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REVIEW ARTICLE

Intravenous iron therapy in heart failure with reduced ejection fraction: evidence from recent trials and meta-analyses

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Summary

Anemia is a frequently observed comorbidity in patients with heart failure (HF) and it contributes to increased morbidity and mortality. Even though the etiology of anemia in HF patients is polymorphic, chronic inflammation and iron deficiency (ID) are reported as the most frequent underlying causes. Anemia is a strong prognostic marker in both acute and chronic HF, while ID, even in the absence of anemia, has a negative impact on patients' symptoms, functional capacity, and quality of life (QOL). In chronic HF, functional ID is often present due to impaired iron utilization, but it may coexist with absolute ID, where iron stores are depleted.

Intravenous (IV) iron therapy has been shown to have a beneficial effect on improving functional status, reducing symptoms, and lowering the rate of hospital readmissions. This has led to its inclusion in the latest guidelines of the European Society of Cardiology (ESC) as a recommended treatment for symptomatic patients with heart failure with reduced ejection fraction (HFrEF). Several studies have also described a consistent trend toward reduced mortality.

The aim of this paper is to summarize current knowledge on the importance of ID and the therapeutic effects of iron supplementation in HFrEF patients. Timely recognition and correction of ID should be considered a cornerstone of individualized HfrEF management.

Keywords: heart failure, intravenous iron, iron deficiency, anemia

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INTRODUCTION

Heart failure (HF) is a multifaceted clinical syndrome characterized by the heart's inability to adequately deliver oxygenated blood to peripheral tissues, leading to tissue hypoxia. Approximately 2% of the global population is affected, with rising incidence and prevalence being driven by an aging population, increasing comorbidities, and improved management of multiple cardiovascular diseases. The lifetime risk of HF has increased to 24%, which means that approximately one in four individuals will develop HF during their lifetime (1).

The latest major epidemiological research, HF STATS 2024, published in January 2025, indicates that by 2050, the number of affected individuals could increase to 11.4 million. Subsequently, due to these rising numbers, HF-related hospitalizations and mortality are also increasing (2).

One of the most common comorbidities of HF is anemia, which has been associated with reduced functional capacity, increased hospitalization, and higher mortality rates (3).

Its prevalence in HF ranges from 10% to 50%, depending on the population being studied, the diagnostic criteria for HF, and the presence of anemia. Using the World Health Organization (WHO) definition, hemoglobin (Hb) levels below <13 g/dL in men and <12 g/dL in women are sufficient for diagnosis of anemia. Iron deficiency (ID), the most frequent underlying cause of anemia in HF, may be present even in the absence of anemia. It is diagnosed if serum ferritin levels are <100 μg/L or ferritin levels are 100–299 μg/L and the saturation of transferrin (TSAT) is <20% (4).

According to the latest European Society of Cardiology (ESC) guidelines for HF management, intravenous (IV) iron repletion is a class I recommendation in symptomatic HFrEF patients (1, 4).

The complex interaction between anemia and HF has been observed in many trials. The underlying mechanisms of anemia are diverse and are closely linked to the pathophysiology of HF. Anemia directly restricts oxygen delivery to peripheral tissues, and HF is responsible for various mechanisms like chronic inflammation, neurohormonal activation, iron dysregulation, and hemodilution. Low-grade and chronic inflammation is most significant in the development of anemia. Pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β), promote the production of hepcidin, a liver-derived peptide hormone, that is the main driver of iron metabolism regulation. Hepcidin binds to ferroportin (FPN), the iron exporter in enterocytes, macrophages, and hepatocytes. At higher levels of hepcidin, the iron export into blood is decreased, resulting in functional ID. In chronic diseases, such as HF, functional ID can coexist with absolute ID, where iron stores are depleted. As a result of chronic hypoperfusion and reduced cardiac output, the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) are chronically activated, leading to blunted erythropoietin (EPO) (3, 4).

Besides inflammatory mechanisms, progressive left ventricular remodeling after acute myocardial infarction (AMI) is still the main etiological factor of HFrEF. It increases myocardial wall stress, oxygen consumption, and reduces perfusion of the subendocardial tissue. A short early filling deceleration time on the first day after AMI is shown to be an independent predictor of adverse left ventricular remodeling and increased long-term cardiac mortality. This mechanism contributes to further deterioration of HF. It may also promote anemia through impaired oxygen delivery and increased metabolic demands (5-7).

Several studies have demonstrated that ID is present in approximately 49–82% of patients with AMI, even in the absence of anemia, and it has been linked to impaired recovery, ST segment resolution, adverse ventricular remodeling, and increased long-term morbidity and mortality. Despite its clinical relevance, iron status testing is still rarely performed in routine care of AMI patients (8-10).

Another HF-related mechanism is hemodilution, an expansion of plasma volume, which leads to relative anemia. It causes overestimation of the severity of anemia, resulting in inadequate therapeutic intervention. Hemodilution also leads to increased cardiac workload, and greater blood volume must be pumped out by an already compromised heart, leading to *circulus vitiosus* (11, 12).

Serum ferritin is commonly elevated during AMI due to its role as an acute-phase reactant. Based on recent studies, it has been proposed that the definition of ID in chronic HF should rely exclusively on low TSAT (13, 14). In the context of negative outcomes and higher mortality, early identification of patients who are at high risk for developing HFrEF after AMI allows for prompt implementation of targeted therapy. In addition to the four foundational pillars (angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, sodium glucose-cotransporter 2 (SGLT2) inhibitors, and mineralocorticoid receptor antagonists (MRAs), this approach also includes recognizing patients who could benefit from early iron supplementation (15).

The purpose of this review is to summarize previous knowledge on the use, efficacy, and safety of IV iron in patients with HF, highlighting its beneficial effects, while also addressing its limitations with respect to mortality.

METHODS

The literature search was performed using the PubMed database, focusing on studies published in the last five years. The search included studies written in English and conducted only on human subjects. A few studies

published outside this timeframe were also included due to their scientific relevance. The following keywords were used: "heart failure", "iron deficiency", "intravenous iron", and "anemia". Priority was given to RCTs, systematic reviews, and meta-analyses. Reference lists of the selected articles were also reviewed to identify any further relevant publications.

LARGE-SCALE CLINICAL TRIALS OF IV IRON THERAPY IN HFREF

The majority of randomized control studies (RCTs) have focused on the effects of IV iron therapy given the established link between ID and poor clinical outcomes in HF.

The FAIR-HF trial is the first large RCT to explore IV iron supplementation using ferric carboxymaltose (FCM) in HFrEF patients. The primary endpoints were the self-reported Patient Global Assessment (PGA) and the New York Heart Association (NYHA) functional class. Secondary endpoints included the six-minute walk distance (6MWT) and health-related quality of life (QOL) questionnaire. Half of the patients having FCM showed an improvement in PGA compared to less than 30% in the placebo group, which was statistically significant. There was an increased QOL in the IV iron group and enhanced exercise capacity by 6MWT compared to the control group. A consistent improvement in 6MWT and QOL was registered just 4 weeks after the treatment and persisted at 12 and 24 weeks. This trial showed an improvement of 35 ± 8m in the FCM group (all p values were < 0.001). The FAIR HF trial, published in 2009, served as the gateway that enabled IV FCM to be included in the ESC recommendations in 2016 (16, 17).

The extension of this trial was CONFIRM-HF, which focused on the long-term effects of IV FCM in HF patients with ID. The primary outcome was only the improvement in 6MWT at week 24. After 24 weeks, there was an increase in 6MWT distance by 18 + 8m in the FCM group, while it decreased by 16 ± 8m in the placebo group. There was a consistent and sustained improvement in 6MWT over time and across all subgroups. According to Professor Ponikowski, the chief investigator, benefits like this have only been observed with cardiac resynchronization therapy. There was a sustained improvement in functional capacity over 52 weeks, reduced hospitalization rate for 61% due to worsening of HF, better symptom control, and NYHA functional class improvement. The patients with diabetes and impaired renal function responded better to IV iron therapy (18).

In the FAIR-HF trial, the dosage of FCM was calculated using the Ganzoni equation, based on the patient's weight, target, and current Hb values. This approach was tailored to patients' individual needs, but complicated for routine clinical practice. The dosing frequency was initially weekly until repletion was achieved, and then maintained every 4 weeks. On the other hand, the CONFIRM-HF trial used a simpler dosing regimen, starting with a single high dose of FCM, followed by additional smaller doses administered only as needed, based on follow up measurements of iron parameters. This simplified dosing strategy enabled efficient correction of ID in everyday clinical practice. More than 75% of the patients required no more than two doses of FCM for correction and maintenance of iron levels. Irrespective of dosage regimen an improvement in NYHA functional class was observed in both trials after 24 weeks of treatment (16, 18).

The AFFIRM-HF trial conducted from 2017 to 2020 specifically assessed IV iron in patients hospitalized for acute HF (AHF) decompensation. The main rationale for this study was the fact that approximately 80% of patients with acute HF have ID (19).

Also, de novo AHF and acute decompensation of chronic HF represent clinically and pathophysiological distinct entities, but both are associated with high intrahospital and one-year mortality. And even though they fall under the same clinical syndrome, these two forms differ in severity of clinical presentation, laboratory findings, and treatment response (20).

Results of AFFIRM-HF showed 26% reduced risk of HF rehospitalization rate in the IV iron group, with no significant reduction in cardiovascular mortality. The AFFIRM-HF provided strong evidence for IV iron therapy as a strategy for short-term clinical improvement. However, the relatively short follow-up period of 52 weeks and the lack of mortality benefit enhanced the need for further long-term studies. Benefits were independent of baseline Hb levels, reinforcing the concept that ID itself, rather than anemia alone, could be a key therapeutic target in HF (19).

The IRONMAN trial conducted from 2016 to 2021 was the first large RCT that evaluated the long-term effects and safety of IV iron gathering information from 70 UK hospitals. The trial used IV ferric derisomaltose, rather than FCM, providing insight into the differences between IV iron formulations in HF. Ferric derisomaltose can be administered in high doses via infusion. It is already commonly used in other medical specialties, including nephrology, gastroenterology, gynecology, and in the preoperative setting. The primary endpoint was a composite of recurrent HF hospital admissions and cardiovascular death. Although the trial itself did not reach statistical significance for this outcome (p=0.07), when interpreted alongside the AFFIRM-AHF trial (which used a different iron formulation) the overall conclusion supports the clinical benefit of this type of treatment in HFrEF patients. Because of the impact of the COVID-19 pandemic, the chief investigator professor Karla conducted a pre-specified subgroup analysis of 1063 patients enrolled prior to March 31, 2020, before the first lockdown. In this analysis, IV iron therapy was associated

with a 24% relative risk reduction (RRR) in the primary outcome compared to usual treatment, reaching its statistical significance (p=0.047). Additionally, in a post hoc analysis where follow-up was censored at one year to allow direct comparison with AFFIRM-AHF, the observed treatment effect was even more pronounced (21).

The latest multicenter RCT, the FAIR-HF2 trial, challenged previously established findings on HF hospitalization rates. It is essential to note that this trial simultaneously evaluated three distinct primary endpoints, in contrast to previous trials that focused on a composite primary endpoint. As a consequence, it required statistical correction of p-values, using the Hochberg procedure, to avoid the type one error rate and false positive results. This method is more rigorous, but it also reduces the statistical power, making it harder to achieve statistical significance. In contrast, composite endpoints may mask differential effects on individual outcomes. There was a consistent RRR of approximately 21% in all three primary endpoints, but none of them reached statistical significance. The first primary endpoint was time to cardiovascular death or first hospitalization due to HF. Although the IV iron group showed a lower event rate with a raw p-value of 0.04, this difference was no longer statistically significant after correcting it. The second primary endpoint was total hospitalizations for HF, which also showed no statistically significant difference between groups. The third primary outcome targeted a specific subgroup of patients with TSAT below 20%, as earlier studies had suggested they might have the most benefit from IV iron. In the 1105 patients included, 70% of them met this criterion; yet, the observed hazard ratio of 0.74 (p = 0.07) did not achieve statistical significance.

Notably, in the FAIR HF2 trial, sex-specific differences emerged. Male patients showed more favorable outcomes, while female patients exhibited no significant reduction in cardiovascular events or hospitalizations. This may be a reflection of differences in iron metabolism, hormonal regulation, or even underrepresentation in clinical trials. Similarly, no significant differences were observed between ischemic and non-ischemic etiologies of HF, suggesting a broadly consistent therapeutic effect across subtypes. Also, this trial spanned the COVID-19 pandemic, which we believe may have influenced patient recruitment, care delivery, and outcome rates. This could partly explain the neutral findings, as similar disruptions were observed in other cardiovascular trials conducted during the same period. Despite these limitations, the FAIR-HF2 confirms the benefits of IV-iron therapy on quality of life and patient self-reported health status (22).

Over a decade later from publishing FAIR HF and IV iron entering the ESC recommendations, the biggest HEART-FID trial sought to resolve this therapy-mortality evidence gap by evaluating the impact of IV FCM on a hierarchical composite endpoint including all-cause mortality, HF hospitalizations, and functional status. Despite a larger sample size and more rigorous methodology, this trial failed to show a statistically significant reduction in mortality, although it confirmed benefits mentioned in previous trials. These findings highlight that while IV iron therapy plays a crucial role in symptom management and reducing morbidity, its effect on survival remains uncertain, emphasizing the need for further large-scale research (23).

The summary of all studies is presented in **Table 1**.

This table summarizes the main findings of key randomized controlled trials investigating intravenous iron therapy in patients with HfrEF, emphasizing improvements in functional capacity and hospitalization rate.

In the meta-analysis by Graham et al., which included over 3000 patients, IV iron therapy was associated with a 25% RRR in the primary composite outcome of recurrent HF hospitalizations and cardiovascular mortality. A reduction in HF hospitalizations predominantly drove this result, while the impact on mortality remained inconsistent. Implementing IV iron in HF treatment reduced cardiovascular death by 14% and overall mortality by 7% but the difference did not reach statistical significance. Subgroup analysis revealed that patients with ischemic heart disease appeared to derive a greater benefit from IV iron (odds ratio 0.84) compared to those with non-ischemic etiologies (odds ratio 0.98), although this difference was not statistically significant (p = 0.28). Similarly, patients with TSAT

Table 1. Summary of key trials investigating intravenous iron in heart failure

Study	Year	Number of patients	Primary outcome	Main result
FAIR-HF[16]	2009	459	PGA and NYHA class improvement	PGA, NYHA class, 6MWT and QQL improvement
CONFIRM-HF[18]	2014	304	6MWT	Improved functional capacity, NYHA class, reduced hospitalizations for 61%
AFFIRM-HF[19]	2020	1132	HHF or CV death	Reduction in rehospitalizations
IRONMAN[21]	2023	1137	HHF or CV death	Reduction in hospitalizations; mortality showed a trend toward reduction
FAIR-HF2[22]	2024	1105	3 distinct primary outcomes	No significant difference in neither hospitalization nor mortality
HEART-FID[23]	2024	3065	Hierarchical composite outcome	Functional improvement and fewer hospitalizations; mortality without statistical difference

PGA, Patient Global Assessment; NYHA, New York Heart Association functional class; HF, heart failure; CV, cardiovascular; 6MWT, 6-minute walking test; HHF, heart failure hospitalization; QOL, quality of life

Table 2. Major recent meta-analyses on intravenous iron therapy in heart failure

Study	Year	Journal	Patients included	Main Focus	Key Findings
Graham et al.[24]	2023	European Journal of Heart Failure	3373	Recurrent HHF, CV death and all-cause mortality	IV iron reduces HHF especially in ischemic HF and patients with lower TSAT
Ahmed et al.[25]	2025	ESC Heart Failure	6651	Composite outcome (first HHF and CV death)	Reduced incidence of the composite outcome
Anker et al.[27]	2025	Nature Medicine	7175	Composite outcomes, functional parameters	IV iron reduces hospitalizations; CV death

HF, heart failure, HHF, heart failure hospitalization, CV, cardiovascular, ESC, European Society of Cardiology, IV intravenous, TSAT, saturation of transferrin

<20% experienced more pronounced benefit (odds ratio 0.67) than those with higher values of TSAT. Overall, the heterogeneity of data across the meta-analysis was low (24).

The meta-analysis conducted by Ahmed et al. included 14 RCTs and a total of 6,651 patients. Importantly, their meta-analysis included the most recent large trial HEART-FID (25).

There was a consistent trend toward reduction in overall mortality, 1-year and overall cardiovascular mortality, although no statistical significance was observed. High heterogeneity was registered when analyzing NYHA class, 6MWT, and left ventricular ejection fraction (LVEF). To address this, the authors conducted "leave-one-out" sensitivity analyses, identifying outlier studies that contributed most to variability. Excluding the trial undertaken by Dhoot et al., heterogeneity in LVEF analysis was reduced to 0%. Those results revealed a significant improvement in LVEF for 7.02% ($p < 0.00001$). The reason for that could be that the study by Dhoot et al. included a small sample size (n = 70), Indian population, and a short follow-up duration of only 12 weeks (26).

Additionally, by removing the trial by Kalra et al. heterogeneity when analyzing the 6MWT distance, the reduction was increased to 72%, demonstrating a significant benefit (MD = 30.25 m, $p = 0.03$). However, NYHA class remained highly heterogeneous despite exclusion strategies. These findings confirm the rationale and patient-reported benefits observed in prior studies such as CONFIRM-HF and FAIR-HF. This could be attributed to the variation in follow-up length and patient characteristics among the included studies (25).

At the same time when the FAIR HF2 trial results were released, Anker et al. published a Bayesian meta-analysis that pooled data from six major RCTs. The meta-analysis included more than 7,100 patients and showed a 28% reduction in recurrent HF hospitalizations and cardiovascular death within 12 months ($p = 0.010$), as well as a 13–18% reduction in cardiovascular mortality, confirming the therapeutic value of iron supplementation in HFrEF. These findings strengthen and support the idea that the inconsistency of dosing beyond the first year may have impacted outcomes in the FAIR HF2 trial (27).

Major recent meta analyses on IV iron therapy in HF are summarized in **Table 2**.

This table presents recent meta-analyses evaluating the impact of IV iron therapy in heart failure, with a focus on composite outcomes hospitalization reduction, and mortality trends.

CONCLUSION

In recent decades, many studies have contributed to showing the clinical benefit of iron supplementation in patients with chronic diseases and ID. In HF, due to the pathophysiological role of hepcidin, oral administration of iron has not been shown to be as an effective treatment approach. On the contrary, IV iron repletion, without significant side effects, emerged as a proper therapeutic method. Benefits such as improved functional status, reduced HF hospitalization, and cardiovascular mortality justify the cost-effectiveness of IV iron. Notably, meta-analyses have shown a consistent trend toward reducing all-cause mortality, which extends beyond correcting anemia. Hence, IV iron should be viewed primarily as a morbidity-modifying intervention until more conclusive mortality data become available.

In future, new studies should aim for more extended follow-up periods and work towards standardizing IV iron dosing regimens across clinical trials. Well-established study protocols are needed to fully integrate iron repletion into HF management, regardless its phenotype.

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INTRAVENSKA TERAPIJA GVOŽĐEM KOD SRČANE ISUFICIJENCIJE SA SMANJENOM EJAKCIONOM FRAKCIJOM: DOKAZI IZ SKORAŠNJIH KLINIČKIH STUDIJA I META-ANALIZA

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Sažetak

Anemija je čest komorbiditet kod pacijenata sa srčanom insuficijencijom (SI) i utiče na njihov morbiditet i mortalitet. Iako je etiologija anemije kod ovih bolesnika višestruka, hronična inflamacija i nedostatak gvožđa najčešći su uzroci. Anemija je snažan prognostički pokazatelj kako u akutnoj, tako i u hroničnoj SI, dok nedostatak gvožđa, čak i u odsustvu same anemije pogoršava simptome, funkcionalni kapacitet i kvalitet života pacijenata. Kod hronične SI često se sreće funkcionalni nedostatak gvožđa, koji nastaje usled poremećaja korišćenja gvožđa, ali može koegzistirati sa apsolutnom deficijencijom, kada same zalihe gvožđa nedostaju.

Terapija intravenskim gvožđem pokazala je brojne koristi u vidu poboljšanja funkcionalnog statusa, ublažavanja simptoma i redukcije stope ponovnih hospitalizacija. Na osnovu ovih dokaza, najnovije smernice Evropskog udruženja kardiologa preporučuju suplementaciju gvožđa kod simptomatskih pacijentata sa srčanom slabošću i redukovanom ejekcionom frakcijom (HFrEF). Poslednje meta analize pokazuju trend ka smanjenju ukupne smrtnosti.

Cilj ovog revijalnog članka je da prikaže trenutne uvide u značaj nedostatka gvožđa i terapijske efekte njegove nadoknade kod pacijenata sa HFrEF-om. Pravilno razumevanje ovog stanja i njegovo blagovremeno lečenje predstavljaju važan korak ka individualizovanom i sveobuhvatnom pristupu terapiji SI.

Ključne reči: srčana insuficijencija, intravensko gvožđe, deficijencija gvožđa, anemija

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