospitalization or CV death |
| FAIR-HF2 | [71] | Wolfram Doehner, Prof | August 2017 | July 2021 | Randomized, placebo-controlled trial | Carboxymaltose 750mg IV 15ml | The difference of 6-minute walking distance |
| PRISONER-HF | [70] | José Luis Morales, Rull, MD, PhD | August 23, 2017 | June 2020 | Randomized, placebo-controlled trial | HFE deficiency | 1) Changes in HHA functional class 2) Changes in mortality and heart failure-related hospitalization rates |

**Notes:**
- **FCM:** Ferric Carboxymaltose
- **HFE & Deficiency:** HFE gene mutation and iron deficiency
- **Normal saline solution plus oral lactose capsules:** Placebo
- **SBE-1050 mg within the first 4 weeks:** Placebo
- **6MWT:** 6-minute walk test
- **NYHA:** New York Heart Association
- **PGA:** Global Assessment
- **EQ-5D:** EuroQol-5D
- **HFrEF & Deficiency:** Heart failure with preserved ejection fraction and iron deficiency
- **HFrEF:** Heart failure with reduced ejection fraction
- **II-III heart failure:** NYHA Class II-III heart failure
- **Post-exercise phosphocreatine recovery time measured non-invasively with Cardiomyopathy Questionnaire:** Cardiomyopathy Questionnaire

**Interventions:**
- **Carboxymaltose to Improve Skeletal Muscle Metabolism in Heart Failure:**
  - Stuart Katz, MD | September 7, 2020 | August 2020 | Randomized, double-blind, interventional | Carboxymaltose 750 mg per 15 ml IV | Normal saline | 1) Changes in 6-minute walk test distance from the baseline to 4 weeks 2) Change in Kansas City Cardiomyopathy Questionnaire
| Trial | Patients With Functional Iron Deficiency [72] NCT03218384 | Dr. Harm Wienbergen | September 2020 - December 2021 | Randomized, open-label trial | HFrEF NYHA class III & IV iron deficiency | 1) Intravenous iron supplementation with Ferric carboxymaltose, subsequent (after 2 months) exercise training program 2) Exercise training program, subsequent (after 2 months) intravenous iron supplementation with Ferric carboxymaltose | 31P-magnetic resonance spectroscopy score from baseline to 4 weeks | 1) Change in 5-Minute walking distance 2) Change in New York Heart Association class 3) Change in echocardiographic ejection fraction of left ventricular function 4) Combined endpoint cardiovascular hospitalizations and death after 2 and 4 months |
|---|---|---|---|---|---|---|---|---|
| 7 | IronDeficiency [73] NCT03803111 | Essam Nan Saleeb, MD | March 25, 2019 - October 20, 2020 | Observational, cross-sectional | HF (regardless of LVEF) | Complete blood iron status | 1 year | Functional Capacity change from baseline, 12 weeks, and 24 weeks 1) Incidence of all-cause mortality up to 1-year follow-up 2) Incidence of hospitalizations due to heart failure up to 1-year follow-up |
| 8 | Iron Deficiency in Heart Failure Patients [74] NCT03883854 | - | May 15, 2019 - June 30, 2019 | Open-label diagnostic trial | HF (regardless of LVEF & iron deficiency) | Sodium Ferric Gluconate Complex 125 mg IV/day for 3-5 days | standard treatment for heart failure without IV iron | 1) Change in NYHA from baseline to 12 and 24 weeks 2) Incidence of all-cause mortality up to 1-year follow-up 3) Incidence of hospitalizations due to heart failure up to 1-year follow-up |
| 9 | IV Iron in Acute Decompensated Heart Failure [76] NCT04659333 | Mati Karkeas, MD, MBA | June 28, 2019 - June 2023 | RCT (FERRLECTR) | HF (regardless of LVEF & iron deficiency) | Bolus administration of Ferric carboxymaltose (1000 mg) followed by an optional administration of 500-1000 mg within the first 4 weeks (up to a total of 2000 mg which is in-tube) followed by administration of 500 mg at months 4 and 8, except when hemoglobin is > 16.0 g/dL, or ferritin is > 600 µg/L | i.v. NaCl according to the dosing rules for intravenous iron. | 1 year | 1) Change from baseline to week 16 in left-ventricular ejection fraction as determined by cardiac-MRI 2) Difference between treatment groups in the burden of atrial fibrillation from day 93 to 365 as assessed by a routinely implanted event recorder 3) Change from baseline to week 16 in left-ventricular ejection fraction as determined by cardiac-MRI |

**TABLE 3: Summary of Ongoing Clinical Trials**

HF = Heart Failure; HFrEF = Heart Failure Reduced Ejection Fraction; AMI = Acute Myocardial Infarction; CV = Cardiovascular; IV = Intravenous; MRI = Magnetic Resonance Imaging; NYHA = New York Heart Association; LVEF = Left Ventricular Ejection Fraction; ADHF = Acute Decompensated Heart Failure; TSAT = Transferrin Saturation; Hb = Hemoglobin; 6MWT = 6 Minute Walk Test; PE = Primary Endpoint; SE = Secondary Endpoint; NT-proBNP = N Terminal pro Brain Natriuretic Peptide; BNP = Brain Natriuretic Peptide; BMI = Body Mass Index; KCCQ = Kansas City Cardiomyopathy Questionnaire; QoL = Quality of Life; PGA = Patient Global Assessment; RR = Respiratory Rate; ADP = Adenosine Diphosphate; VAS = Visual Analog Scale; VO2 = Rate of Oxygen; LVSD = Left Ventricular Systolic Dysfunction; LVDd = Left Ventricular Diastolic Dysfunction; LVDs = Left Ventricular Systolic Dysfunction
The long-term effectiveness and safety profile of intravenous iron therapy in CHF patients with iron deficiency still need to be confirmed by future large-scale studies. Some clinical questions regarding iron therapy yet to be answered by future studies include the benefit of oral iron therapy compared to intravenous therapy, the benefit and long-term effect of iron therapy in the clinical course of heart failure [56], the use of laboratory parameters as therapeutic response assessment, and the outcome in studies with subjects on a larger scale with a more heterogeneous spread.

Conclusions
Iron deficiency is prevalent in CHF, but it is often overlooked, especially without existing anemia. This comorbid might contribute to a worse clinical outcome in patients. Numerous studies have reported the clinical benefit of iron supplementation, particularly in intravenous preparation, in HF patients with regards to symptoms, functional capacity, and QoL improvement. Therefore, the current guidelines recommend routine screening of iron status in all newly diagnosed heart failure patients. Eventually, intravenous iron replacement is recommended for symptomatic HF patients with iron deficiency, irrespective of anemia.

Additional Information
Disclosures
Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References
1. Ponikowski P, Anker SD, AHalhaf KF, et al.: Heart failure: preventing disease and death worldwide. ESC Heart Fail. 2014, 1:1-25. 10.1002/ehf2.12005
2. Hasenfuss G, Mann DL: Pathophysiology of heart failure. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 11th ed. Elsevier, Philadelphia, PA; 2019.
3. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE: Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). Am J Cardiol. 2008, 101:1016-22. 10.1016/j.amjcard.2007.11.061
4. Ponikowski P, Voors AA, Anker SD, et al.: 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016, 37:2129-200. 10.1093/eurheartj/ehw128
5. Mann DL, Bristow MR: Mechanisms and models in heart failure: the biomechanical model and beyond. Circulation. 2005, 111:2857-49. 10.1161/CIRCULATIONAHA.104.500546
6. Floras JS: Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. J Am Coll Cardiol. 2009, 54:575-85. 10.1016/j.jacc.2009.03.061
7. Katz AM: Heart failure: a hemodynamic disorder complicated by maladaptive proliferative responses. J Cell Mol Med. 2005, 7:1-10. 10.1111/j.1582-4954.2005.tb00197.x
8. Cohen-Solal A, Lecerq C, Dery G, et al.: Iron deficiency: an emerging therapeutic target in heart failure. Heart. 2014, 100:1414-20. 10.1136/heartjnl-2014-305669
9. Thomas DW, Hinchliffe RF, Briggs C, Macdougall IC, Littlewood T, Cavill I: Guideline for the laboratory diagnosis of functional iron deficiency. Br J Haematol. 2015, 161:639-48. 10.1111/bjh.13311
10. Yancy CW, Jessup M, Bozkurt B, et al.: 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/Amereican Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013, 62:e147-239. 10.1016/j.jacc.2013.05.019
11. Jankowska EA, von Haehling S, Anker SD, Macdougall IC, Ponikowski P: Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. Eur Heart J. 2013, 34:816-29. 10.1093/eurheartj/ehs224
12. Klip IT, Comin-Colet J, Voors AA, et al.: Iron deficiency in chronic heart failure: an international pooled analysis. Am Heart J. 2015, 165:575-582.e5. 10.1016/j.ahj.2015.03.017
13. Neubauer S: The failing heart — an engine out of fuel. N Engl J Med. 2007, 356:1140-51. 10.1056/NEJMra063052
14. Lygate CA, Schneider JE, Neubauer S: Investigating cardiac energetics in heart failure. Exp Physiol. 2013, 98:801-S. 10.1113/expphysiol.2012.064709
15. Wang J, Guo T: Metabolic remodeling in chronic heart failure. J Zhejiang Univ Sci B. 2013, 14:688-95. 10.1631/jzus.B1300137
16. Ardebali H, Sabbah HH, Burke MA, et al.: Targeting myocardial substrate metabolism in heart failure: potential for new therapies. Eur J Heart Fail. 2012, 14:120-9. 10.1093/eurjhf/hfr173
17. Chen L, Knowlton AA: Mitochondrial dynamics in heart failure. Congest Heart Fail. 2011, 17:257-61. 10.1111/j.1553-3059.2010.00255.x
18. Sarantitis I, Papapanoupolou P, Manouss I, Baikoussis NG, Apostolakis E: The cytoskeleton of the cardiac muscle cell. Hellenic J Cardiol. 2012, 53:567-79.
19. Bayeva M, Gherghidei M, Ardebali H: Mitochondria as a therapeutic target in heart failure. J Am Coll Cardiol. 2013, 62:147-239. 10.1016/j.jacc.2013.05.019
20. Hasenfuss G, Mann DL: The cytoskeleton of the cardiac muscle cell. Circ Res. 2007, 101:1016-22. 10.1161/01.RES.0000277489.86479.00
in anemic patients with chronic heart failure and renal insufficiency.

Toblli JE, Lombraña A, Duarte P, Di Gennaro F:

Dilation, mitochondrial ultrastructural aberrations and cytochrome c release: involvement of nitric oxide.

Dong F, Zhang X, Culver B, Chew HG Jr, Kelley RO, Ren J:

Iron metabolism: interactions with normal and disordered erythropoiesis.

Ganz T, Nemerth E: Iron metabolism.

Ebner N, von Haehling S:

Iron deficiency in heart failure: a practical guide.

Sargent PJ, Farnaud S, Evans RW: Structure/function of proteins involved in iron storage and transport.

Kohgo Y, Ikuta K, Ohtake T, Torimoto Y, Kato J: Body iron metabolism and pathophysiology of iron overload.

Brannon PM, Taylor CL: Iron supplementation during pregnancy and infancy: uncertainties and implications for research and policy.

Weiss G:

Ordway GA, Garry DJ:

Wittenberg JB, Wittenberg BA:

Maeder MT, Khammy O, dos Remedios C, Kaye DM:

Soppi ET:

Flögel U, Merx MW, Gödecke A, Decking UKM, Schrader J:

Pietrangelo A:

Okonko DO, Mandal AK, Missouris CG, Poole-Wilson PA:

Weiss G:

Okonko DO, Mandal AK, Missouris CG, Poole-Wilson PA:

Okonko DO, Mandal AK, Missouris CG, Poole-Wilson PA:

Anemia, renal dysfunction, and their interaction in patients with chronic heart failure.

Am J Cardiol. 2006, 98:391-8.

10.1093/eurheartj/ehq158

Iron status and neural functioning.

Nadadur SS, Sirisame K, Modipalli A: Iron transport & homeostasis mechanisms: their role in health & disease.

Indian J Med Res. 2008, 128:535-44.

Rishi G, Wallace DF, Subramaniam V:

10.1152/0006-2572-20040700-00004

Ganz T: Hepcidin in iron metabolism.

Curr Opin Hematol. 2004, 11:251-4.

10.1097/00062752-20040700-00004

Abbaspour N, Hurrell R, Kelishadi R: Review on iron and its importance for human health.

J Res Med Sci. 2014, 19:164-74.

Ganz T, Nemerth E: Iron metabolism.

10.1110/chejsperspect.a011668

Ebner N, von Haehling S:

10.3399/ntn.95

Sargent PJ, Farnaud S, Evans RW: Structure/function of proteins involved in iron storage and transport.

Carr Med Chem. 2005, 12:2683-93.

10.2174/092986705774462969

Pietrangelo A: Hemochromatosis: an endocrine liver disease.

Hepatology. 2007, 46:1291-301.

10.1002/hep.21886

Gros G, Wittenberg BA, Jue T: Myoglobin’s old and new clothes: from molecular structure to function in living cells.

J Exp Biol. 2010, 213:2715-25.

10.1242/jeb.045075

Garry DJ, Kanatous SB, Mannen PPA: Emerging roles for myoglobin in the heart.

Trends Cardiovasc Med. 2003, 13:111-6.

10.1016/s1050-1738(02)00256-6

O’Dwyer GA, Garry DJ: Myoglobin: an essential hemoprotein in striated muscle.

J Exp Biol. 2004, 207:5441-6.

10.1242/jeb.01172

Wittenberg JB, Wittenberg BA: Myoglobin-enhanced oxygen delivery to isolated cardiac mitochondria.

J Exp Biol. 2007, 210:2082-90.

10.1242/jeb.005947

Flögel U, Gödecke A, Klotz LO, Schrader J: Role of myoglobin in the antioxidant defense of the heart.

FASEB J. 2004, 18:1156-8.

10.1096/fj.03-1582fj

Flögel U, Mers MW, Gödecke A, Decking UKM, Schrader J: Myoglobin: a scavenger of bioactive NO.

Proc Natl Acad Sci. 2001, 16:735-40.

10.1073/pnas.98.2.735

Mannen PPA, Kanatous SB, Yuhanna IS, Shaul PW, Garry MG, Balaban RS, Garry DJ: Hypoxia-induced left ventricular dysfunction in myoglobin-deficient mice.

Am J Physiol Heart Circ Physiol. 2005, 285:H2132-41.

10.1152/ajpheart.00147.2005

Mada AI, Ughasoro MD: Anaemia of chronic disease: an in-depth review.

Med Princ Pract. 2017, 26:1-9.

10.1159/000452104

Okonkwo DO, Mandal AK, Missouris CG, Poole-Wilson PA: Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival.

Am J Cardiol. 2011, 58:1241-51.

10.1016/j.jacc.2011.04.040

Weiss G: Iron metabolism in the anemia of chronic disease.

Biochim Biophys Acta. 2009, 1790:682-93.

10.1016/j.bbadgen.2008.08.006

Nanas JN, Matsouka C, Karageorgopoulos D, et al.: Etiology of anemia in patients with advanced heart failure.

J Am Coll Cardiol. 2006, 48:2485-9.

10.1016/j.jacc.2006.08.054

Maeder MT, Khamnun O, dos Remédios C, Kaye DM: Myocardial and systemic iron depletion in heart failure implications for anemia accompanying heart failure.

J Am Coll Cardiol. 2011, 58:474-80.

10.1016/j.jacc.2011.01.059

Naito Y, Tsujino T, Matsumoto M, Sakoda T, Ohyanagi M, Masuyama T: Adaptive response of the heart to long-term anemia induced by iron deficiency.

Am J Physiol Heart Circ Physiol. 2009, 296:H585-95.

10.1152/ajpheart.00465.2008

Jankowska EA, Rozentryp P, Witkowska A, et al.: Iron deficiency: an ominous sign in patients with systolic chronic heart failure.

Eur Heart J. 2010, 31:1872-80.

10.1093/eurheartj/ehq158

Soppi ET: Iron deficiency without anemia - a clinical challenge.

Clin Case Rep. 2018, 6:1082-6.

10.1002/ccr3.1529

de Silva R, Rigby AS, Witte KK, et al.: Anemia, renal dysfunction, and their interaction in patients with chronic heart failure.

Am J Cardiol. 2006, 98:391-8.

10.1016/j.amjcard.2006.01.107

Dong F, Zhang X, Culver B, Chew HG Jr, Kelley RO, Ren J: Dietary iron deficiency induces ventricular dilation, mitochondrial ultrastructural aberrations and cytochrome c release: involvement of nitric oxide synthase and protein tyrosine nitration.

Clin Sci (Lond). 2005, 109:277-86.

10.1242/CS20040278

Beard JL, Connor JR: Iron status and neural functioning.

Annu Rev Nutr. 2005, 25:34-51.

10.1146/annurev.nutr.25.020102.075739

Toblli JE, Lombraña A, Duarte P, Di Gennaro F: Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency.

J Am Coll Cardiol. 2007, 50:1657-65.

10.1016/j.jacc.2007.07.054
54. Anker SD, Comin Colet J, Filippatos G, et al.: Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009, 361:2456-48. 10.1056/NEJMoa0908355

55. Beck-da-Silva L, Piardi D, Soder S, et al.: IRON-HF study: a randomized trial to assess the effects of iron in heart failure patients with anemia. Int J Cardiol. 2015, 188:15-22. 10.1016/j.ijcard.2013.04.181

56. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al.: Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J. 2015, 36:657-68. 10.1093/eurheartj/eht385

57. Toblli JE, Di Gennaro F, Rivas C.: Changes in echocardiographic parameters in iron deficiency patients with heart failure and chronic kidney disease treated with intravenous iron. Heart Lung Circ. 2015, 24:886-93. 10.1016/j.hlc.2014.12.161

58. van Veldhuisen DJ, Ponikowski P, van der Meer P, et al.: Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. Circulation. 2017, 136:1574-85. 10.1161/CIRCULATIONAHA.117.027497

59. Yancy CW, Jessup M, Bozkurt B, et al.: 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017, 70:776-805. 10.1016/j.jacc.2017.04.025

60. Auerbach M, Coyne D, Ballard H: Intravenous iron: from anathema to standard of care. Am J Hematol. 2008, 83:580-8. 10.1002/ajh.21154

61. Ganzoni AM: Intravenous iron-dextran: therapeutic and experimental possibilities [Article in German]. Schweiz Med Wochenschr. 1970, 100:301-3.

62. Lewis GD, Malhotra R, Hernandez AF, et al.: Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency. The IRONOUT HF Randomized Clinical Trial. JAMA. 2017, 317:1958-66. 10.1001/jama.2017.5427

63. Ambrosy AP, Lewis GD, Malhotra R, et al.: Identifying responders to oral iron supplementation in heart failure with a reduced ejection fraction: a post-hoc analysis of the IRONOUT-HF trial. J Cardiovasc Med (Hagerstown). 2019, 20:223-5. 10.2459/JCM.0000000000000756

64. Ye TJ, Yeo PS, Hadi FA, et al.: Single-dose intravenous iron in Southeast Asian heart failure patients: a pilot randomized placebo-controlled study (PRACTICE-ASIA-HF). ESC Heart Fail. 2018, 5:544-53. 10.1002/ehf2.12250

65. Charles-Edwards G, Amaral N, Sleigh A, et al.: Effect of iron isomaltoside on skeletal muscle energetics in patients with chronic heart failure and iron deficiency. Circulation. 2019, 139:2386-98. 10.1161/CIRCULATIONAHA.118.038516

66. Nüesch J, Miliana G, Cardelli L, et al.: Noninvasive imaging estimation of myocardial iron repletion following administration of intravenous iron: the Myocardial-IRON Trial. J Am Heart Assoc. 2020, 9:e014254. 10.1161/JAHA.119.014254

67. Intravenous iron in patients with systolic heart failure and iron deficiency to improve morbidity & mortality. (2021). Accessed: July 9, 2021: https://clinicaltrials.gov/ct2/show/NCT035056462.

68. Randomized placebo-controlled trial of FCM as treatment for heart failure with iron deficiency. (2021). Accessed: July 9, 2021: https://clinicaltrials.gov/ct2/show/NCT03057951.

69. Study to compare ferric carboxymaltose with placebo in patients with acute heart failure and iron deficiency. (2021). Accessed: July 9, 2021: https://clinicaltrials.gov/ct2/show/NCT02937454.

70. Effect of IV iron in patients with heart failure with preserved ejection fraction. (2020). Accessed: July 9, 2021: https://clinicaltrials.gov/ct2/show/NCT05074591.

71. Effects of iron therapy in heart failure with preserved ejection fraction and iron deficiency (PREFER-HF). (2019). Accessed: July 9, 2021: https://clinicaltrials.gov/ct2/show/NCT03833336.

72. Ferric carboxymaltose to improve skeletal muscle metabolism in heart failure patients with functional iron deficiency. (2021). Accessed: July 9, 2021: https://clinicaltrials.gov/ct2/show/NCT03218384.

73. Effects of iron therapy and exercise training in patients with heart failure and iron deficiency. (2021). Accessed: July 9, 2021: https://clinicaltrials.gov/ct2/show/NCT03803111.

74. Iron deficiency in heart failure patients. (2019). Accessed: July 7, 2020: https://clinicaltrials.gov/ct2/show/NCT03838354.

75. Study of the prevalence of iron deficiency in patients with heart failure (CARENFER IC). (2019). Accessed: July 7, 2020: https://clinicaltrials.gov/ct2/show/NCT035924258.

76. IV iron in acute decompensated heart failure. (2019). Accessed: July 7, 2020: https://clinicaltrials.gov/ct2/show/NCT04063035.

77. Iron in patients with cardiovascular disease (ICH-F2). (2019). Accessed: July 7, 2020: https://clinicaltrials.gov/ct2/show/NCT03591000.