

Iron deficiency in heart failure

More than just anaemia

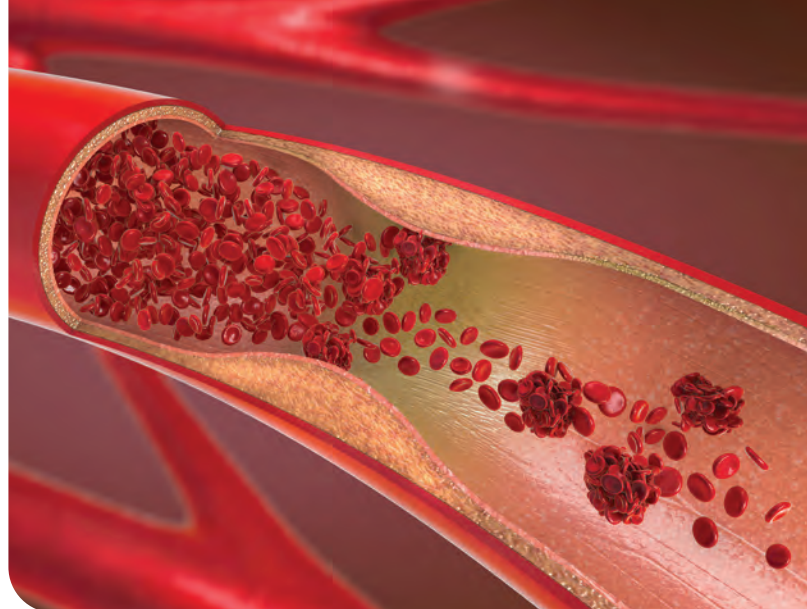
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Iron deficiency is common in patients with heart failure and is associated with poorer outcomes, irrespective of the presence or absence of anaemia. Intravenous iron replenishment in these patients improves exercise capacity, symptoms and quality of life, and likely reduces heart failure hospitalisation.

KEY POINTS

- Iron is an essential micronutrient for many cellular functions, including both haematopoietic and cellular metabolic processes.
- Iron deficiency is common in patients with heart failure and often occurs independently of anaemia, and is associated with poor clinical outcomes, including increased mortality.
- Patients with heart failure are considered iron deficient with a serum ferritin level less than 100 mcg/L, or serum ferritin level 100 to 300 mcg/L combined with transferrin saturation less than 20%.
- Intravenous iron replenishment in patients with heart failure and iron deficiency improves exercise capacity, symptoms and quality of life. Recent evidence suggests that intravenous iron replenishment likely also reduces heart failure hospitalisation and is a cost-effective treatment. Oral iron supplementation does not appear to be effective.



In 2017, more than half a million (about 511,000) people in Australia had heart failure (HF), representing 2.1% of the population, with a projected estimate of 657,000 patients by 2025.¹ However, Australian studies suggest that HF may be under-recognised in the primary care setting, contributing to lower rates of guideline-directed therapies for this vulnerable patient cohort.^{2,3} Patients with HF represent a high proportion of primary care presentations, on average visiting their GPs 12.4 times a year and representing 3.6% of all patients presenting to primary practice.^{4,5} Therefore, primary care practitioners have a unique opportunity and are well positioned to help optimise their patients' HF management.

Iron deficiency (ID) is estimated to affect 2% of men and 9% of women in developed countries.^{6,7} Patients with HF are at greater risk of ID compared with the general population, and although exact estimates vary, the prevalence of ID in the HF population ranges from 37% to 61%, depending on differences in the cohorts studied.⁸⁻¹² Patients with HF have altered iron uptake and turnover, contributing to higher rates of ID. Patients with HF and ID have a poor prognosis, associated with increased hospitalisation and mortality.^{9,11} ID is, therefore, an important therapeutic target, with intravenous iron replenishment shown to improve exercise capacity, symptoms and quality of life (QoL) and likely reduce HF hospitalisations.^{13,14}

This article discusses the mechanisms of ID in patients with HF, the role of iron in cardiac function and the evidence and guidelines supporting intravenous iron replenishment in patients with HF and ID.

Why do patients with heart failure become iron deficient?

Dietary iron is reduced to ferrous iron in the duodenal and jejunal lumen, which then enters the enterocytes, and is exported into the circulation by ferroportin, situated on the basolateral membrane of the enterocyte.¹⁵ Ferrous iron (Fe^{2+}), once it enters the circulation, is

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then oxidised to ferric iron (Fe^{3+}) and transported in the circulation, bound to plasma transferrin. This complex is then taken up by the liver, spleen and bone marrow, where it is stored as ferritin.

Hepcidin is an important small peptide that acts as a regulatory hormone to maintain iron homeostasis. Hepcidin is formed and released by the liver. The level of circulating hepcidin is increased in states of inflammation and iron overload.¹⁶ Hepcidin inhibits gastrointestinal iron absorption by binding and degrading ferroportin on the enterocyte basolateral membrane, thereby preventing the export of ferrous iron from the enterocyte into the circulation. Iron is not actively secreted; however, the action of hepcidin results in iron accumulation within the enterocyte itself, and eventual excretion via shedding of the intestinal cells. Ferroportin is also present in the macrophages of the reticuloendothelial system, where the action of hepcidin results in iron sequestration in the reticuloendothelial system and a reduction in the availability of iron for utilisation, a process known as reticuloendothelial block. This explains the reduced efficacy of oral iron supplementation in improving clinical status in patients with HF and ID.

ID may be absolute or functional. Absolute ID reflects depleted body stores and is reflected by a low serum ferritin level. Functional ID reflects the impaired availability and utilisation of iron owing to reticuloendothelial block, which is reflected by low transferrin saturation (T_{sat}).^{17,18} Patients with HF are at increased risk of both absolute and functional ID.¹⁸

HF increases the risk of ID through a number of multifactorial and complex mechanisms.^{8,19,20} First, patients with HF have reduced gastrointestinal iron uptake, mediated via poor appetite, dietary changes, gastrointestinal ischaemia or venous congestion, dysbiosis of the gut microbiome and concurrent medications, including proton pump inhibitors and histamine H2 receptor antagonists.²¹ Second, patients with HF are at risk of increased gastrointestinal losses through occult bleeding associated

with oesophagitis, gastritis, duodenitis or gastrointestinal ulceration. Importantly, although most patients with HF are on concomitant antiplatelet or anticoagulants for associated cardiovascular indications, meta-analyses have shown that this does not correlate with increased rates of ID in this population.¹² Third, and importantly, the HF syndrome is characterised by a chronic inflammatory state.^{21,22} Chronic inflammation results in high levels of hydroxyl molecules (OH^-) in the intestinal wall, which may inhibit the absorption of ferrous iron (Fe^{2+}) and its conversion to ferric iron (Fe^{3+}).

Notably, whereas hepcidin plays a key mediator role in both acute and chronic inflammation, the precise role of hepcidin in HF and ID is less clear. Studies have demonstrated that asymptomatic patients with HF have markedly increased levels of circulating hepcidin; however, with increasing HF severity, this progresses to decreased levels of circulating hepcidin, despite the presence of increased chronic inflammation.¹⁸ The reason underlying the drop in hepcidin levels in more advanced stages of HF remains unclear, but a reduced hepatic capacity to produce hepcidin may be contributory. Hepcidin may, therefore, contribute to reduced gastrointestinal iron absorption and enhanced reticuloendothelial block at certain stages of HF, but its exact role at different timepoints through the progression of HF and, particularly, its role in the more advanced stages of HF require further evaluation. Lower circulating hepcidin levels, in both acute and chronic settings, are independently associated with higher mortality in patients with HF.^{18,23}

Role of iron in cardiac function

Iron has a well-recognised role in erythropoiesis, and ID remains the leading cause of anaemia in both the developed and developing world.²⁴ Beyond its role in erythropoiesis, however, iron is also an essential micronutrient for a wide variety of cellular processes, including oxygen transport and storage, electron transfer reactions, mitochondrial respiration, gene

regulation, cellular immunity and cellular reproduction.^{25,26} The importance of iron in these extrahaematopoietic, metabolic cellular processes may explain the fatigue that occurs in non-anaemic patients with ID.²⁷ Iron has a crucial role in metabolic functioning; therefore, maintaining adequate iron availability is particularly important for cells with a high metabolic demand, such as cardiac and skeletal myocytes.⁹

Therefore, even though ID has traditionally been linked with anaemia, it is important to distinguish the two conditions and emphasise that they do not necessarily coexist. ID is substantially more prevalent than anaemia in patients with HF.²⁸ ID is also present in about 32% of patients with HF who are non-anaemic.⁹ Studies have also shown that in HF, ID is poorly linked with red cell indices, indicating that ID in these patients should be viewed independently of their erythropoietic status.^{29,30}

Diagnosis of iron deficiency in heart failure

Iron status is ordinarily assessed by measuring serum ferritin levels, with a standard threshold of less than 30 mcg/L being diagnostic for ID in the general population. This cutoff in an unselected (non-HF) population gives a sensitivity of 92% and specificity of 98% for ID, and a positive predictive value of 83%, when assessed against a gold standard of bone marrow aspirate or documented response to iron therapy.³¹

However, the interpretation of serum ferritin in inflammatory states is problematic, as ferritin is an acute-phase reactant that rises in acute inflammation. The standard cutoff of serum ferritin, therefore, becomes insensitive for ID in proinflammatory conditions such as HF. This was demonstrated in a study, wherein out of 37 patients with HF, 73% had ID as confirmed on bone marrow aspiration, despite a mean serum ferritin of 75 ± 59 mcg/L in the ID group.³² Inflammation also impairs iron availability and utilisation for red cell production, leading to reticuloendothelial

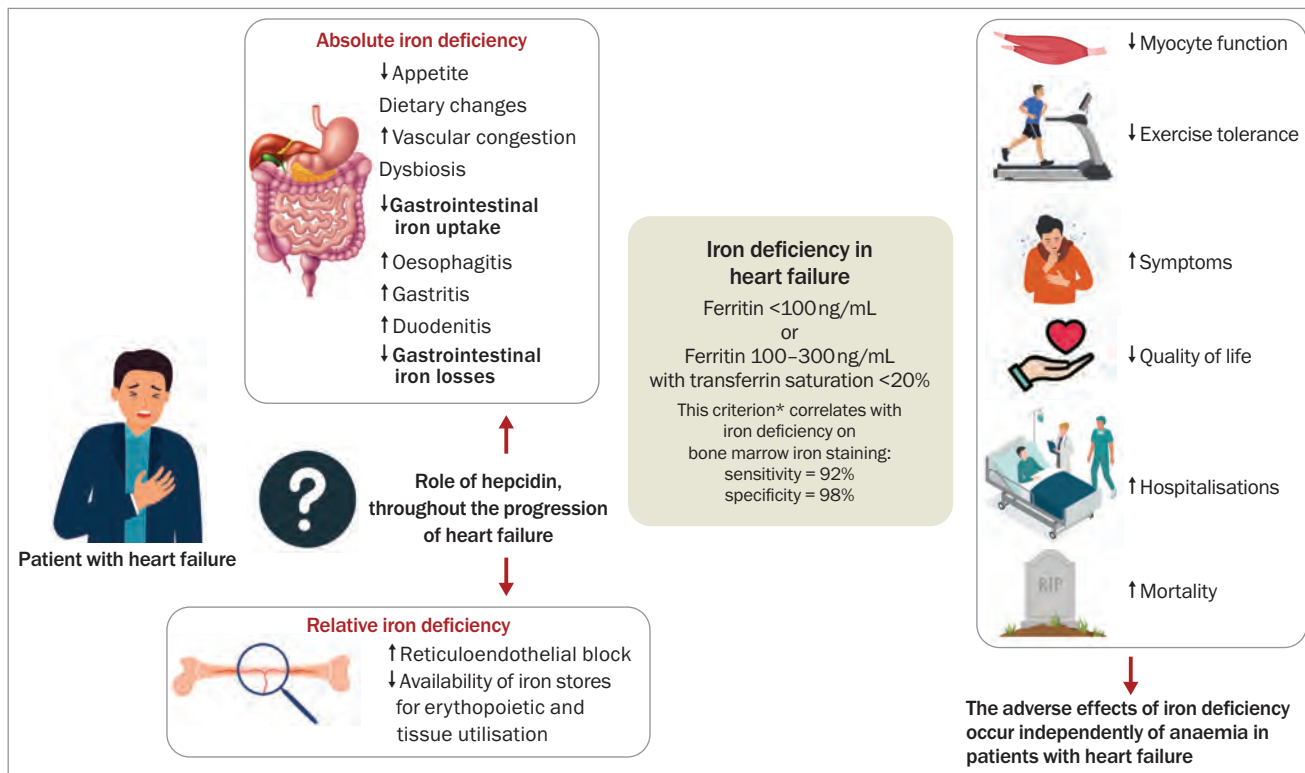


Figure. Causes and effects of iron deficiency in patients with heart failure.

Key: ↑ = increase; ↓ = decrease.

* Based on criteria as outlined in Beverborg NG, et al. *Circ Heart Fail* 2018; 11: e004519.³³

block, an iron sequestration syndrome and iron-restricted erythropoiesis, a state known as functional ID.²⁷ This is not reflected by serum ferritin levels, but rather reflected in a low T_{sat} . Currently, in patients with HF, a diagnosis of ID can be made if:

- serum ferritin level is less than 100 mcg/L (absolute ID), OR
- serum ferritin level is 100 to 300 mcg/L, combined with T_{sat} less than 20% (functional ID).

This criterion is based on cutoffs used in landmark clinical trials assessing iron replacement in patients with HF and ID (Table 1). This criterion was shown to yield a sensitivity of 82% and specificity of 72% when assessed against a gold standard of bone marrow iron staining in a cohort of patients with HF undergoing coronary artery bypass grafting surgery.³³ This criterion has since been incorporated into Australian, European, American and Asia-Pacific HF guidelines.³⁴⁻³⁷ This is also

consistent with diagnostic thresholds for ID in other chronic inflammatory conditions including chronic kidney disease and inflammatory bowel disease.²⁷

Iron deficiency in patients with heart failure is associated with poor outcomes

Findings of animal studies have suggested that ID has deleterious effects on cardiac myocyte function. A study showed that rats induced with ID anaemia developed cardiac hypertrophy by 12 weeks and left ventricular dilatation with pulmonary congestion by 20 weeks.³⁸ In rats with ID anaemia, intraperitoneal iron infusion improved exercise endurance when compared with saline placebo, independent of changes in haemoglobin levels.³⁹

Studies in human cohorts have demonstrated that ID in patients with HF is associated with a range of deleterious clinical outcomes, including poorer

exercise capacity, symptoms and QoL. A study showed that patients with HF and ID had poorer exercise capacity with lower mean oxygen consumption on cardiopulmonary exercise testing, a relationship seen independent of haemoglobin levels.⁴⁰ ID has also been shown to predict exercise intolerance, irrespective of the patient's underlying haemoglobin level or severity of HF.⁴¹ Two studies showed that ID was associated with worse QoL measures, and multivariate analysis in both these studies confirmed that ID, not anaemia, is independently associated with poorer QoL.^{42,43}

ID is associated with increased mortality in patients with HF.^{9,40} International pooled analysis showed that patients with HF and ID had significantly higher mortality at six months (8.7% vs 3.6%) and persisting out to a median follow up of 1.9 years.¹² Further, ID was shown to be an independent predictor for mortality (hazard ratio 1.42, confidence interval [CI]

1.14–1.77, $p=0.002$), whereas anaemia was not. The effects of ID in patients with HF are illustrated in the Figure.³³

Clinical trial evidence for iron replacement in patients with heart failure

Numerous randomised controlled clinical trials have been conducted to assess the role and clinical benefits of intravenous iron replacement in patients with heart failure with reduced ejection fraction (HFrEF) and ID. The key randomised control trials are summarised in Table 1.

The landmark FAIR-HF trial randomised stable, ambulatory patients with HFrEF and ID to ferric carboxymaltose or placebo.⁴⁴ The trial revealed that iron replenishment with intravenous ferric carboxymaltose improved exercise capacity (as measured by the 6-Minute Walk Test [6MWT]), symptoms (as measured based on the Patient Global Assessment [PGA] and New York Heart Association [NYHA] classification) and QoL (as measured using the Kansas City Cardiomyopathy Questionnaire [KCCQ]) at 26 weeks of follow up. These findings were confirmed in the CONFIRM-HF trial, which similarly found that iron replenishment with intravenous ferric carboxymaltose resulted in improved exercise capacity (as measured by the 6MWT), symptoms (as measured based on the PGA and NYHA classification) and QoL (as measured using the KCCQ), as well as a reduction in HF hospitalisations at 52 weeks of follow up.⁴⁵

Subsequently, more recent cardiovascular outcome trials (CVOTs) have assessed the role of intravenous iron replenishment and their effects on ‘hard’ endpoints of cardiovascular death and HF hospitalisations. These include the AFFIRM-HF, IRONMAN and HEART-FID trials.^{46–48}

The AFFIRM-HF trial randomised patients hospitalised for acute HF with ID to intravenous ferric carboxymaltose or placebo, with a primary composite endpoint of cardiovascular death and HF hospitalisation. Although the findings supported a trend of improved outcomes

in the iron treatment group, this trial narrowly failed to meet statistical significance (rate ratio [RR] 0.75, CI 0.62–1.91, not significant). The study was partially interrupted by the COVID-19 pandemic.⁴⁶

The IRONMAN trial randomised patients with a prior HF hospitalisation or elevated levels of natriuretic peptides within the preceding six months, and ID, to intravenous ferric derisomaltose or usual care (unblinded study), assessed against a primary composite endpoint of cardiovascular death and HF hospitalisation. Similarly, this trial supported a trend of improved outcomes in the iron treatment group, but narrowly failed to meet statistical significance (RR 0.82, CI 0.66–1.02, not significant), and was also partially interrupted by the COVID-19 pandemic.⁴⁷

It is prudent to acknowledge that the COVID-19 pandemic impacted the results of these two trials. Sensitivity analyses reported by both of these trials (performed by censoring patients following the COVID-19 outbreak) would have yielded nominally statistically significant primary outcomes for both trials (see Table 1, footnote).

The HEART-FID trial randomised patients with a prior HF hospitalisation or elevated levels of natriuretic peptides within the preceding 12 months, and ID, to intravenous ferric carboxymaltose or placebo, assessed against a primary hierarchical composite outcome of death, HF hospitalisation or change in 6MWT results. Although the findings supported a trend towards improved outcomes in the iron treatment group, this trial narrowly failed to meet statistical significance (unmatched win ratio 1.10, CI 0.99–1.23, not significant).⁴⁸

An individual patient data meta-analysis of the CONFIRM-HF, AFFIRM-HF and HEART-FID studies demonstrated that intravenous ferric carboxymaltose reduced one of the co-primary endpoints comprising total cardiovascular hospitalisations and cardiovascular deaths, to 52 weeks (RR 0.86, CI 0.75–0.98, $p=0.029$).¹³ This

was predominantly driven by reductions in HF hospitalisation (RR 0.84, CI 0.71–0.98, $p=0.025$) with no apparent difference in cardiovascular death. There was no significant heterogeneity in treatment effects across prespecified subgroups of age, sex and baseline serum ferritin. Of note, the IRONMAN study was excluded from this meta-analysis as the study used a different criterion for ID, the treatment included ferric derisomaltose and the study was unblinded; however, sensitivity analysis incorporating the IRONMAN study censored at 12 months also confirmed this co-primary endpoint.

No established role for oral iron replenishment

The role of high-dose, oral iron polysaccharide repletion was examined in the IRONOUT HF trial, which showed no difference in the clinical outcomes of exercise capacity (based on the peak oxygen uptake and 6MWT) or QoL (as measured using the KCCQ).⁴⁹ Furthermore, oral iron replenishment produced only minimal improvements in iron stores. Therefore, there is currently insufficient evidence to recommend oral iron replenishment in patients with HF and ID, but this is currently the subject of further study (IVOFER-HF trial 2017-005053-37).

Practical recommendations

Australian and international HF guideline recommendations for iron replacement are summarised in Table 2.

Iron studies should be conducted at the time of diagnosis of HF, and at regular intervals, including at each HF hospitalisation. Intravenous iron replenishment should be considered in patients with HFrEF, persistent symptoms and ID to improve symptoms and QoL. In the context of newer evidence, intravenous iron replenishment may reduce HF hospitalisation.¹³

Importantly, it should be noted that these recommendations for ferric carboxymaltose were first introduced to HF guidelines following the results of the FAIR-HF study, which showed an improvement in

TABLE 1. SUMMARY OF KEY RANDOMISED CONTROLLED TRIALS OF INTRAVENOUS IRON REPLENISHMENT IN PATIENTS WITH HEART FAILURE⁴⁴⁻⁴⁸

Name	Study design	Patient characteristics and key inclusion criteria	Study duration	Key outcomes
FAIR-HF 2009⁴⁴ (Anker et al., 2009)	<ul style="list-style-type: none"> Randomised, double-blinded, placebo controlled n=459 Ferric carboxymaltose (n=304) vs placebo (n=155) 	<ul style="list-style-type: none"> LVEF <45% NYHA class II–III Hb 9.5–13.5 g/dL Ferritin <100 ng/mL, or ferritin 100–299 ng/mL and T_{sat} <20% Stable ambulatory patients with HF 	26 weeks	<p><i>Primary outcomes:</i></p> <ul style="list-style-type: none"> Patient Global Assessment at week 24: improvement in 50% vs 28%, OR 2.51 (CI, 1.75–3.61), p<0.001 NYHA class at week 24: improvement OR 2.40 (CI, 1.55–3.71), p<0.001 <p><i>Secondary endpoints:</i></p> <ul style="list-style-type: none"> Change in 6MWT at week 24: +29 m vs +8 m, improvement p<0.001 QoL measured by change in KCCQ: +14 vs +6, improvement p<0.001
CONFIRM-HF 2015⁴⁵ (Ponikowski et al., 2015)	<ul style="list-style-type: none"> Randomised, double-blinded, placebo controlled n=304 Ferric carboxymaltose (n=152) vs placebo (n=152) 	<ul style="list-style-type: none"> Age >18 years LVEF <45% NYHA class II or III Hb <15 g/dL Ferritin <100 ng/mL, or ferritin 100–300 ng/mL and T_{sat} <20% Stable ambulatory patients with HF with elevated natriuretic peptide levels 	52 weeks	<p><i>Primary outcome:</i></p> <ul style="list-style-type: none"> Change in 6MWT at week 24: +18 ± 8 m vs -16 ± 8 m (difference +33 m), p=0.002 <p><i>Secondary outcomes:</i></p> <ul style="list-style-type: none"> NYHA class: improvement, p<0.001 at weeks 36 and 52 Patient Global Assessment: improvement, p=0.001 at weeks 36 and 52 QoL measured by KCCQ: improvement, p<0.05 at weeks 12, 36 and 52 Hospitalisation for worsening HF: 10 vs 42, HR 0.39 (CI, 0.19–0.082), p=0.009
AFFIRM-HF 2020^{46*} (Ponikowski et al., 2020)	<ul style="list-style-type: none"> Randomised, double-blinded, placebo controlled n=1132 Ferric carboxymaltose (n=558) vs placebo (n=550) 	<ul style="list-style-type: none"> Age >18 years LVEF <50% Hb 8.0–15.0 g/dL Ferritin <100 ng/mL, or ferritin 100–299 ng/mL and T_{sat} <20% Hospitalisation for acute HF at time of enrolment and randomisation 	52 weeks	<p><i>Primary outcome:</i></p> <ul style="list-style-type: none"> Composite of cardiovascular death and HF hospitalisation up to 52 weeks of follow up: 293 vs 372, RR 0.75 (CI, 0.62–1.01), NS* <p><i>Secondary outcomes:</i></p> <ul style="list-style-type: none"> Composite of cardiovascular death and total HF hospitalisations: 370 vs 451, RR 0.80 (CI, 0.61–1.00), p=0.050 Cardiovascular death: 77 vs 78, NS HF hospitalisations: 217 vs 294, RR 0.74 (CI, 0.58–0.94), p=0.013
IRONMAN 2022^{47*} (Kalra et al., 2022)	<ul style="list-style-type: none"> Randomised, open-label n=1137 Ferric derisomaltose (n=569) vs usual care (n=568) 	<ul style="list-style-type: none"> Age >18 years LVEF <45% NYHA class II–IV Hb <13 g/dL (female) or Hb <14 g/dL (male) Ferritin <100 ng/mL or T_{sat} <20% HF hospitalisation or elevated natriuretic peptide level within prior 6 months 	Median follow up: 2.7 years	<p><i>Primary outcome:</i></p> <ul style="list-style-type: none"> Composite of cardiovascular death and HF hospitalisation: 336 vs 411, RR 0.82 (CI, 0.66–1.02), NS <p><i>Secondary outcomes:</i></p> <ul style="list-style-type: none"> Death: 184 vs 193, HR 0.95 (CI, 0.78–1.17), NS HF hospitalisation: 250 vs 313, HR 0.80 (CI, 0.62–1.03), NS MLHFQ at 4 months: 18.2 vs 20.2, -1.16, p=0.0071 6MWT at 4 months: 286 m vs 287 m, -1.6 (CI, -28.2 to 24.9), NS
HEART-FID 2023^{48*} (Mentz et al., 2023)	<ul style="list-style-type: none"> Randomised, double-blinded, placebo controlled n=3065 Ferric carboxymaltose (n=1532) vs placebo (n=1533) 	<ul style="list-style-type: none"> Age >18 years LVEF ≤40% NYHA class II–IV Hb 9.0–13.5 g/dL (female) or Hb 9.0–15.0 g/dL (male) Ferritin <100 ng/mL, or ferritin 100–300 ng/mL and T_{sat} <20% HF hospitalisation or elevated natriuretic peptide level within prior 12 months 	Median follow up: 1.9 years	<p><i>Primary outcome:</i></p> <ul style="list-style-type: none"> Hierarchical composite of death within 12 months, HF hospitalisation within 12 months, or change in 6MWT at 6 months: unmatched win ratio 1.10, CI 0.99–1.23, NS <p><i>Secondary outcomes:</i></p> <ul style="list-style-type: none"> Composite of cardiovascular death or HF hospitalisation: 475 vs 494, HR 0.93 (CI, 0.81–1.06), NS Death: 131 vs 158, HR 0.86 (CI, 0.72–1.03), NS HF hospitalisation: 297 vs 332 Increase in 6MWT: 5 ± 71 m vs 4 ± 72 m

Abbreviations: 6MWT = 6-minute walk test; CI = confidence interval; Hb = haemoglobin; HF = heart failure; HR = hazard ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NS = nonsignificant; NYHA = New York Heart Association; OR = odds ratio; RR = rate ratio; QoL = quality of life; T_{sat} = transferrin saturation.

* The HEART-FID, IRONMAN and AFFIRM-HF trials were affected by the COVID-19 pandemic, which may have affected results. The HEART-FID study did not perform a COVID-19 analysis. The IRONMAN study reported a COVID-19 sensitivity analysis including all patients assigned until 31 March 2020 (around the start of the first national lockdown in the United Kingdom), with a censoring date at six months following this date. This analysis resulted in a nominally statistically significant finding for the primary composite outcome of cardiovascular death and HF hospitalisation: 210 vs 280, RR 0.76 (CI, 0.58–1.00), p=0.047. The AFFIRM-HF study reported a pre-COVID-19 sensitivity analysis wherein patients were censored at the date when the first COVID-19 case was reported in each participating country. This analysis resulted in a nominally statistically significant finding for the primary composite outcome of cardiovascular death and HF hospitalisations: 274 vs 363, RR 0.75 (CI, 0.59–0.96), p=0.024.

functional outcomes. They first appeared in the Australia and New Zealand Guidelines in 2011 and ESC Guidelines in 2012.^{50,51} Subsequent to this, the more recent three moderate-sized CVOTs (AFFIRM-HF, IRONMAN and HEART-FID) suggest that although iron replacement may reduce HF hospitalisation, these studies did not meet their primary endpoints and failed

TABLE 2. AUSTRALIAN AND SELECTED INTERNATIONAL HF GUIDELINE RECOMMENDATIONS FOR IRON ASSESSMENT AND THERAPY³⁴⁻³⁷

Guideline	Recommendation	Class or grade of recommendation	Level of recommendation or quality of evidence
NHFA/CSANZ 2018: <i>Guidelines for the prevention, detection and management of HF in Australia</i> ³⁴ (Atherton et al., 2018)	In patients with HFrEF associated with persistent symptoms despite optimised therapy, iron studies should be performed and, if the patient has ID (i.e. ferritin <100 mcg/L, or ferritin 100–300 mcg/L with T _{sat} <20%), intravenous iron should be considered, to improve symptoms and QoL	Strong FOR	Moderate
ESC 2021:* <i>Guidelines for the diagnosis and treatment of acute and chronic HF</i> ³⁵ (McDonagh et al., 2021)	All patients with HF should be periodically screened for anaemia and ID with a full blood count, serum ferritin concentration measurement and T _{sat} measurement	I	C
	Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic patients with LVEF <45% and ID, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with T _{sat} <20%, to alleviate symptoms, improve exercise capacity and QoL	Ila	A
	Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic patients with HF recently hospitalised for HF and with LVEF <50% and ID, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with T _{sat} <20%, to reduce the risk of HF hospitalisation	Ila	B
AHA/ACC/HFSA 2022:† <i>Guideline for the management of HF</i> ³⁶ (Heidenreich et al., 2022)	For patients who are diagnosed with HF, laboratory evaluation should include the following to optimise management: <ul style="list-style-type: none"> • complete blood count • urinalysis • measurement of serum electrolytes • blood urea nitrogen test • measurement of serum creatinine and glucose levels • lipid profile assessment • liver function tests • iron studies • measurement of thyroid-stimulating hormone levels 	1	C-EO
	In patients with HFrEF and ID with or without anaemia, intravenous iron replacement is reasonable to improve functional status and QoL	2a	B-R
APSC 2023: <i>Consensus statements on the diagnosis and management of chronic HF</i> ³⁷ (Sim et al., 2023)	Intravenous ferric carboxymaltose should be considered in symptomatic patients with HFrEF and ID (serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with T _{sat} <20%)	-	Moderate
	Intravenous ferric carboxymaltose may be considered in symptomatic patients with HFmrEF and ID (serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with T _{sat} <20%)	-	Low

Abbreviations: ACC = American College of Cardiology; AHA = American Heart Association; APSC = Asian Pacific Society of Cardiology; CSANZ = Cardiac Society of Australia and New Zealand; ESC = European Society of Cardiology; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; ID = iron deficiency; LVEF = left ventricular ejection fraction; NHFA = National Heart Foundation of Australia; T_{sat} = transferrin saturation; QoL = quality of life.

* ESC Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. Class IIa: Conflicting evidence and/or a divergence of opinion about the usefulness/ efficacy of the given treatment or procedure; weight of evidence/ opinion is in favour of usefulness/ efficacy. Level of evidence A: Data derived from multiple randomised clinical trials or meta-analyses. Level of evidence B: Data derived from a single randomised clinical trial or large nonrandomised studies. Level of evidence C: Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

†AHA/ACC/HFSA Class I: Strong. Class 2a: Moderate. Level (quality) of evidence B-R (randomised): Moderate-quality evidence from one or more randomised controlled trials (RCTs), meta-analyses of moderate-quality RCTs. Level (quality) of evidence C-EO (expert opinion): Consensus of expert opinion based on clinical experience.

to show any improvement in mortality.⁴⁶⁻⁴⁸ Guideline recommendations for iron replenishment in patients with HF and ID are, therefore, to improve symptoms and QoL, and may likely reduce HF hospitalisation, but has not been shown to improve mortality.

Intravenous administration has the advantage of bypassing the gastrointestinal tract, thereby avoiding issues with gastrointestinal uptake present in patients with HF and the consequent proinflammatory state. Ferric carboxymaltose (in Australia, Ferinject) is the formulation used in most clinical trials with evidence in the HF population.⁵²

Cost effectiveness

Cost-effectiveness analyses have suggested that intravenous ferric carboxymaltose is a cost-effective treatment when modelled in the United Kingdom, the USA, Switzerland and Italy using outcomes from the AFFIRM-AHF trial and in Sweden, Spain and South Korea when modelled on the FAIR-HF outcomes.⁵³⁻⁵⁶ No cost-effectiveness analyses have been conducted in an Australian context and this remains an opportunity for future research; however, the average cost for a HF hospitalisation in Australia has previously been reported to be \$6,699 in a HF therapy cost-effectiveness analysis.⁵⁷

Future directions and unanswered questions

First, it remains controversial how to best diagnose ID in patients with HF. Diagnostic cutoffs that are currently used are based on those used in other chronic inflammatory conditions, including chronic kidney disease and inflammatory bowel disease, and are based on the criteria used to define ID in the FAIR-HF study. However, previous work has shown that both low serum iron levels and a reduced T_{sat} may have better test characteristics (i.e. sensitivity, specificity) than the currently used definition.³³ Investigations are also continuing to examine alternative markers of iron deficiency, including

serum transferrin receptor levels and the serum transferrin receptor–ferritin index.

Second, there remains ongoing debate as to the precise role of intravenous iron replacement in patients with HFrEF and concomitant ID, particularly in light of the three recent CVOTs failing to meet the primary endpoints and failing to show benefits in terms of cardiovascular mortality. Of note, although individual patient meta-analyses of these studies suggest an improvement in heart failure hospitalisation, this is hypothesis-generating only and does not constitute a randomised clinical trial finding.

Third, the current guideline recommendations for iron replacement pre-date the results of these three CVOTs and should be interpreted in this context.

Fourth, intravenous iron supplementation is not without risk, and the potential hazards need to be considered prior to prescribing, including risks of increased allergy and infusion reactions, inflammation, infection, hypophosphataemia and concerns of oncogenesis seen in animal models.

Fifth, the cost effectiveness of intravenous iron has not been assessed specifically in the Australian context.

Sixth, the role of oral iron replenishment is not yet established. Oral iron repletion has a theoretical appeal as it is cheaper than intravenous iron, readily available, and does not bypass the hepcidin system, which physiologically maintains iron homeostasis. Therefore, serious toxicity from oral iron supplementation is exceedingly rare. However, the IRONOUT HF trial failed to show functional benefits of oral iron replenishment and showed only a minimal improvement in iron stores; thus, the role of oral iron replenishment is not yet established and warrants further investigation.⁴⁹

Finally, the role of iron replenishment in heart failure with preserved ejection fraction (HFpEF) is less clear and warrants further study. The prevalence of ID in HFpEF reaches 59%; however, studies evaluating iron replenishment in this area are lacking,

with the recently published FAIR-HFpEF trial being discontinued because of slow recruitment after only 39 patients.^{58,59}

Conclusion

Patients with HF are prone to developing ID, which may occur concurrently with, or independently of, anaemia. ID in patients with HF is associated with poor outcomes including a reduced exercise capacity, increased symptoms, reduced QoL and increased mortality. Randomised controlled trials have established that intravenous iron replacement improves exercise capacity, symptoms and QoL in patients with HF and concomitant ID. Meta-analyses have suggested that intravenous iron replenishment likely reduces HF hospitalisation. However, three recent moderate-sized CVOTs of intravenous iron replenishment failed to meet primary endpoints and did not show any improvements in mortality.

Australian and international HF guidelines currently recommend that intravenous iron replenishment be considered in patients with HF and ID. There are ongoing studies in this area to further define the role and benefits of intravenous iron replenishment. Primary care physicians have a unique opportunity and an important role in assessing and optimising their patients' HF therapies, including iron replenishment. **MT**

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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Iron deficiency in heart failure

More than just anaemia

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