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Title: Iron Deficiency in Heart Failure: Pathophysiology, Diagnosis, and Therapeutic Strategies – A Narrative Review

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Abstract

Introduction and Purpose: Heart failure (HF) imposes a significant global burden. Iron deficiency (ID) constitutes a prevalent comorbidity affecting up to 50% of patients, independently worsening prognosis regardless of anemia status. This review analyzes the pathophysiology of ID, specifically impaired myocardial energetics, clarifies diagnostic criteria, and compares the efficacy of oral versus intravenous therapeutic strategies. A comprehensive literature search was conducted using PubMed, Scopus, and Embase (2015–2026). The review focuses on landmark randomized trials (AFFIRM-AHF, IRONMAN, HEART-FID), recent meta-analyses, and current international guidelines .

Description of the state of knowledge: ID impairs mitochondrial oxidative phosphorylation and myocardial contractility. In HF, chronic inflammation may upregulate hepcidin, which induces the internalization and degradation of ferroportin, blocking intestinal iron absorption.

Consequently, evidence from randomized trials suggests that oral iron supplementation has not demonstrated consistent clinical benefit in repleting iron stores or improving functional capacity in patients with heart failure. In contrast, intravenous iron formulations (ferric carboxymaltose, ferric derisomaltose) bypass these regulatory barriers. Evidence indicates that intravenous repletion significantly improves exercise capacity and quality of life, and reduces the risk of recurrent HF hospitalizations.

Summary: Assessment of iron status using serum ferritin and transferrin saturation is a vital aspect of modern heart failure management. Due to physiological absorption barriers and systemic inflammation, oral iron supplementation has not demonstrated consistent clinical benefit in this population. Current evidence supports intravenous iron repletion as an effective, evidence-based strategy for improving symptoms and reducing the risk of hospitalizations, specifically in symptomatic patients with HFrEF or HFmrEF and concomitant iron deficiency.

Keywords: Heart Failure; Iron Deficiency; Ferritin; Hepcidin; Intravenous Iron Therapy.

Introduction and purpose

Heart failure (HF) represents a major global public health challenge, characterized by a chronic, progressive course that imposes a substantial clinical and economic burden on healthcare systems worldwide [1, 2, 3]. Despite significant advancements in guideline-directed medical therapies, mortality and rehospitalization rates remain alarmingly high [1, 4]. Within this population, iron deficiency (ID) has emerged as one of the most prevalent and clinically significant comorbidities, affecting approximately 50% of chronic heart failure patients and reaching a prevalence of 60–80% in acute heart failure cohorts [5, 6, 7]. It is imperative to distinguish iron deficiency from anemia, as they represent distinct physiological and pathological states. While anemia is defined by hemoglobin concentrations below 13.0 g/dL in men and 12.0 g/dL in women [3, 5], ID is a systemic metabolic disorder involving the depletion or sequestration of iron stores essential for cellular bioenergetics and mitochondrial function [8].

Crucially, ID has been consistently associated with worse clinical outcomes—including reduced exercise capacity (peak VO_2), diminished quality of life, and a heightened risk of hospitalization or death—regardless of whether a patient is concurrently anemic [9, 10, 11]. The clinical landscape for managing iron status in heart failure has undergone a profound transformation, necessitating a comprehensive re-evaluation of current evidence. This evolution is driven by the results of landmark clinical trials, such as AFFIRM-AHF, which investigated the impact of intravenous iron repletion at hospital discharge [12], and IRONMAN,

which demonstrated a non-significant trend toward a reduction in the risk of cardiovascular death and heart failure hospitalizations in its primary analysis, but showed a significant benefit when adjusting for the impact of the COVID-19 pandemic [13]. These findings have prompted critical revisions in international guidelines, most notably within the 2021 ESC Guidelines and the subsequent 2023 Focused Update, which now recommend routine screening for iron deficiency and advise considering intravenous ferric carboxymaltose or ferric derisomaltose in symptomatic patients to improve clinical outcomes [14, 15]. Given the recent publication of large-scale metaanalyses and the latest evidence from trials such as HEART-FID, a consolidated review of this topic is highly relevant for modern cardiovascular medicine [16, 17, 18]. Therefore, the aim of this narrative review is to summarize the current state of knowledge regarding iron deficiency in heart failure. While the pathophysiological burden of iron depletion spans the entire heart failure spectrum, this review will place a specific focus on contemporary therapeutic strategies and clinical evidence predominantly established for patients with heart failure with reduced (HFrEF) or mildly reduced (HFmrEF) ejection fraction, in alignment with current guideline recommendations.

To achieve this objective, a targeted search of the PubMed, Scopus, and Embase databases was conducted. The search strategy utilized Boolean operators and specific keywords, including: ("heart failure") AND ("iron deficiency" OR "intravenous iron") AND ("mitochondrial energetics"). Priority was given to literature published between January 2015 and February 2026 to ensure the integration of the most current evidence, while seminal trials and foundational epidemiological studies were included to provide essential historical and scientific context. From an initial screening of over 150 records, approximately 42 peer-reviewed sources—including landmark randomized controlled trials (AFFIRM-AHF, IRONMAN, HEART-FID) [12, 13, 18], contemporary metaanalyses [16, 19, 20], and international clinical guidelines [14, 15, 21]—were selected based on their clinical and mechanistic relevance [22]. Non-English language publications, animal-only models, and studies lacking clear clinical or mechanistic relevance were excluded to maintain a high level of academic rigor and clinical applicability. The synthesized evidence aims to provide a cohesive perspective on the diagnostic and therapeutic aspects of iron deficiency management in heart failure [9, 17].

Description of the State of Knowledge

2.1. Pathophysiology: Iron and Cellular Energetics

Iron is a critical micronutrient essential for the fundamental physiological functioning of the human body, serving as an integral component of biomolecules such as hemoglobin and myoglobin [22]. However, the biological significance of iron extends far beyond its role in erythropoiesis; it functions as an essential cofactor for multiple enzymes regulating cellular metabolism in nonhematopoietic tissues, specifically cardiomyocytes and skeletal muscle cells [5, 22]. Because these tissues possess exceptionally high energy requirements, they are uniquely sensitive to limited iron utilization and decreased systemic iron supplies [5, 22].

Within the mitochondria, iron acts as a vital cofactor for specific enzymes integral to the citric acid cycle and the electron transport chain [22]. It is a constitutive element of cytochromes and nonheme iron-sulfur proteins, most notably the TCA cycle enzyme aconitase and multiple complexes within the respiratory chain [22, 23]. Furthermore, iron is essential for the formation of iron-sulfur (Fe-S) clusters, which are indispensable for electronic transfer within mitochondrial Complexes I, II, and III [9, 24]. Through these mechanisms, iron is required for the maintenance of effective oxidative phosphorylation and the generation of adenosine triphosphate (ATP) [24, 25].

The depletion of intracellular iron may contribute to impaired myocardial energetics through mitochondrial dysfunction and compromised ATP production [24, 26]. This bioenergetic insult appears to contribute to reduced myocardial contractility and impaired exercise capacity through pathways that function independently of hemoglobin levels or the presence of concomitant anemia [24]. Direct analysis of human failing hearts has indicated that myocardial iron content is significantly reduced and is strongly correlated with diminished enzymatic activity within the mitochondrial respiratory chain [26]. However, these findings are based on limited *ex vivo* tissue analyses and require confirmation in larger clinical studies.

Beyond metabolic dysfunction, chronic iron deficiency induces profound structural and ultrastructural alterations. Cellular hallmarks of iron depletion include mitochondrial swelling, abnormal sarcomere structure, and a significant reduction in mitochondrial volume density and cristae surface density [25]. These alterations may contribute to maladaptive "metabolic remodeling" of the heart, which has been hypothesized to influence ventricular structure and global systolic performance [25, 27]. Preliminary evidence suggests that intravenous iron repletion may partially restore myocardial bioenergetics [24]. Furthermore, small randomized studies have indicated that iron repletion may promote favorable cardiac reverse remodeling in highly selected populations, such as those undergoing cardiac resynchronization therapy, although larger studies are required to confirm these structural benefits across the broader heart failure spectrum [28].

2.2. Regulation of Iron Transport: The Role of Hepcidin

Hepcidin, a small peptide hormone synthesized primarily by hepatocytes is widely recognized as the principal regulator of systemic iron homeostasis [5, 29]. It acts as a critical homeostatic regulator by controlling both the intestinal absorption of iron and the release of iron from internal stores [22, 30, 31]. In the context of heart failure, which is characterized by a chronic low-grade systemic inflammatory state, elevated levels of pro-inflammatory cytokines—specifically Interleukin-6 (IL-6)—significantly upregulate the hepatic production and circulatory release of hepcidin [31]. This inflammatory surge often results in inappropriately high levels of hepcidin, even when systemic iron stores are actually depleted [16].

At the molecular level, hepcidin exerts its regulatory function by binding directly to ferroportin, the only known mammalian transmembrane protein responsible for exporting iron from the intracellular environment into the systemic circulation [5, 29]. The binding of hepcidin triggers the internalization and subsequent lysosomal degradation of ferroportin. By degrading this essential transporter, hepcidin effectively closes the only available cellular gateway for iron efflux, leading to a profound disruption of systemic iron availability [5, 22, 31].

The primary consequence of this interaction is the "reticuloendothelial block," a pathological state where iron remains sequestered and "trapped" within macrophages, hepatocytes, and enterocytes [5, 31]. This sequestration prevents the mobilization of iron to target tissues with high metabolic demands, such as the myocardium and skeletal muscles, precipitating functional iron deficiency [5, 24]. Simultaneously, the loss of ferroportin on the basolateral membrane of enterocytes inhibits the export of dietary iron from the duodenum and proximal jejunum into the circulation [5, 31]. This hepcidin-mediated inhibition of intestinal iron transport is a fundamental reason why oral iron supplementation has not demonstrated clinically meaningful benefit in randomized trials of heart failure patients, as it cannot overcome the cellular barriers created by systemic inflammation [24, 25].

2.3. Diagnostic Criteria and Clinical Consequences

The diagnosis of iron deficiency (ID) in heart failure (HF) requires laboratory thresholds distinct from those used in the general population to account for the chronic inflammatory milieu associated with the disease [14, 22]. According to current European Society of Cardiology (ESC) guidelines, absolute iron deficiency is defined as a serum ferritin concentration <100 µg/L, whereas functional iron deficiency—a state where iron stores are present but sequestered—is recognized when serum ferritin is between 100 and 299 µg/L provided the transferrin saturation (TSAT) is <20% [6, 14]. Within this diagnostic framework, the assessment of TSAT is crucial, as it serves as a reliable marker of the iron immediately available for metabolic processes in the bone marrow and peripheral tissues [5, 32]. Because ferritin acts as an acute-phase reactant, its levels can be paradoxically elevated by systemic inflammation, potentially masking a true iron-depleted state if TSAT is not concurrently evaluated [14, 32]. Despite the widespread adoption of the ESC criteria, some experts propose that TSAT <20% should be considered the primary and more reliable marker of tissue iron depletion, as a TSAT-only approach may identify a high-risk population currently overlooked by more restrictive ferritin-based criteria [32, 33].

The clinical impact of ID in heart failure is pervasive, affecting multi-organ systems and significantly impairing functional status regardless of the presence of anemia [3, 10]. Patients with ID frequently report debilitating symptoms, including severe fatigue and shortness of breath, which translate into markedly lower health-related quality of life (QoL) scores [5, 33, 34]. Objective assessments of functional capacity consistently demonstrate that iron deficiency is a potent predictor of reduced exercise tolerance, characterized by lower peak oxygen consumption (peak VO_2) and shorter distances achieved in the 6-minute walk test (6MWD) [32, 35, 36]. These impairments are driven by systemic bioenergetic deficits, particularly within skeletal muscles, where ID induces a metabolic shift from oxidative metabolism to less efficient glycolysis and reduces mitochondrial volume and cristae surface density [5, 37].

From a prognostic perspective, iron deficiency is established as a robust and independent predictor of adverse cardiovascular outcomes [10]. Foundational research has demonstrated that iron deficiency is consistently associated with an increased risk of all-cause mortality and recurrent heart failure hospitalizations, a relationship that appears to persist regardless of hemoglobin levels [3, 10]. Prospective analyses indicate that non-anemic patients with ID face a significantly higher risk of death or heart transplantation compared to patients with sufficient iron stores [10]. Furthermore, contemporary evidence indicates that this prognostic weight extends beyond populations with reduced ejection fraction, and has been associated with adverse outcomes in patients with mildly reduced ejection fraction (HFmrEF), although the clinical impact in this phenotype continues to be further characterized [3, 4, 5].

2.4. Therapeutic Strategies

The Inefficacy of Oral Supplementation

While oral iron repletion is a standard intervention in general clinical practice, its application in symptomatic heart failure has not demonstrated clinically meaningful benefit in randomized clinical trials [25, 27]. The failure of oral repletion in this population appears to be multifactorial. Beyond the hepcidin-mediated inhibition of iron transport, therapeutic efficacy is further compromised by impaired intestinal absorption related to gut edema and reduced mesenteric blood flow, as well as high rates of gastrointestinal intolerance that often lead to poor patient adherence [22, 25, 31]. The landmark IRONOUT-HF trial provided compelling evidence regarding the limited efficacy of this approach, demonstrating that 16 weeks of high-dose oral iron polysaccharide failed to improve peak oxygen consumption (peak VO_2), 6-minute walk distance (6MWD), or health status in patients with HFrEF [25]. Furthermore, oral preparations are frequently associated with high rates of gastrointestinal side effects, which, combined with the poor absorption induced by gut edema, render this route unsuitable for effective repletion [25, 31]. Consequently, current guidelines no longer recommend oral iron as a primary strategy for iron deficiency (ID) management in HF [14, 17].

Evidence for Intravenous Repletion

Intravenous (IV) iron supplementation bypasses the hepcidin-mediated intestinal barrier, allowing for the direct and rapid restoration of iron stores in metabolic tissues [3, 22]. Contemporary evidence, predominantly utilizing ferric carboxymaltose (FCM) and ferric derisomaltose (FDI), has established IV iron as a recommended treatment strategy for symptomatic improvement and risk reduction in this population [14, 16].

Landmark Clinical Trials

The clinical utility of IV iron has been validated across several pivotal randomized controlled trials (RCTs):

FAIR-HF and CONFIRM-HF (Symptomatic Benefit): Initial evidence from the FAIR-HF trial demonstrated that FCM significantly improved self-reported patient global assessment, NYHA functional class, and QoL as early as 4 weeks into treatment [33]. These findings were extended by the CONFIRM-HF study, which confirmed sustained improvements in 6MWD and functional capacity over a 52-week period, alongside a secondary signal of reduced hospitalizations for worsening HF [35].

AFFIRM-AHF (Hospitalization Reduction in Acute HF): This trial focused on patients stabilized after an episode of acute HF [12]. The administration of FCM prior to hospital discharge resulted in a significant 26% reduction in total heart failure hospitalizations (RR 0.74), although the primary composite endpoint of CV death and total hospitalizations narrowly missed the traditional significance threshold ($p=0.059$) [12, 23]. Notably, COVID-19-adjusted sensitivity analyses demonstrated a statistically significant benefit for the primary outcome [12, 16].

IRONMAN (Outcomes in Chronic HF): Utilizing FDI in a predominantly ambulatory population, the IRONMAN trial demonstrated a trend toward reduced CV death and recurrent HF hospitalizations (RR 0.82, $p=0.070$) [13]. Similar to AFFIRM-AHF, a prespecified COVID-19 analysis, which censored data at the onset of the pandemic, achieved statistical significance, reinforcing the clinical value of long-term iron repletion [13, 16].

HEART-FID (Safety and Trends): As the largest RCT to date, HEART-FID reported a statistically neutral result on its primary composite endpoint. Due to the trial's complex hierarchical statistical design, a stricter prespecified significance threshold was required ($p<0.01$).

Consequently, the primary outcome ($p=0.019$) did not meet formal statistical significance [16, 18]. However, the study confirmed the long-term safety of FCM and provided additional data that, when integrated into subsequent meta-analyses, reinforced the overall evidence base regarding the reduction of hospitalization risk [1, 16].

Current Clinical Consensus

Reflecting this robust body of evidence, the 2021 ESC Guidelines and the 2023 Focused Update provide a Class I (Level A) recommendation for IV iron therapy in symptomatic patients with HFrEF and HFmrEF to alleviate symptoms and improve QoL [14, 15]. Additionally, IV iron holds a Class IIa recommendation for the reduction of recurrent HF hospitalizations in these populations [15]. The latest individual patient data and Bayesian meta-analyses reinforce this consensus, confirming that treating iron deficiency significantly reduces cardiovascular events and hospital burden [16, 19].

2.5. Discussion and Limitations of Current Evidence

The Mortality Debate: Hospitalization vs. Survival

The therapeutic landscape for iron deficiency (ID) in heart failure (HF) presents a clear dichotomy between the restoration of functional status and the impact on hard survival endpoints. There is high-quality, consistent evidence from landmark trials and contemporary meta-analyses that intravenous (IV) iron—specifically ferric carboxymaltose (FCM) and ferric derisomaltose (FDI)— significantly reduces the risk of recurrent HF hospitalizations and improves symptoms and healthrelated quality of life [16, 33, 36]. However, the effect of IV iron on mortality remains a subject of intense academic debate [1, 16, 19]. Earlier individual patient data (IPD) meta-analyses suggested a potential mortality benefit, particularly when analyzing composite endpoints [19, 38]. While HEART-FID confirmed the safety of FCM, it did not demonstrate a statistically significant reduction in all-cause mortality, though it provided data that reinforced the overall evidence base when integrated into subsequent meta-analyses [16, 18]. The most recent Bayesian meta-analyses synthesize these conflicting results to show that while IV iron definitively reduces total cardiovascular events, the evidence for a standalone reduction in all-cause mortality is currently insufficient to meet traditional significance levels [1, 16, 39].

Economic Perspective and Cost-Effectiveness

From a pharmacoeconomic standpoint, the higher acquisition and administration costs associated with IV iron preparations must be weighed against their clinical utility in reducing healthcare resource utilization [40]. Heart failure imposes a staggering economic burden, primarily driven by expensive inpatient care for acute decompensation episodes [2, 41]. Cost-offset modeling and multinational analyses utilizing data from the AFFIRM-AHF trial indicate that IV iron repletion is a cost-effective, and in some jurisdictions cost-saving, intervention [14, 15]. The prevention of even a single heart failure hospitalization significantly offsets the upfront expenditure for the drug and infusion infrastructure [39, 40]. Furthermore, claims-based studies have demonstrated that untreated iron deficiency is associated with higher all-cause healthcare costs and longer hospital stays compared to iron-replete patients, reinforcing the economic rationale for systematic repletion [39].

The Implementation Gap in Clinical Practice

Despite the presence of Class I and IIa recommendations in the 2021 ESC Guidelines and the 2023 Focused Update, a profound gap persists between evidence-based guidelines and real-world clinical practice [6, 14, 15, 42]. Real-world evidence highlights a significant screening deficit; for instance, a large-scale population study using United Kingdom electronic health records found that iron status was evaluated in fewer than 40% of patients following a heart failure diagnosis [6]. Similar patterns of under-diagnosis have been documented in international registries, where screening rates for ferritin and transferrin saturation remain suboptimal despite strong guideline recommendations [6, 42]. This under-diagnosis is particularly concerning given that the prevalence of ID in both acute and chronic settings remains high regardless of ejection fraction phenotype [4]. Barriers to implementation include clinician knowledge gaps, logistical challenges of providing intravenous infusions, and historical reliance on biomarkers like isolated ferritin, which can be misleading in chronic inflammatory states [17, 33, 42]. Innovative management toolkits, standardized institutional protocols, and a shift toward adopting more specific diagnostic markers, such as transferrin saturation (TSAT), are necessary to bridge this gap and ensure that eligible patients receive clinically meaningful therapy [9, 32, 42].

Limitations of Current Evidence

The current evidence base for intravenous iron repletion in heart failure is characterized by significant methodological heterogeneity, particularly regarding biochemical definitions of iron deficiency and varying patient inclusion criteria. While many trials adopted the consensus definition—serum ferritin <100 µg/L or 100–299 µg/L with transferrin saturation (TSAT) <20%— the scientific foundation for these specific thresholds remains a subject of academic discussion [1, 16, 17]. Inconsistencies across major trials are evident; for instance, the IRONMAN trial included patients with ferritin levels up to 400 µg/L [13], whereas HEART-FID enrolled a population with higher mean baseline TSAT levels, which likely influenced the observed treatment effect [1, 17, 18]. Furthermore, clinical heterogeneity arises from the inclusion of diverse patient states, ranging from acute decompensated stabilization in AFFIRM-AHF to chronic ambulatory management in IRONMAN and HEART-FID [1, 12, 13, 18]. A profound evidence gap also remains regarding patients with preserved ejection fraction (HFpEF), as robust data are predominantly concentrated in HFrEF and HFmrEF populations [4, 5, 20].

Furthermore, the absence of head-to-head randomized controlled trials directly comparing different intravenous iron formulations, such as ferric carboxymaltose and ferric derisomaltose, prevents definitive conclusions regarding the comparative superiority of specific dosing strategies [17, 42]. While pooled meta-analyses consistently indicate a significant reduction in heart failure hospitalizations, standalone individual trials have yet to demonstrate consistent, statistically significant reductions in all-cause mortality as a primary endpoint [1, 16, 20]. It is also noteworthy that landmark studies like AFFIRM-AHF and IRONMAN achieved their primary significance levels predominantly through pre-specified sensitivity analyses designed to mitigate the impact of the COVID-19 pandemic [12, 13, 16]. Finally, the long-term safety and cost-effectiveness of repeated iron repletion over several years require further investigation [17, 41]. Concerns regarding potential oxidative tissue stress and the necessity of advanced monitoring, such as magnetic resonance-based imaging to evaluate myocardial iron distribution, represent critical directions for future prospective research [22, 26, 42].

Summary.

Iron deficiency represents a common and clinically relevant comorbidity in heart failure and may contribute to impaired myocardial energetics, potentially through mechanisms involving mitochondrial dysfunction, a process occurring independently of anemia. Given its substantial impact on clinical outcomes, routine screening using serum ferritin and transferrin saturation is recommended in current clinical guidelines, particularly for patients with symptomatic heart failure with reduced (HFrEF) or mildly reduced (HFmrEF) ejection fraction. Current evidence indicates that oral iron supplementation has not demonstrated consistent clinical benefit in randomized trials involving patients with heart failure and iron deficiency, and is therefore not recommended as firstline therapy. Consequently, intravenous iron therapy has emerged as a therapeutic strategy supported by growing evidence for improving symptoms, enhancing health-related quality of life, and reducing the risk of recurrent hospitalizations in selected patients. However, significant research gaps remain; future large-scale trials are needed to clarify the efficacy of iron repletion in patients with preserved ejection fraction (HFpEF), establish the long-term safety of repeated intravenous dosing, and definitively determine its impact on overall cardiovascular mortality.

DISCLOSURE

Author Contributions

Conceptualization, F.J. and Z.M.; methodology, M.S. and Ł.W.; formal analysis, N.G.; investigation, H.B., A.D. and M.J.,; resources, K.Z.;
data curation, F.J., Z.M. and M.S.;
writing—original draft preparation, F.J., Z.M., M.S., Ł.W., N.G., H.B., A.D. and K.Z.; writing—review and editing, F.J. and J.C.; visualization, Ł.W. and N.G.; supervision, F.J.; project administration, F.J.

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