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Management of Iron Deficiency in Chronic Heart Failure

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About the Expert



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This article provides an overview of iron deficiency in chronic heart failure including discussion of its pathophysiology and management and evidence for the use of IV iron replacement. This review is sponsored by an educational grant from Aspen New Zealand.

Anaemia is a frequent finding in patients with chronic heart failure (CHF), being present in approximately one-third of patients with CHF.¹⁻³ Anaemia in CHF increases the risk of hospitalisation and death,⁴ and also leads to substantial reductions in exercise tolerance and quality of life (QOL).^{5,6} Consequently, healthcare management costs are higher for CHF patients with anaemia than for those without anaemia.^{7,8}

The pathophysiology of anaemia in CHF is multifactorial.^{9,10} Major factors contributing to the presence of anaemia in patients with CHF involve chronic kidney disease, the renin-angiotensin system, chronic inflammation, haemodilution (due to hypervolaemia), and iron deficiency.

Iron deficiency is the most common cause of anaemia in patients with CHF,¹¹ and it is increasingly being recognised that CHF is an iron-deficient state.¹²

Iron deficiency

Studies suggest that the prevalence of iron deficiency may be as high as 30%-50% in CHF, even in the absence of anaemia.¹³ Indeed, CHF patients do not have to be anaemic to be iron deficient.¹⁴ In a large pooled cohort study that found a 50% prevalence of iron deficiency in patients with CHF, about 45% of patients were non-anaemic.¹⁵ The prevalence of iron deficiency is higher in advanced stages of CHF (NYHA class III and IV), women, and patients with high levels of inflammatory markers.¹⁴

Physiological role of iron

Iron is an important micronutrient: in addition to its primary role in erythropoiesis, iron is required for the maintenance of metabolic health.^{12,16} Not only is it critical for both oxygen transport (as a component of haemoglobin) and oxygen storage (as a component of myoglobin), iron is essential for mitochondrial function and oxidative metabolism (as a co-factor for oxidative enzymes and respiratory chain proteins), especially in the energy-demanding cardiac and skeletal muscle cells.^{12,17}

Iron deficiency in CHF

Patients with CHF are at higher risk of developing iron deficiency due to inadequate dietary iron intake, repeated venepunctures, reduced GI iron absorption, GI bleeding (often aggravated by concomitant medication), uraemia, and chronic inflammation (**Table 1**).^{17,18}

The chronic inflammatory state associated with CHF leads to increased levels of pro-inflammatory cytokines, such as interleukin-1 (IL-1) and IL-6.^{17,18} These cytokines induce the synthesis of hepcidin, a regulatory hormone that controls the amount of iron in the body (see **Diagnosis** section). Released by the liver in response to inflammatory stimuli, hepcidin inhibits the absorption of iron as well as its release from iron stores, hence restricting the availability of iron for erythropoiesis.

Definitions

Based on pathophysiological mechanisms, iron deficiency can be characterised as either absolute or functional (**Figure 1**):^{12,18,20}

- **Absolute iron deficiency:** Total body iron stores are depleted even though iron homeostasis is intact. It is usually defined as serum ferritin <100 µg/L (see **Diagnosis** section). Absolute iron deficiency is due to the pathophysiological changes in CHF that lead to impaired iron intake and iron loss.
- **Functional iron deficiency:** Iron supply is inadequate to meet the demand for erythropoiesis and other cellular functions despite normal total body iron stores. It is usually defined as transferrin saturation <20% (see **Diagnosis** section). Functional iron deficiency is due to the systemic inflammatory state (and hence increased production of hepcidin) that accompanies heart failure.

Patients with CHF are susceptible to both forms of iron deficiency.¹⁷

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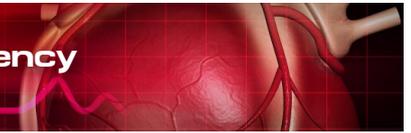
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Potential cause	Mechanism(s)
Inadequate dietary intake	<ul style="list-style-type: none"> Low protein (and thus low iron) diet Anorexia Food components interactions (e.g., phytates, oxalates, polyphenols) Drug interactions (e.g., PPIs)
Impaired GI absorption	<ul style="list-style-type: none"> Mucosal oedema (due to alteration of intestinal cell permeability) Reduced gastric emptying/modified GI motility (due to sympathetic nervous system overactivity, concomitant drugs)
Impaired GI transportation	<ul style="list-style-type: none"> Reduced expression of intestinal membrane iron transport proteins (due to increased hepcidin levels)
GI bleeding	<ul style="list-style-type: none"> Gastritis and ulcers (GI tract damage leading to iron loss via GI bleeding)
Uraemia	<ul style="list-style-type: none"> Loss of iron in protein (due to proteinuria arising from chronic renal disease)
Medication	<ul style="list-style-type: none"> Anti-platelet drugs and anticoagulants (contribute to GI blood loss) EPO-stimulating agents (increased erythropoiesis aggravates iron deficiency)
Chronic generalised inflammation	<ul style="list-style-type: none"> Increased hepcidin levels (which inhibits GI iron absorption) Impaired release of iron from storage cells (i.e. functional iron deficiency)
Venepuncture	<ul style="list-style-type: none"> Repeated venepuncture for blood tests (contributes to blood loss)

Table 1. Pathophysiology of iron deficiency in CHF: Proposed mechanisms.¹⁷⁻¹⁹ Abbreviations: EPO = erythropoietin; GI = gastrointestinal tract; PPIs = proton pump inhibitors.

Clinical consequences

Iron deficiency in CHF is associated with a worse prognosis.^{14,17} Iron deficiency reduces function and limits survival in patients with CHF, with this poor prognosis being independent of the presence of anaemia.¹⁶ The clinical consequences and symptoms of iron deficiency in patients with CHF include:^{12,13}

- Fatigue.
- Reduced exercise capacity.
- Reduced cognitive performance.
- Reduced QOL.
- Increased hospitalisation.
- Increased risk of death.

In addition to iron deficiency compromising the process of erythropoiesis, the pathophysiological consequences of impaired oxidative metabolism and energy production contribute substantially to the clinical manifestations of iron deficiency in CHF (**Figure 1**).^{12,13}

Fatigue and reduced exercise performance, the main symptoms of iron deficiency in CHF patients, are due to reduced oxygen storage in myoglobin, impaired energy efficiency, and mitochondrial dysfunction.¹³ Poorer clinical outcomes and a higher

risk of death associated with iron deficiency are due to its contribution to cardiac and peripheral muscle dysfunction. In terms of the magnitude of the increased risk of death, the presence of iron deficiency was associated with a 3-fold increase in mortality, irrespective of the presence of anaemia, in a study that prospectively assessed the clinical significance of iron metabolism in CHF patients.²¹

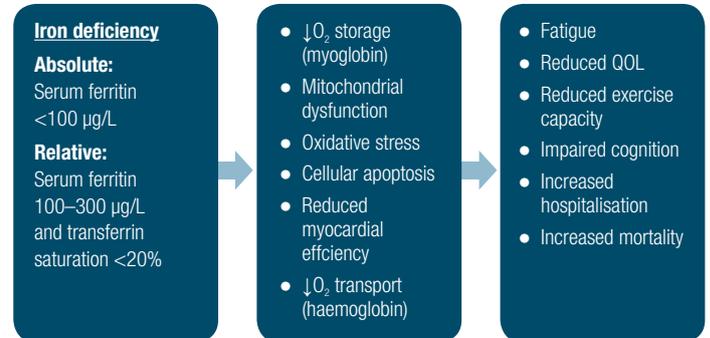


Figure 1. Summary of the definitions of iron deficiency and its pathophysiological and clinical consequences in patients with CHF.¹²

Diagnosis

The gold standard for measurement of total body iron stores and diagnosis of iron deficiency is bone marrow examination with the absence of iron granules on specific staining.^{12,20} However, this is not practical in routine clinical settings and for pragmatic reasons the use of serum markers, ferritin and transferrin saturation, is more common:

- **Ferritin:** Is an intracellular protein responsible for storing iron and its controlled release. Despite being an intracellular molecule, some ferritin is able to enter the systemic circulation and can be measured.¹² Because serum ferritin is a sensitive indicator of iron status, iron deficiency can be diagnosed when the serum ferritin level is below the assay reference range (usually 15–30 µg/L depending on assay method).
- **Transferrin:** Is a glycoprotein that is responsible for binding and transporting iron and hence acts as a marker of iron availability. Transferrin saturation (TSAT) <20% is considered the most accurate measure of functional iron deficiency as it reflects the circulating iron available for metabolism.²⁰

Measurement of serum ferritin alone cannot exclude iron deficiency in patients with CHF. Ferritin is an acute phase reactant and levels increase in response to inflammation, which complicates the diagnosis of iron deficiency.²² Inflammation also triggers an increase in hepcidin, a key regulator of iron metabolism, which results in reduced dietary iron absorption and increased iron storage. Hence, the availability of iron for erythropoiesis may be restricted in patients with CHF, despite normal or high levels of serum ferritin. The standard threshold for iron deficiency (serum ferritin <30 µg/L) therefore does not apply in an inflammatory condition such as CHF and additional testing, usually by assessment of transferrin saturation (TSAT) is required. A serum ferritin threshold of <100 µg/L or TSAT <20% can be considered diagnostic for iron deficiency in CHF. If serum ferritin is 100-300 µg/L, TSAT <20% is required to confirm iron deficiency.

Due to the inflammation associated with CHF, diagnosis of iron deficiency in patients with CHF should be based on both serum ferritin levels and TSAT as follows:²⁰

- Ferritin <100 µg/L (absolute iron deficiency); or
- Ferritin 100–300 µg/L with TSAT <20% (functional iron deficiency).

Given that many CHF patients have iron deficiency without being anaemic, it is important to screen for iron deficiency even in patients whose haemoglobin is within the normal laboratory range (as defined by the WHO): Haemoglobin <120 g/L in female and <130 g/L in male patients.^{12,23}



Oral iron therapy

Although relatively inexpensive and widely available, oral iron is unlikely to provide optimal iron replacement in the context of treating iron deficiency in patients with CHF due to oral iron being:^{12,13,18}

- Poorly tolerated because of GI adverse effects (constipation, diarrhoea, and dyspepsia), which often reduces patient adherence to treatment.
- Poorly absorbed as a result of the GI oedema and reduced GI blood flow associated with CHF and requiring a long time (>6 months) to replenish iron stores.
- Poorly absorbed because of interactions with food constituents and some medications.

Moreover, evidence from clinical studies, including a small randomised trial (IRON-HF²⁴) that compared the effects of oral and IV iron replacement on exercise capacity in iron-deficient CHF patients, suggests that oral iron therapy is unlikely to be effective in patients with CHF.^{12,25}

Australia and New Zealand 2018 guidelines practice advice:¹¹

- Oral iron supplementation is ineffective at normalising iron status or improving QOL in patients with CHF.

IV iron therapy

IV administration allows iron to bypass the GI tract so that the absorption difficulties and GI-related adverse effects associated with oral iron are avoided.^{12,18} Increasing clinical study evidence indicates that IV iron replacement is effective in iron-deficient CHF patients.

Australian and New Zealand 2018 guidelines practice advice:¹¹

- IV iron should be considered in patients with CHF associated with iron deficiency, with or without anaemia.

Iron sucrose was the subject of most early clinical studies investigating IV iron replacement in patients with CHF. These small-scale studies, which include the FERRIC-HF single-blind randomised trial in non-anaemic as well as anaemic iron-deficient CHF patients,²⁶ consistently showed the correction of iron deficiency and improved cardiac function (New York Heart Association [NYHA] functional class and left ventricular ejection fraction [LVEF]), symptoms, exercise capacity, and QOL.^{18,25}

More recent studies confirming the clinical benefits of IV iron replacement demonstrated in the earlier smaller trials have mainly involved ferric carboxymaltose.^{12,25} These larger-scale investigations include the 6-month FAIR-HF study, the longer duration CONFIRM-HF trial, which had an extended observation period of 12 months (primary endpoint result shown in **Figure 2**), and the 6-month EFFECT-HF trial, which featured exercise capacity as the primary endpoint.

Australia and New Zealand 2018 guidelines practice advice:¹¹

- IV ferric carboxymaltose was evaluated in most of the RCTs conducted to date.

Based on the evidence from FAIR-HF and CONFIRM-HF, the Australia and New Zealand 2018 guidelines for the prevention, detection, and management of heart failure, as well as other international guidelines, recommend that IV iron replacement be considered in iron-deficient CHF patients to provide symptomatic relief and improve exercise capacity and QOL.^{11,28,29} The long-term benefits of IV iron supplementation in CHF have still to be demonstrated, however, and the findings of ongoing large outcome trials with this objective are awaited.¹²

Australia and New Zealand 2018 guidelines recommendation:¹¹

- In patients with heart failure and reduced ejection fraction associated with persistent symptoms despite optimised therapy, iron studies should be performed and, if the patient is iron deficient, IV iron should be considered, to improve symptoms and QOL.

The effects of IV iron therapy on the hard endpoints of hospitalisation and mortality have been assessed in two meta-analyses of randomised clinical trials: a standard meta-analysis (5 trials; n=851)³⁰ and an individual patient data meta-analysis (4 trials; n=839).³¹ They identified statistically significant reductions in all-cause mortality, cardiovascular hospitalisation, and CHF hospitalisation associated with IV iron replacement in iron-deficient CHF patients,^{30,31} as well as statistically significant improvements in NYHA class, exercise capacity, QOL, and symptoms.³⁰ However, the reductions in mortality and hospitalisations with IV iron therapy suggested by these meta-analyses require confirmation in well-designed RCTs that have the power to detect significant differences in hard endpoints.²⁵

Safety

A meta-analysis of RCTs comparing IV iron with another comparator (oral iron, no iron, placebo, or IM iron) found that IV iron is not associated with an increased risk of severe adverse events or infections and that GI effects were reduced with IV iron.³² Subgroup analysis demonstrated a lower rate of serious adverse events when IV iron was used in patients with heart failure.

Australia and New Zealand 2018 guidelines statement on benefits and harms:¹¹

- The benefits of IV iron replacement outweigh the potential harms; however, in patients who are congested, clinicians should monitor fluid status and favour lower-volume infusion. Long-term effects are uncertain.

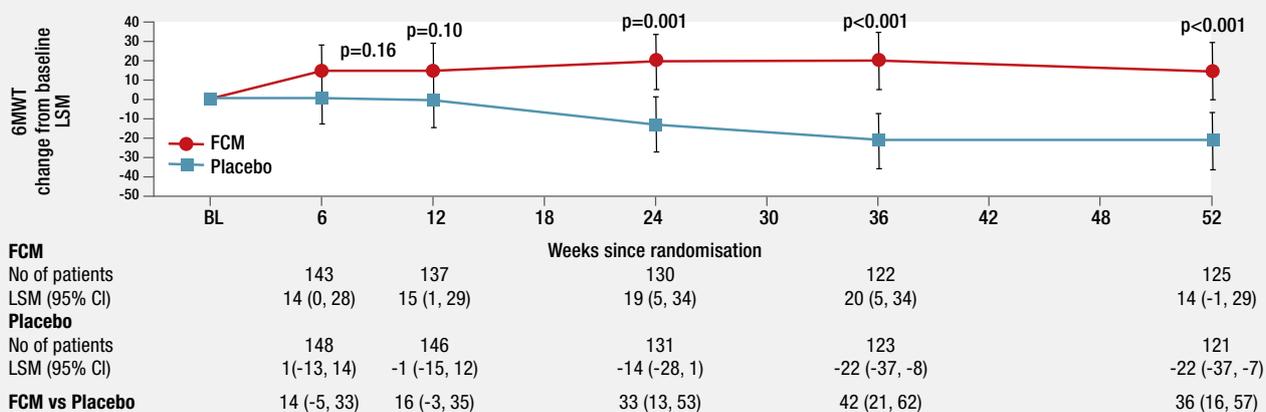
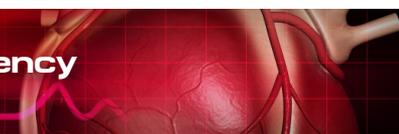


Figure 2. In the CONFIRM-HF trial, IV iron supplementation was associated with a statistically significant increase (vs placebo) in exercise capacity in CHF patients as measured by the 6-minute walk test distance test (6MWT; primary endpoint). After 24 weeks there was a 33m difference (p=0.001) in the 6MWT and after 52 weeks the difference was 36m (p<0.001).²⁷ Abbreviations: BL = baseline; CI = confidence interval; FCM = ferric carboxymaltose; LSM = least squares mean.



EXPERT'S CONCLUDING COMMENTS

IV iron therapy, specifically ferric carboxymaltose (Ferinject), now has an established place in international heart failure guidelines, including those developed by the European Society of Cardiology (ESC),²⁹ along with other evidence-based therapies.

ESC 2016 guidelines recommendation for the treatment of other co-morbidities in patients with heart failure:²⁹

- IV ferric carboxymaltose should be considered in symptomatic patients with heart failure with reduced ejection fraction and iron deficiency in order to alleviate heart failure symptoms and improve exercise capacity and quality of life.

Ferric carboxymaltose is readily available, easily administered, and well tolerated. In the New Zealand setting, it can be administered as an inpatient, day-stay ward, or in primary care. Thus, the cost and burden of hospitalisation can be reduced. Patients' well-being is often immediately and/or significantly improved in my experience. I would encourage screening for and treating iron deficiency in all heart failure patients whether anaemic or not.

TAKE-HOME MESSAGES

- Iron deficiency, with or without anaemia, may be present in as many as one in two patients with CHF.
- Iron deficiency in CHF contributes to impaired patient QOL, reduced exercise capacity, and increased mortality.
- Many patients with CHF have iron deficiency without being anaemic; hence, it is important to screen for iron deficiency even in patients with normal haemoglobin levels.
- The criteria for diagnosis of iron deficiency in CHF are: ferritin <100 µg/L (absolute iron deficiency) or ferritin 100–300 µg/L with TSAT <20% (functional iron deficiency).
 - Two different ranges are provided because ferritin is an acute phase reactant and may become elevated in the presence of CHF-associated inflammation.
- If iron deficiency is diagnosed, IV iron replacement should be considered in addition to standard CHF therapy.
- IV iron replacement improves symptoms, exercise capacity, and QOL in iron-deficient CHF patients.
- More evidence for the effects of IV iron replacement on hard endpoints (hospitalisation and mortality) and long-term clinical outcomes and safety is needed.

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