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REVIEW

Iron supplementation in heart failure and iron deficiency: does it help?

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Abstract

Iron deficiency (ID) is present in 30-80% of patients with heart failure (HF) and is associated with poor prognosis. Intravenous (IV) iron therapy has been evaluated in several randomized controlled trials and consistently shown to improve functional outcomes. In FAIR-HF, 50% of patients receiving FCM achieved NYHA class improvement to I or II by 24 weeks *vs* 30% with placebo. CONFIRM-HF showed a significant 33-meter increase in 6-minute walk distance (6MWD) at 24 weeks (p=0.002), alongside improvements in NYHA class. The recent trial FAIR-HF2 demonstrated smaller but significant gains in 6MWD (+10.7 m) and global well-being at 12 months. Cardiovascular outcomes have been more variable. AFFIRM-AHF showed a 26% reduction in total HF hospitalizations (HR 0.74; 95% CI, 0.58-0.94) with IV iron *vs* placebo. Although the composite of cardiovascular death or first HF hospitalization was narrowly non-significant (HR 0.79; 95% CI, 0.62-1.01), the effect may still be clinically meaningful. IRONMAN, using ferric derisomaltose *vs* placebo, was neutral for the primary endpoint of HF hospitalization and cardiovascular death (RR 0.82; 95% CI, 0.66-1.02) but showed benefit in a COVID-censored sensitivity analysis (RR 0.76; 95% CI, 0.58-1.00). In HEART-FID, involving over 3,000 patients, no benefit was also seen with IV iron for the composite of death, HF hospitalization, and 6MWD at 99% CI, however was significant at 95% CI. FAIR-HF2 showed a 21% reduction in the primary endpoint (HR 0.79; 95% CI 0.61-1.02) with IV iron, which did not meet statistical significance, but a prespecified 12-month sensitivity analysis demonstrated a 29% reduction in first cardiovascular death or HF hospitalization (0.71 (95% CI, 0.53-0.94) and a 35% reduction in total HF hospitalizations (RR 0.65; 95% CI, 0.47-0.90). The most recent meta-analysis (n>7,000) showed a 28% reduction of composite of cardiovascular death and HF hospitalizations at 1 year (RR 0.72; 95% CI, 0.55-0.89) with IV iron. Benefits were sustained at longer term follow up and were consistent across most subgroups. The totality of evidence supports IV iron in HFrEF with ID to improve symptoms and reduce HF hospitalizations, especially in the first year. Future research should explore optimal long-term dosing, sex-specific responses, and the role of IV iron in HF with preserved ejection fraction.

Key words: iron deficiency; intravenous iron therapy; clinical trials; heart failure.

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Introduction

Heart failure (HF) is a chronic, progressive syndrome that affects approximately 1-2% of the general adult population globally, with prevalence rising to over 10% among individuals aged 65 years and older.[1] Iron deficiency (ID) is a common comorbidity in HF and is associated with a worse clinical profile, including greater symptom burden, reduced exercise tolerance, diminished quality of life (QoL), and increased rates of hospitalization and mortality.[2] The prevalence of ID in HF varies from 30-35% of patients with stable, asymptomatic chronic HF to up to 80% in acute decompensated HF.[1,3]

Iron repletion, particularly by intravenous (IV) iron, is recommended by both American and European guidelines to improve quality of life (QoL) and symptoms in patients with HF and reduced ejection fraction (HFrEF) and iron deficiency (ID).[4,5] In most clinical trials evaluating iron therapy in HF, iron deficiency has been defined using a combination of serum ferritin and transferrin saturation (TSAT) thresholds. Specifically, ID is defined as a serum ferritin concentration <100 µg/L, or a ferritin level between 100-299 µg/L in the presence of a TSAT <20%.[1,3] However, this definition has not been validated with the gold standard, which is iron staining of bone marrow biopsy, a test too invasive to be used routinely.[6] Since ferritin

may be increased in chronic inflammatory conditions such as HF, TSAT has been proposed to be a more reliable marker.

Clinical evidence of benefit

Functional outcomes

Earlier trials assessed intravenous (IV) iron therapy for its effects on exercise capacity, symptoms, and quality of life (QoL) in patients with HF and ID (Table 1). Across multiple randomized controlled trials (RCTs), particularly in those with HFrEF, IV iron -most commonly ferric carboxymaltose (FCM)- improved patient-centered functional outcomes (Figure 1).

The FAIR-HF (Ferinject Assessment in Patients With Iron Deficiency and Chronic Heart Failure) trial demonstrated that treatment with FCM in 459 ambulatory HFrEF patients led to significant improvements in New York Heart Association (NYHA) class and patient global assessment (PGA) over 24 weeks.[7] Approximately 50% of patients in the FCM group achieved NYHA class I or II compared to 30% in the placebo group, and benefits were apparent as early as week 4. This early response suggests the need for closer short-term follow-up and may support earlier reassessment of iron status to guide timely redosing. In the CONFIRM-HF (Ferric Carboxymaltose Evaluation on Performance in Patients With Iron Deficiency in Combination With Chronic Heart Failure) trial, 304 patients with symptomatic HFrEF received FCM or placebo over 52 weeks.[8] Treatment with FCM significantly improved 6-minute walk distance (6MWD) at 24 weeks (mean difference +33±11 meters; p=0.002) along with NYHA class, PGA, and QoL scores. The recently published FAIR-HF2 (Intravenous Ferric Carboxymaltose and Outcomes in Heart Failure with Iron Deficiency), which enrolled 1137 ambulatory patients with HFrEF and ID, confirmed sustained improvements in functional status.[9] Patients receiving FCM had significant improvement in 6MWD (+10.7 m; 95% CI, 1.44-22.9) and EQ-5D (EuroQol 5-Dimension) health utility score (+0.032; 95% CI, 0.008-0.057), and an improvement in PGA at 12 months. Together, these data demonstrate that IV iron improves functional capacity, symptom burden, and QoL in HFrEF patients with ID, supporting its role in the management of symptomatic disease. Conversely, there is limited data in patients with heart failure with preserved ejection fraction (HFpEF). Recently, the FAIR-HFpEF (Ferric carboxymaltose and exercise capacity in heart failure with preserved ejection fraction and iron deficiency) trial showed that FCM improved 6MWD (+45 m; 95% CI, 5-93; p=0.029) in 39 participants with HFpEF and ID, but slow recruitment led to early termination, leaving its efficacy in this population needing further evaluation.[10]

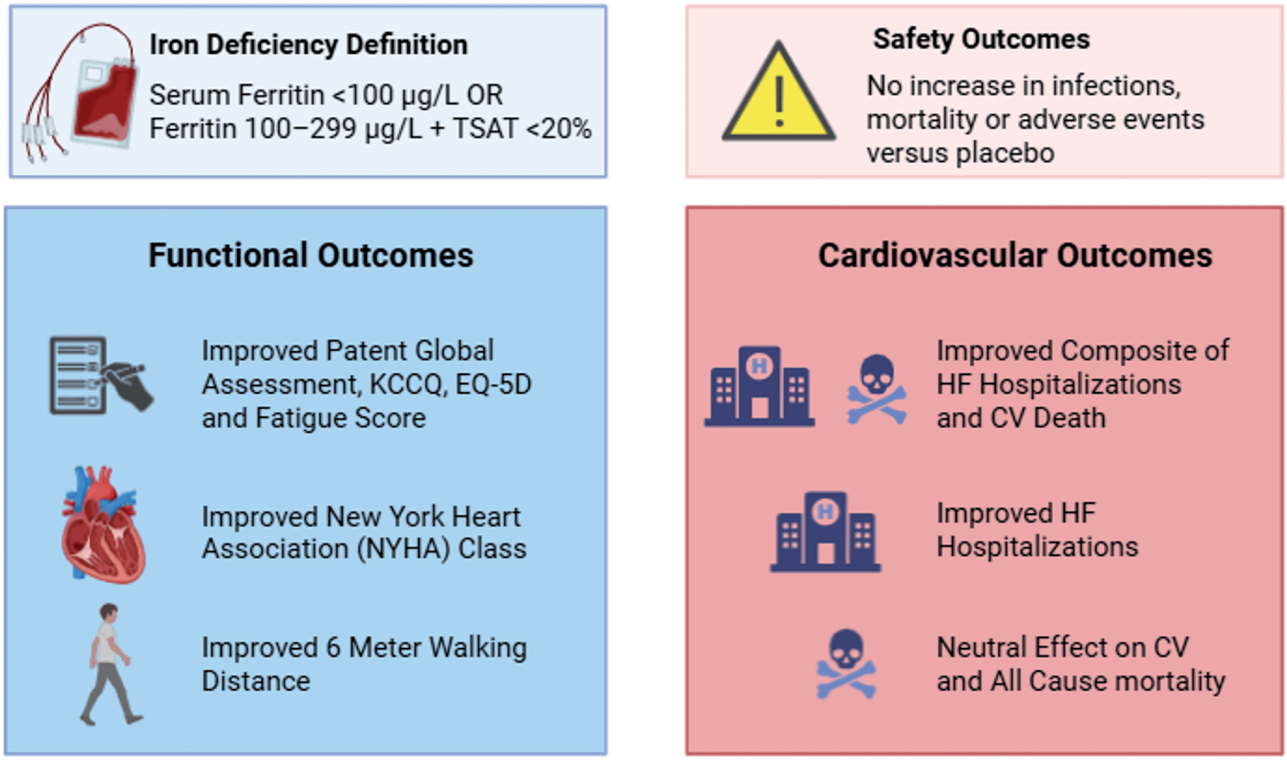

Figure 1. Intravenous iron therapy in heart failure and iron deficiency. Clinical trials have defined iron deficiency in heart failure as serum ferritin a serum ferritin concentration <100 µg/L, or a ferritin level between 100-299 µg/L in the presence of a TSAT <20%. Totality of evidence from major clinical trials and meta-analyses suggest that iron therapy in heart failure with iron deficiency is safe, improves functional outcomes, improves composite of heart failure hospitalizations and cardiovascular death, heart failure hospitalizations but have had a neutral effect on all-cause and cardiovascular mortality. TSAT, transferrin saturation; KCCQ, Kansas City Cardiomyopathy Questionnaire; HF, heart failure; CV, cardiovascular.

Table 1. Key features of major clinical trials evaluating iv iron therapy in heart failure with iron deficiency.

Trial (year)	Sample size (iron/placebo)	Population	Iron deficiency definition	Iv iron formulation and dosing	Baseline TSAT % (iron/placebo)	Baseline ferritin µg/L (iron/placebo)	Mean follow-up	Key findings
FAIR-HF (2009)	459 (304/155)	Chronic HF (NYHA II–III), LVEF ≤45%	Ferritin <100 µg/L or 100–299 µg/L with TSAT <20%; Hb 9.5–13.5 g/dL	Ferric carboxymaltose (FCM), 200 mg weekly until repletion, then every 4 weeks	17.7/16.7	52.5/60.1	6 months	PGA and NYHA class improvement, improved QoL and 6MWD
CONFIRM-HF (2015)	301 (150/151)	Chronic HF (NYHA II–III), LVEF ≤45%	Same ID criteria; Hb <15 g/dL	FCM (500–2000 mg) at baseline, with maintenance doses at 12, 24, 36 weeks	20.2/18.2	57.0/57.1	12 months	Improvement in 6MWD, NYHA class, QoL scores, reduced HF hospitalization
AFFIRM-AHF (2020)	1,108 (558/550)	Hospitalized acute HF, LVEF <50%	Same ID criteria; Hb 8–15 g/dL	FCM at discharge, week 6, then every 6–12 weeks if ID persisted	15.2/14.2	83.9/88.5	12 months	No change in composite of total HF hospitalizations and CV death, reduction in total HF hospitalization and composite of first HF hospitalization or CV death
IRONMAN (2022)	1,137 (569/568)	New or chronic HF, recent hospitalization, NYHA II-IV, LVEF ≤40%	Ferritin <100 µg/L or TSAT <20%; Hb ≤13 g/dL (women) or ≤14 g/dL (men)	Ferric derisomaltose on day 0 and 28, then every 4 months if ID persisted	15/15	49.0/50.0	32 months	No change in composite recurrent HF hospitalizations and CV death, reduction in composite of CV death or CV hospitalization
HEART-FID (2023)	3,065 (1,533/1,532)	HF hospitalization in last year, NYHA II-IV, LVEF ≤40%	Same ID criteria; Hb 9-13.5 g/dL (women), <15 g/dL (men)	FCM weekly 1500 mg, then every 6 months if ID or anemia	23.9/23.0	56.0/57.3	25 months	No change in composite of death, HF hospitalization, and change in 6MWD, no change in any other outcomes
FAIR-HF2 (2025)	1,105 (558/547)	Ambulatory chronic HF; LVEF ≤45%	Same ID criteria; Hb 9.5–14 g/dL	1000 mg FCM initially, then 500–1000 mg in 4 weeks, then 500 mg every 4 months	18.6/17.9	72/74	17 months	No change in time to first HF hospitalizations and CV death, total HF hospitalization, no change in patients with TSAT <20%, improvement in functional outcomes

HF, heart failure; IV, intravenous; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; Hb, hemoglobin; FCM, ferric carboxymaltose; ID, iron deficiency; TSAT, transferrin saturation; PGA, patient global assessment; QoL, quality of Life; 6MWD 6-minute walk distance; CV, cardiovascular.

Although IV iron has consistently demonstrated functional benefits in patients with HF and ID, the clinical utility of oral iron remains limited. Studies evaluating oral iron therapy in this population have been small and inconsistent, with no completed trials directly comparing oral and IV iron.[1,11] The IRONOUT HF (Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency) trial found no improvement in exercise capacity over 16 weeks in HFrEF patients.[12] Overall, oral iron has not shown consistent improvements in exercise capacity or patient-reported outcomes, likely due to lack of adherence, polypharmacy, poor absorption and hepcidin-mediated regulation in chronic HF.[1,11] Hepcidin, which is upregulated by iron repletion and inflammation, downregulates ferroportin, thereby reducing intestinal iron absorption and iron release.[12] In heart failure, inflammation may dysregulate hepcidin and further limit the response to oral iron.

Cardiovascular outcomes

In addition to improving symptoms, several RCTs have evaluated whether IV iron therapy reduces clinically significant cardiovascular (CV) outcomes such as HF hospitalizations and mortality (Table 1). While trials consistently show reduced hospitalization risk, mortality outcomes have been more inconclusive (Figure 1).

The AFFIRM-AHF (Study to Compare Ferric Carboxymaltose with Placebo in Patients With Acute Heart Failure and Iron Deficiency) trial randomized 1108 patients stabilized after hospitalization for acute HF.[13] Although the primary composite outcome of total HF hospitalizations and CV death was narrowly non-significant (hazards ratio [HR], 0.79; 95% CI, 0.62-1.01; *p*=0.059), FCM significantly reduced total HF hospitalizations (HR, 0.74; 95% CI, 0.58-0.94) and time to first hospitalization or CV death (HR, 0.80; 95% CI, 0.66-0.98). The IRONMAN (Intravenous Iron Treatment in Patients With Heart Failure and Iron Deficiency) trial tested ferric derisomaltose in 1137 patients with HFrEF.[14] The primary endpoint, a composite of HF hospitalization and CV death, was neutral (rate ratio, 0.82; 95% CI, 0.66-1.02, *p*=0.070). However, a pre-specified sensitivity analysis accounting for COVID-19 censoring found a significant benefit (rate ratio, 0.76; 95% CI, 0.58-1.00, *p*=0.047).

In the HEART-FID trial (Randomized Placebo-Controlled Trial of Ferric Carboxymaltose as Treatment for Heart Failure With Iron Deficiency), which enrolled 3065 patients, the composite endpoint of mortality, HF hospitalization, and 6MWD did not reach statistical significance at the pre-specified 99% CI (rate ratio, 1.10; 99% CI, 0.99-1.23), though conventional analysis with a 95% CI was statistically significant.[15] Notably, the median TSAT in HEART-FID was 24%, considerably higher than the 15% reported in both AFFIRM-AHF and IRONMAN. This raises concerns that the true prevalence of ID in the HEART-FID population may have been lower than intended, potentially affecting the observed treatment effect.

Most recently, results from the FAIR-HF2 trial showed that while IV iron lowered the primary composite of time to first HF hospitalizations and CV death by 21%, the between-group difference did not reach statistical significance (HR, 0.79; 95% CI 0.63 to 0.99, *p*=0.038).[9] Moreover, primary endpoint results were similar in patients with TSAT <20% (HR, 0.79; 95% CI 0.61-1.02, *p*=0.070), indicating no greater benefit in this subgroup. In a sensitivity analysis limited to the first 12 months of treatment - when IV iron dosing was at its peak- the hazard ratio for time to first CV death or HF hospitalization was 0.71 (95% CI, 0.53-0.94), and the rate ratio for total HF hospitalizations was 0.65 (95% CI, 0.47-0.90), indicating a significant early treatment benefit.[9]

In light of these inconclusive results from clinical trials, several meta-analyses have been conducted to expand on the effect of IV iron in HF patients with ID. The individual patient data meta-analysis by Ponikowski *et al*., which pooled data from 4501 patients across three randomized trials, demonstrated that IV FCM significantly reduced the risk of the composite outcome of CV hospitalizations and CV death (rate ratio 0.86; 95% confidence interval 0.75-0.98; *p*=0.029).[2] The primary endpoint was largely driven by hospitalizations as there was a significant reduction in risk of HF hospitalizations but not CV or all-cause mortality. An updated 2025 meta-analysis by Anker *et al*., which included over 7,000 patients from all major contemporary IV iron trials, including FAIR-HF2, reaffirmed and expanded upon these findings.[16] It reported a significant reduction in the composite of CV death and HF hospitalizations at one year (rate ratio, 0.72; 95% CI, 0.55-0.89, *p*=0.007), and a sustained, though attenuated, effect over longer-term follow-up (rate ratio, 0.81; 95% CI, 0.63-0.97) was observed. There were no differences in results when stratified according to age, NYHA class, ischemic versus non-ischemic HF, hemoglobin, ferritin or TSAT. However, sex differences existed, with women showing no improvement in the primary outcome with IV iron.

Interpretation and future direction

Despite some individual trials falling short on their primary endpoints related to CV events, the totality of evidence supports a clinically meaningful benefit of IV iron therapy in patients with HFrEF and iron deficiency. Across trials risk of CV death and particularly HF hospitalization was lower in those receiving IV iron compared to placebo, particularly in the first year of treatment. Many of the recent trials were affected by the COVID-19 pandemic, which resulted in suboptimal dosing in subsequent years.[16] These disruptions may have reduced statistical power and limited the generalizability of their findings. Future trial designs can incorporate adaptive measures such as flexible visit schedules, remote assessments, and predefined approaches to handling missing data. Hospitalizations adversely impact patient QoL and contribute to a significant financial burden to patients and healthcare systems.[16] Hence, IV iron has the potential to benefit patients and reduce healthcare costs. Patients also experienced consistent improvements in functional outcomes such as NYHA class, 6MWD and QoL scores. While long-term effects on mortality remain uncertain, the safety profile of IV iron has been reassuring, with no significant differences in adverse events- including all-cause mortality, CV mortality, or infection- at three years.[2,16] Economic analysis of the AFFIRM-AHF trial

demonstrated that IV FCM is a cost-effective therapy for patients with HF and IDA, reinforcing its potential value for healthcare systems and policy decision-making.[17]

Future studies are needed to evaluate the impact of higher doses of IV iron following the initial loading phase. Additionally, there is a need to revisit the definition of iron deficiency, with TSAT <20% potentially serving as a standalone criterion.[18] Recent observational data indicate that this threshold may better predict adverse outcomes in heart failure than the traditional combined ferritin/TSAT definition, which could influence future guidelines and trial design.[19] However, findings from FAIR-HF2 showed no greater benefit in patients with TSAT <20%, highlighting the need for future studies to explore the optimal TSAT cutoff for defining iron deficiency in HF. Emerging biomarkers, such as soluble transferrin receptor (sTfR), either alone or in combination with other indices such as the sTfR to ferritin ratio, or a combination of TSAT with C-reactive protein, may enhance the assessment of iron deficiency in HF, although their clinical utility requires further investigation.[18] Notably, women did not appear to benefit from IV iron, with no observed reduction in HF hospitalizations or cardiovascular mortality, highlighting the need for further investigation into sex-specific responses. Potential explanations include sex-related differences in iron metabolism, such as menstrual blood loss and greater iron turnover in premenopausal women and low estrogen levels in postmenopausal women leading to elevated hepcidin, reduced iron absorption, and diminished response to IV iron.[20] These findings underscore the need for future trials to stratify enrollment and be adequately powered for sex-specific analyses to clarify these disparities. Lastly, trials are also warranted to assess the efficacy of IV iron in patients with HF with preserved ejection fraction.

Contributions

All author made a substantive intellectual contribution; read and approved the final version of the manuscript and agreed to be accountable for all aspects of work.

Conflict of interest

The authors declare that they have no competing interests, and all authors confirm accuracy.

Availability of data and material

The content is based on existing literature and publicly available data.

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