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Review

Iron Deficiency in Heart Failure After HEART-FID and FAIR-HF2: A Narrative Review on Rethinking Diagnostic Criteria and Patient Selection for Intravenous Iron Therapy

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Abstract

Iron deficiency (ID) is common in heart failure (HF) and is independently associated with impaired functional capacity, worse symptoms, recurrent hospitalizations, and higher mortality, regardless of anemia. Current diagnostic criteria combine serum ferritin and transferrin saturation (TSAT), but inflammation may confound ferritin levels, resulting in a biologically heterogeneous population. Following HEART-FID and FAIR-HF2, the key question is which patients are most likely to benefit from intravenous (IV) iron. This narrative review synthesized randomized trials of IV iron in HF, individual patient data, aggregate meta-analyses, guideline and scientific statement documents, and mechanistic studies. PubMed was searched through 12 August 2026 using terms related to HF, ID, IV iron, circulating biomarkers, HF with preserved ejection fraction, inflammation, myocardial iron and sex differences. Key references were also searched. No systematic-review protocol or quantitative pooling was used. Six major randomized trials in HF with reduced or mildly reduced ejection fraction define the current evidence base. HEART-FID did not meet its prespecified significance threshold, and FAIR-HF2 did not clear the multiplicity adjustment; the trials differed substantially in the proportion of patients with TSAT below 20%. Across trials and pooled analyses, the most reproducible effect of ferric carboxymaltose or ferric derisomaltose is reduced HF hospitalization, with improvements in symptoms, functional capacity, and quality of life; a mortality benefit remains uncertain. TSAT below 20% is the most consistent marker of greater treatment response, whereas ferritin has not emerged as an effect modifier. Serum iron at or below 13 µmol/L is prognostically informative but remains an exploratory, cohort-derived marker that has not been prospectively validated for treatment selection. Randomized evidence in HF with preserved ejection fraction is limited to small or prematurely terminated trials and is inconclusive. In symptomatic HF with reduced or mildly reduced ejection fraction and ID, IV iron reduces HF hospitalizations and improves patient-centered outcomes, but no mortality benefit has been established. Current evidence supports restricting circulating iron availability in a treatment-responsive manner, best approximated by TSAT below 20%, rather than relying on ferritin alone to define ID. Prospective biomarker validation and adequately powered trials in HF with preserved ejection fraction and in women are priorities.

Keywords: heart failure; heart failure, systolic; iron deficiencies; ferritins; transferrin; iron; ferric compounds; infusions, intravenous

1. Introduction

Heart failure (HF) is a clinical syndrome arising from structural or functional cardiac abnormalities that reduce cardiac output or increase intracardiac pressures, with dyspnea, fatigue, and fluid retention as the usual clinical manifestations [1]. About 64 million people are affected worldwide [2]. Pharmacological and device-based therapies have improved prognosis, yet HF remains associated with recurrent hospitalization, reduced quality of life, and high healthcare expenditure.

Iron deficiency (ID) is one of the most common comorbidities in HF. Its reported prevalence ranges from about 37% to 75%, depending on the cohort, clinical setting, and diagnostic definition applied; it exceeds 50% in ambulatory HF and approaches 75% during hospitalization for acute decompensation [3,4]. ID is not merely a marker of disease severity. It contributes to impaired mitochondrial function, reduced exercise capacity, worse symptoms, and adverse cardiovascular outcomes, and these associations are observed whether or not anemia is present [5,6]. The clinical relevance of ID therefore extends beyond erythropoiesis and should be understood as a systemic and tissue-level limitation of iron availability.

The current HF definition of ID was not originally derived from HF-specific biology. It was adapted from criteria developed in advanced chronic kidney disease and then operationalized in HF trials and guidelines [7]. Patients are classified as iron-deficient when serum ferritin is below 100 µg/L, or when ferritin is between 100 and 299 µg/L with transferrin saturation (TSAT) below 20%. This definition has clear pragmatic value: it is simple, inexpensive, and clinically familiar. Its weakness is biological heterogeneity. More than one third of patients labeled iron-deficient by guideline criteria may have TSAT above 20%, and available analyses suggest that this subgroup derives little measurable benefit from intravenous (IV) iron [8].

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The problem has become more important after the most recent trials. HEART-FID, the largest randomized trial of IV iron in HF, did not meet its prespecified primary endpoint, and only about 40% of participants had TSAT below 20% [9]. FAIR-HF2, published later, reproduced a directional benefit but did not clear the formal multiplicity-adjusted threshold for its co-primary endpoints [10]. Taken superficially, these trials could be interpreted as a weakening of the IV iron evidence base. A more coherent interpretation is that the therapeutic question has changed. The field is no longer asking only whether IV iron works in HF, but which biological phenotype of iron restriction predicts benefit.

This review therefore takes HEART-FID and FAIR-HF2 as a turning point. It examines the mechanistic basis of ID in HF, the limitations of ferritin-based definitions, the prognostic and predictive role of circulating iron markers, and the practical use of IV iron in contemporary care. Unlike previous overviews that mainly catalog the trial program, it reframes the central question from whether iron deficiency is present by ferritin-based criteria to whether circulating iron availability is restricted in a way that predicts response to treatment, and develops this distinction into a framework for patient selection and future trial design anchored on TSAT, with serum iron treated as a candidate marker that still requires prospective evaluation. Its central premise is that future progress will depend less on repeating broad trials of IV iron and more on identifying the patients in whom iron availability is truly limiting for myocardial, skeletal muscle, and systemic function. The conceptual framework linking systemic drivers, circulating biomarkers, tissue iron restriction and clinical consequences is summarized in Fig. 1.

2. Methods

This is a narrative review. It is not a systematic review, and PRISMA methodology was not applied. The evidence base was assembled from the major randomized controlled trials of IV iron in HF, including FAIR-HF, CONFIRM-HF, AFFIRM-AHF, IRON-MAN, HEART-FID, FAIR-HF2, FAIR-HFpEF and IRON-HFpEF [9,10,11,12,13,14,15,16]; from the principal meta-analyses and individual-patient-data analyses published through 2025 [17,18,19,20,21]; from European and North American guideline and scientific statement documents [1,22,23]; and from mechanistic studies of systemic, myocardial, and skeletal muscle iron handling.

Priority was given to randomized trials when they reported clinical outcomes, functional outcomes, or prespecified safety analyses, and to pooled analyses when they examined the interaction between treatment effect and iron indices. Particular attention was paid to TSAT, serum iron, ferritin, trial eligibility criteria, ejection fraction phenotype, acute versus chronic HF setting, and formulation-specific safety. PubMed was searched through 12 August 2026 using combinations of the terms “heart failure”, “iron deficiency”, “ferric carboxymaltose”, “ferric derisomaltose”, “transferrin saturation”, “intravenous iron”, “heart failure with preserved ejection fraction”, “iron-carbohydrate complex”, “macrophage”, “hepcidin”, “myocardial iron” and “sex differences”, supplemented by hand-searching the reference lists of key articles and relevant guideline documents. No formal protocol governed inclusion, and no quantitative pooling was performed by the authors.

3. Iron Metabolism in Heart Failure: Systemic and Myocardial Mechanisms

3.1 Cardiomyocyte Iron and Energetics

Iron is required for cardiac energy production. Cardiomyocytes generate most of their adenosine triphosphate (ATP) through fatty acid oxidation, the citric acid cycle, and oxidative phosphorylation. Iron is a constituent of heme proteins and iron-sulfur clusters that transfer electrons along the mitochondrial respiratory chain [24,25]. When intracellular iron falls, mitochondrial respiration deteriorates, ATP output declines, and anaerobic glycolysis is upregulated as an incomplete compensatory response. Human cardiomyocytes exposed to iron depletion show reduced mitochondrial function and impaired contractile performance [5].

Iron enters cardiomyocytes mainly through TfR1-mediated uptake; under non-transferrin-bound iron-loading conditions, divalent metal transporter (DMT1), L- and T-type calcium channels may provide additional entry routes [26,27]. These routes can operate independently of erythropoietic demand, so myocardial iron status is not reducible to hemoglobin concentration. Experimental evidence that cardiomyocyte iron retention is itself required for normal contractile function is considered in the following section.

3.2 Local Regulation: The Cardiac Hepcidin-Ferroportin Axis

Cardiomyocytes are not passive recipients of systemic iron. They express ferroportin for iron export and produce hepcidin autonomously [28]. This autocrine arrangement allows the myocardium to retain iron when supply is limited and to modulate cellular iron traffic in response to systemic iron status, local oxygenation, and inflammatory signaling. Its functional importance has been shown directly. Mice with cardiomyocyte-specific deletion of hepcidin, or with knock-in of a hepcidin-resistant ferroportin, maintain essentially normal systemic iron homeostasis yet develop myocardial iron depletion with metabolic and contractile dysfunction and fatal heart failure [29]. The phenotype develops in adult animals, which attributes it to cell-autonomous loss of iron retention rather than to a defect of cardiac development. In HF, where inflammation, hypoxia, renal dysfunction, and venous congestion often coexist, systemic indices may therefore only partially reflect myocardial iron availability.

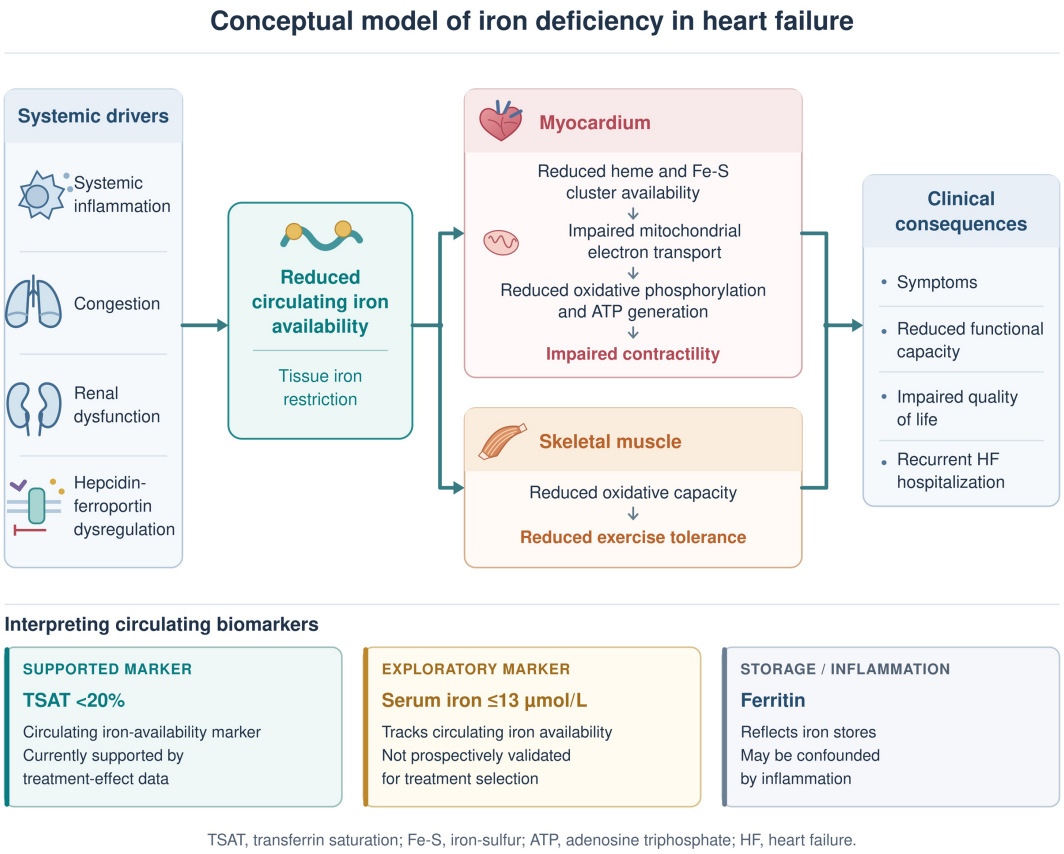


Fig. 1. Conceptual model of iron deficiency in heart failure. Systemic inflammation, congestion, renal dysfunction, and hepcidin-ferroportin dysregulation reduce circulating iron availability and promote tissue iron restriction. In the myocardium, reduced iron availability limits heme- and iron-sulfur-cluster-dependent mitochondrial electron transport, lowering oxidative phosphorylation and ATP generation. In skeletal muscle, the same restriction impairs oxidative capacity and exercise tolerance. These branches converge on symptoms, reduced functional capacity, impaired quality of life, and recurrent HF hospitalization. TSAT below 20% is the circulating-availability marker currently supported by treatment-effect data; serum iron at or below 13 µmol/L tracks the same compartment but remains exploratory and has not been prospectively validated for treatment selection. Ferritin reflects storage iron and may be confounded by inflammation. The figure is a conceptual schematic that does not represent primary data and was created using ChatGPT (OpenAI). HF, heart failure; TSAT, transferrin saturation; ATP, adenosine triphosphate.

Post-transcriptional control adds a further layer. Iron-regulatory proteins (IRP1 and IRP2) bind iron-responsive elements in untranslated regions of mRNAs encoding TfR1, ferroportin, and ferritin. Under intracellular iron scarcity, IRPs stabilize TfR1 and DMT1 transcripts and suppress translation of ferritin and ferroportin, thereby increasing iron uptake and reducing storage/export. Mice deficient in cardiac IRPs appear normal at rest but develop reduced functional reserve and higher mortality after myocardial infarction [30].

Stored iron can be mobilized by ferritinophagy, the selective autophagic degradation of ferritin mediated by nuclear receptor coactivator 4 (NCOA4) [31,32]. This pathway becomes particularly relevant when bioavailable iron is constrained. Disturbance of ferritinophagy may help explain why circulating iron indices and myocardial iron content are discordant in some HF studies: the serum compartment, storage compartment, and myocardial functional compartment are related but not interchangeable.

3.3 Anemia, Inflammation, and Extracardiac Mechanisms

Anemia in HF is multifactorial, and ID is its leading contributor, accounting for roughly half to three quarters of cases in some cohorts [33]. Chronic inflammation drives hepatic and cardiomyocyte hepcidin production; hepcidin binds and degrades ferroportin on enterocytes, hepatocytes, and macrophages, restricting iron release for erythropoiesis even when total body stores are apparently adequate [34]. This produces a functional iron-restricted state in which the problem is not necessarily the absence of stored iron, but its limited availability for tissues.

Several extracardiac mechanisms reinforce this pattern. Intestinal edema from right-sided congestion limits dietary iron absorption, and mucosal abnormalities have

been documented in more than half of HF patients with ID [35]. Renal dysfunction reduces erythropoietin production, while cytokine-mediated resistance of erythroid progenitors impairs erythropoietic response [36]. Hemodilution may mimic anemia in acutely decompensated HF [37]. These overlapping mechanisms explain why oral iron is often ineffective and why correction of anemia alone cannot capture the full clinical significance of ID in HF.

3.4 Fate of Intravenous Iron-Carbohydrate Complexes and Inflammation-Dependent Bioavailability

Intravenous iron products are not simple iron salts. Ferric carboxymaltose (FCM), ferric derisomaltose (FDI) and related preparations are nanoparticulate iron-carbohydrate complexes that behave as pro-drugs, and they are not automatically interchangeable. The semi-crystalline iron core and the carbohydrate shell determine complex stability, plasma half-life, the rate of cellular uptake and the kinetics of iron release [38]. A substantial fraction is taken up by reticuloendothelial macrophages, mainly in spleen, liver and bone marrow, where endolysosomal degradation liberates iron that can either be stored in ferritin or exported through ferroportin and loaded onto transferrin. In a randomized pharmacokinetic comparison of three preparations, all of them transiently generated non-transferrin-bound iron, with markedly different magnitude and timing; the pattern was consistent with two routes of release, direct dissociation from circulating complex and delayed, macrophage-mediated release [38].

This has implications for how ferritin should be read after treatment. Serum ferritin is derived predominantly from reticuloendothelial macrophages through a non-classical secretory pathway rather than from leakage of cytosolic ferritin alone [39]—that is, from the same compartment that handles much of an infused iron-carbohydrate complex. A sustained rise in ferritin after IV iron may therefore reflect, at least in part, macrophage iron loading or retention rather than delivery of iron to functional compartments. In an inflammatory, hepcidin-high environment, ferroportin is internalized and degraded and macrophage export may be constrained, so redistribution of iron to erythroid precursors, skeletal muscle and myocardium could plausibly be limited. This is a mechanistic hypothesis consistent with the underlying biology. It has not been demonstrated to be the principal determinant of clinical response in HF.

The macrophage-centred model is also incomplete. In patients receiving FCM, myocardial T1 fell within 3 h and remained low at 42 days, whereas the splenic signal changed later and the rise in ferritin was delayed; in mice and isolated cardiomyocytes the labile iron pool rose rapidly after FCM exposure and this was prevented by inhibitors of non-transferrin-bound iron transporters, including T- and L-type calcium channels and DMT1 [40]. Some myocardial uptake therefore appears to occur early and independently of reticuloendothelial processing. A rise in ferritin after infusion should not be equated with successful myocardial, skeletal muscle or erythroid repletion, and the same total dose may not produce the same tissue distribution across formulations or across degrees of inflammation.

4. Diagnostic Criteria for Iron Deficiency in Heart Failure: Strengths and Limitations

The European Society of Cardiology (ESC) definition of ID in HF (ferritin <100 µg/L, or ferritin 100–299 µg/L with TSAT <20%) classifies about 68% of ambulatory patients with chronic HF as iron-deficient [8]. As a prognostic marker, however, it performs poorly. In multivariable analyses, the guideline definition does not predict mortality, and lower serum ferritin is, if anything, associated with better survival [8]. This apparent paradox is informative. Ferritin behaves partly as a storage marker and partly as an inflammatory marker; in HF, the inflammatory component may dominate.

The largest dataset addressing this issue comes from Masini and colleagues, who studied 4422 patients with chronic HF across the ejection fraction spectrum [8]. TSAT below 20% and serum iron at or below 13 µmol/L were independently associated with all-cause mortality (HR 1.27, 95% CI 1.14–1.43; and HR 1.37, 95% CI 1.22–1.54, respectively). The guideline definition was not. Serum ferritin below 100 µg/L trended toward lower mortality (HR 0.91, 95% CI 0.81–1.01; $p = 0.09$). A serum iron threshold of 13 µmol/L had previously performed well against bone marrow iron staining in a much smaller validation study [41]. Both sources are observational. They support a prognostic and diagnostic role for serum iron rather than a predictive one: no randomized trial has used serum iron to select patients or tested it as a treatment target, and because serum iron is closely correlated with TSAT, any incremental value over TSAT remains to be shown. Serum iron at or below 13 µmol/L is therefore best regarded as an exploratory, cohort-derived marker and not as a stand-alone criterion for treatment.

Serum iron and TSAT were tightly correlated (r = 0.92), as expected when almost all circulating iron is transferrin-bound. Ferritin correlated weakly with serum iron (r = 0.27) and with TSAT (r = 0.41) [8]. This pattern is biologically plausible. Inflammatory activation increases ferritin synthesis and intracellular iron sequestration, so serum ferritin may be normal or high even when circulating iron available for tissue delivery is low [42,43].

One subgroup deserves particular attention. Patients with TSAT below 20% and ferritin above 300 µg/L have low hemoglobin and the highest five-year mortality (adjusted HR 3.37, 95% CI 2.57–4.42) [8]. Most trials excluded such patients for fear of iron overload. That caution is understandable, but it may also have removed a high-risk phenotype in which bioavailable iron is low despite elevated ferritin. This point should not be read as a recommen-

Table 1. Diagnostic markers for iron deficiency in heart failure.

Marker	Threshold/definition	What it reflects	Main limitations	Interpretation in HF
Serum ferritin	<100 µg/L (absolute deficit)	Storage iron; also acute-phase response	Raised by inflammation; weak correlation with TSAT and serum iron	Useful but insufficient alone; low ferritin may not identify highest-risk patients
TSAT	<20%	Circulating iron available for tissue delivery	Diurnal variation; affected by transferrin and inflammation	Most consistent marker of risk and treatment response in current analyses
Serum iron	≤13 µmol/L (exploratory, cohort-derived)	Transferrin-bound circulating iron; closely tracks TSAT	Derived mainly from one large observational cohort; not prospectively validated for treatment selection	Promising marker of circulating iron availability; not a current stand-alone treatment criterion
ESC functional ID	Ferritin 100–299 µg/L with TSAT <20%	Combined storage-plus-availability definition	Heterogeneous; ferritin component may be confounded by inflammation	Pragmatic guideline criterion; may not optimally enrich responders
Soluble transferrin receptor	Assay-dependent	Cellular iron demand; less inflammation-dependent	Limited standardization and availability	Potential adjunct marker, not routine
Hepcidin	Assay-dependent	Iron sequestration and ferroportin suppression	Variable assays; not routine	Mechanistically informative, clinically immature
Bone marrow iron staining	Qualitative reference standard	Marrow macrophage storage iron	Invasive and impractical	Diagnostic benchmark, not a clinical strategy
AFII	(albumin × –0.168) + (ferritin/CRP × –0.012) + 6.958	Inflammation- and nutrition-adjusted ferritin signal	Single-center retrospective data; unvalidated	Exploratory tool for prognosis, not yet treatment selection

AFII, Adjusted Ferritin Inflammation Index; CRP, C-reactive protein; ESC, European Society of Cardiology; HF, heart failure; ID, iron deficiency; TSAT, transferrin saturation.

dation to treat outside trial-based criteria; rather, it illustrates how ferritin thresholds may exclude patients whose biology is dominated by inflammation and iron sequestration.

The diagnostic reference standard remains bone marrow iron staining. Against that standard, ferritin below 100 µg/L has a sensitivity of about 82% and a specificity of about 72% in HF [41]. Soluble transferrin receptor and serum hepcidin have diagnostic promise but are not standardized for routine HF practice [44]. A composite metric, the Adjusted Ferritin Inflammation Index (AFII), has recently been proposed to correct ferritin for inflammatory and nutritional status. It combines serum albumin and the ferritin/C-reactive protein (CRP) ratio: AFII = (albumin × –0.168) + (ferritin/CRP × –0.012) + 6.958. In a retrospective single-center cohort of 322 patients with reduced or mildly reduced ejection fraction, an AFII above the derived cut-off independently predicted all-cause mortality, whereas ferritin and TSAT did not [45]. The index remains exploratory and requires external validation. Table 1 summarizes the available markers.

These data suggest that the diagnostic problem is not simply a matter of choosing one laboratory threshold over another. Ferritin, TSAT, serum iron, hepcidin, and soluble transferrin receptor describe different levels of iron biology: storage, circulating availability, regulation, cellular demand, and inflammatory sequestration. For treatment selection, the most relevant construct may be not classical iron deficiency, but treatment-responsive iron restriction. TSAT appears to enrich for this phenotype more consistently than ferritin and is the only marker for which subgroup and pooled treatment-effect data are currently available. Serum iron is a plausible complementary measure whose added value has not been tested prospectively.

5. Evidence From Randomized Trials of Intravenous Iron

5.1 Functional Capacity and Quality of Life

The early randomized evidence focused on symptoms, functional capacity, and patient-reported outcomes. FAIR-HF randomized 459 ambulatory patients with heart failure with reduced ejection fraction (HFrEF) and ID to ferric carboxymaltose (FCM) or placebo. At 24 weeks, FCM improved Patient Global Assessment, NYHA class, and six-minute walk distance (6MWD), with benefit evident by week 4 and independent of anemia [11]. CONFIRM-HF extended the observation to 304 patients with left ventricular ejection fraction (LVEF) below or equal to 45% over 52 weeks. The 6MWD was about 35 m greater with FCM at both 24 and 52 weeks, symptoms and quality of life improved, and HF hospitalization was reduced as a secondary endpoint [12].

These functional improvements are biologically credible. HF symptoms and exercise limitation reflect not only cardiac output but also skeletal muscle oxidative capacity, peripheral oxygen extraction, and mitochondrial function. A mechanistic study with ferric derisomaltose (FDI) showed improvement in skeletal muscle energetics within two weeks of a single infusion [46]. This supports the interpretation that IV iron acts beyond hemoglobin correction and may improve the metabolic phenotype of HF.

Oral iron has not reproduced these effects. IRONOUT-HF administered ferrous polysaccharide 150 mg twice daily to 225 patients with HFrEF and ID and found no improvement in peak oxygen uptake at 16 weeks [47]. The negative result is consistent with the pathophysiology of HF, in which hepcidin upregulation, intestinal edema, and inflammation reduce enteral iron bioavailability. For clinical practice, this distinction is important: the evidence base supporting iron therapy in HF is evidence for IV iron, not for routine oral supplementation.

5.2 Clinical Outcome Trials

AFFIRM-AHF tested FCM versus placebo in 1108 patients hospitalized for acute HF with LVEF below 50% and ID. The primary composite of total HF hospitalizations and cardiovascular death favored FCM without reaching conventional significance (rate ratio (RR) 0.79, 95% CI 0.62–1.01; $p = 0.059$). The prespecified analysis of HF hospitalizations alone was significant (RR 0.74, 95% CI 0.58–0.94; $p = 0.013$), and a COVID-19 sensitivity analysis supported the primary result (RR 0.75, 95% CI 0.59–0.96; $p = 0.024$) [13]. The trial therefore provided the first large outcome-oriented signal that IV iron may reduce recurrent HF events after acute decompensation.

IRONMAN compared FDI with usual care in 1137 predominantly ambulatory patients with LVEF ≤45% over a median follow-up of 2.7 years [14]. The primary composite of recurrent HF hospitalization and cardiovascular death showed a non-significant reduction (RR 0.82, 95% CI 0.66–1.02; $p = 0.07$), reaching significance in the COVID-adjusted analysis (RR 0.76, 95% CI 0.58–1.00; $p = 0.047$). About 76% of participants had TSAT below 20%, a much higher proportion than in HEART-FID. IRONMAN is also important because it used FDI, had longer follow-up, and provided reassurance on longer-term safety.

HEART-FID is the largest trial to date, randomizing 3065 patients with LVEF 40% or less to FCM or placebo [9]. Its hierarchical composite endpoint, analyzed as an unmatched win ratio, ranked death first, then HF hospitalization at 12 months, then change in 6MWD at 6 months. The trial did not meet its prespecified significance threshold, which had been set conservatively at $p < 0.01$, although the observed p value was 0.02. Only about 40% of participants had TSAT below 20%, compared with approximately 80% in AFFIRM-AHF and 76% in IRONMAN. In absolute terms, there were 27 fewer deaths and 35 fewer HF hospitalizations in the FCM group during the first year. These numerical differences should not be overinterpreted, but the trial is difficult to summarize as simply negative. Its design may have reduced the probability of detecting benefit by enrolling a relatively broad iron-deficiency phenotype.

FAIR-HF2 randomized 1105 ambulatory patients with HFrEF (LVEF ≤45%) and ID to FCM or placebo over a median 16.6 months, using a higher maintenance-dose strategy than earlier FCM trials [10]. The hazard ratio for cardiovascular death or first HF hospitalization was 0.79 (95% CI 0.63–0.99; $p = 0.04$), but this did not clear the multiplicity-adjusted threshold set for the co-primary endpoints. Total HF hospitalizations were reduced non-significantly (RR 0.80, 95% CI 0.60–1.06; $p = 0.12$), while quality-of-life and global well-being measures improved. Nearly 70% of patients had TSAT below 20%. FAIR-HF2 therefore adds a clinically coherent but statistically cautious piece of evidence: it points in the same direction as earlier trials, but it does not settle the outcome question alone.

Randomized evidence in HF with preserved ejection fraction (HFpEF) is far more limited. FAIR-HFpEF was designed to enroll 200 patients but was stopped for slow recruitment after 39 had been randomized. At 24 weeks the change in six-minute walk distance favored FCM (least-squares mean difference 49 m, 95% CI 5–93; $p = 0.029$), while changes in secondary endpoints did not differ significantly between groups [15]. The trial had insufficient power to establish either efficacy or safety in HFpEF. IRON-HFpEF, a mechanistic phase II trial in 45 patients with HFpEF and ID but without iron-deficiency anemia, found no effect of FCM on pulmonary capillary wedge pressure during exercise, on myocardial or calf-muscle high-energy phosphate metabolism, on NT-proBNP or on Kansas City Cardiomyopathy Questionnaire score; exploratory analyses showed improvement in right ventricular ejection fraction, in microvascular perfusion and, after adjustment for baseline differences, in six-minute walk distance [16]. Both trials are hypothesis-generating. Neither establishes a clinical indication for IV iron in HFpEF.

5.3 Interpreting Apparently Borderline Trials

The trial program is more coherent when differences in design are considered. First, acute and chronic HF trials ask related but distinct questions. AFFIRM-AHF tests post-discharge vulnerability after decompensation, whereas FAIR-HF, CONFIRM-HF, HEART-FID, and FAIR-HF2 mainly address ambulatory chronic HF. Second, endpoints differ substantially: symptom and exercise endpoints are more sensitive to metabolic improvement, whereas death and hospitalization composites require larger samples, longer exposure, and a sufficiently enriched risk phenotype. Third, the COVID-19 pandemic affected event rates and follow-up in AFFIRM-AHF and IRONMAN, creating sensitivity analyses that should be interpreted cautiously but not ignored.

Fourth, the proportion of patients with TSAT below 20% differs markedly across trials. This may be the most important source of heterogeneity. If low TSAT identifies the biological state in which iron availability limits clinical function, then trials enrolling many patients with TSAT ≥20% are expected to show smaller average effects. HEART-FID is the clearest example. Conversely, AFFIRM-AHF and IRONMAN, both with higher proportions of low-TSAT patients, showed stronger event signals. This does not prove predictive validity for TSAT, but it provides a plausible framework for reconciling results that otherwise appear inconsistent.

Finally, FCM and FDI should not be treated as identical simply because both are IV iron formulations. The available evidence supports both, but formulation, dosing, maintenance strategy, and safety profile differ. FCM has the larger HF trial base, including FAIR-HF, CONFIRM-HF, AFFIRM-AHF, HEART-FID, and FAIR-HF2. FDI is supported by IRONMAN and by mechanistic evidence on skeletal muscle energetics [14,46]. Direct comparisons in HF are lacking. The choice between formulations in practice is therefore guided by local availability, dosing logistics, patient characteristics, and safety considerations rather than definitive head-to-head outcome data. The major trials are compared in Table 2.

6. Meta-Analyses and Patient-Level Evidence: Does TSAT Identify Responders?

Pooled analyses are more consistent than individual trials. A 2023 meta-analysis combining AFFIRM-AHF, IRONMAN, and smaller studies reported a significant reduction in the composite of recurrent HF hospitalization or cardiovascular death with IV iron (RR 0.75, 95% CI 0.61–0.93), driven mainly by fewer hospitalizations [17]. This pattern is aligned with the individual trials: event reductions are seen most consistently for HF hospitalization, while mortality effects are weaker and statistically uncertain.

The signal becomes more clinically informative when stratified by TSAT. In that same 2023 meta-analysis, patients with TSAT below 20% appeared to benefit more for the composite of first HF hospitalization or cardiovascular death (OR 0.67, 95% CI 0.49–0.92) than patients with TSAT ≥20% (OR 0.99, 95% CI 0.74–1.30), although the test for heterogeneity was not conclusive (p = 0.07) [17]. A subsequent meta-analysis with meta-regression, covering 14 trials and 6624 patients, reported reductions in cardiovascular death (OR 0.87, 95% CI 0.76–0.96), in the composite of cardiovascular death and HF admission (OR 0.84, 95% CI 0.75–0.94) and in total HF admissions (rate ratio 0.74, 95% CI 0.66–0.83), and found that trials enrolling cohorts with lower baseline TSAT showed larger effects on HF events [18]. Ferritin has not emerged as a modifier of treatment effect in either analysis. These observations are the empirical basis of the emerging patient-selection framework, and they rest on subgroup and trial-level comparisons rather than on randomization by biomarker status.

An individual-patient-data analysis of CONFIRM-HF, AFFIRM-AHF, and HEART-FID found a reduction in cardiovascular hospitalization and mortality at TSAT below 20% (RR 0.80, 95% CI 0.67–0.95) but not at TSAT ≥20% (RR 1.00, 95% CI 0.81–1.23) [19]. It also raised a hypothesis-generating concern about possible excess events above a TSAT of 24%. This should not be interpreted as evidence of harm at a rigid threshold. It is better viewed as a signal that the therapeutic window for IV iron may be narrower than guideline eligibility implies.

The most recent meta-analysis, including more than 7000 patients and incorporating HEART-FID and FAIR-HF2, confirmed a reduction in the 12-month composite of cardiovascular death and HF hospitalization (RR 0.72, 95% CI 0.55–0.89), again mainly through reduced hospitalization (RR 0.69, 95% CI 0.48–0.88), with a non-significant trend for cardiovascular mortality (HR 0.80, 95% CI 0.61–1.03) [20]. Male sex was the only subgroup with a significant interaction; women showed no clear prognostic improvement (RR 0.98, 95% CI 0.75–1.26). A dedicated FAIR-HF2 analysis reported sex-specific outcomes and a less favorable safety signal in women, but this requires confirmation before it changes practice [48].

A further 2025 meta-analysis pooled 14 randomized trials and 7786 participants, with a literature search extending to 4 March 2024 [21]. IV iron reduced the composite of total HF hospitalization and cardiovascular death (RR 0.82, 95% CI 0.72–0.92) and total HF hospitalization (RR 0.78, 95% CI 0.66–0.91), and improved six-minute walk distance (weighted mean difference 18.99 m, 95% CI 7.41–30.57). For endpoints analysed as dichotomous outcomes the reported estimates were odds ratios: first HF hospitalization or cardiovascular death OR 0.78 (95% CI 0.65–0.93), cardiovascular death OR 0.86 (95% CI 0.76–0.98) and all-cause mortality OR 0.93 (95% CI 0.83–1.04). Benefit again appeared larger in patients with TSAT below 20%. Because the search predated FAIR-HF2, this analysis does not incorporate the most recent randomized data, and the nominally significant estimate for cardiovascular death should not be read as establishing a mortality benefit; the more recent pooled analysis that includes FAIR-HF2 found only a non-significant trend for cardiovascular mortality [20]. What is consistent across these analyses is the reduction in HF hospitalization.

These pooled results support a cautious but actionable interpretation. IV iron should not be presented as a mortality-reducing therapy on current evidence. It should be presented as a therapy that improves symptoms and quality of life and reduces HF hospitalization, particularly when the patient has evidence of reduced circulating iron availability. TSAT below 20% is the most consistent marker of that state, although it remains imperfect and should be interpreted alongside the clinical context.

Table 2. Major randomized trials of intravenous iron in heart failure.

Trial	N/setting	Population and eligibility	Iron strategy	Low-TSAT enrichment	Primary result	Key interpretation
FAIR-HF (2009)	459; ambulatory chronic HF	Symptomatic HFrEF with guideline-defined ID	FCM vs placebo	Not central to design	PGA, NYHA class, and 6MWD improved at 24 weeks	Established symptomatic and functional benefit independent of anemia
CONFIRM-HF (2015)	304; ambulatory chronic HF	LVEF ≤45% with ID	FCM vs placebo, longer follow-up	Not central to design	6MWD improved by about 35 m at 24 and 52 weeks; fewer HF hospitalizations as secondary endpoint	Extended functional evidence and suggested hospitalization benefit
AFFIRM-AHF (2020)	1108; post-acute HF hospitalization	LVEF <50% with ID before discharge	FCM vs placebo	Approx. 80% TSAT <20%	Total HF hospitalization + CV death: RR 0.79 (0.62–1.01), $p = 0.059$; HF hospitalization alone RR 0.74, $p = 0.013$	Strong post-discharge signal, mainly on recurrent HF hospitalization
IRONMAN (2022)	1137; mostly ambulatory; median 2.7 years	LVEF ≤45%; TSAT <20% with ferritin <400 µg/L or ferritin <100 µg/L	FDI vs usual care	Approx. 76% TSAT <20%	Recurrent HF hospitalization + CV death: RR 0.82 (0.66–1.02), $p = 0.07$; COVID-adjusted RR 0.76, $p = 0.047$	Longest follow-up; supports FDI and longer-term safety
HEART-FID (2023)	3065; ambulatory HFrEF	LVEF ≤40% with recent HF hospitalization or elevated natriuretic peptides and ID	FCM vs placebo	Approx. 40% TSAT <20%	Hierarchical death/HF hospitalization/6MWD endpoint: $p = 0.02$, not meeting: $p < 0.01$ threshold	Largest trial; broad eligibility may have diluted treatment effect
FAIR-HF2 (2025)	1105; ambulatory HFrEF	LVEF ≤45% with ID	FCM vs placebo with higher maintenance-dose strategy	Approx. 70% TSAT <20%	CV death or first HF hospitalization: HR 0.79 (0.63–0.99), $p = 0.04$, below multiplicity threshold; total HF hospitalizations RR 0.80, $p = 0.12$	Directional benefit consistent with earlier trials but statistically cautious
FAIR-HFpEF (2024)	39 randomized of 200 planned; ambulatory HFpEF; stopped early for slow recruitment	Symptomatic HFpEF with guideline-defined ID (ferritin <100 pg/L, or 100–299 pg/L with TSAT <20%)	FCM vs placebo (saline)	Not applied as an enrichment criterion	6MWD at 24 weeks: least-squares mean difference 49 m (95% CI 5–93), $p = 0.029$; secondary endpoints not significantly different	Prematurely terminated and underpowered; hypothesis-generating for HFpEF, not definitive evidence of efficacy or safety
IRON-HFpEF (2026)	45; ambulatory HFpEF; mechanistic phase II	LVEF ≥50% with ID, excluding iron-deficiency anemia	FCM vs placebo	Not applied as an enrichment criterion	No effect on exercise pulmonary capillary wedge pressure (mean change –1.0 mmHg, 95% CI –4 to 2; $p = 0.52$); no change in myocardial or calf-muscle high-energy phosphates, NT-proBNP or KCCQ	Small mechanistic trial; exploratory improvement in right ventricular ejection fraction, microvascular perfusion and adjusted 6MWD

6MWD, six-minute walk distance; CV, cardiovascular; FCM, ferric carboxymaltose; FDI, ferric derisomaltose; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ID, iron deficiency; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PGA, Patient Global Assessment; TSAT, transferrin saturation; NYHA, New York Heart Association; RR, rate ratio; HR, hazard ratio; OR, odds ratio; CI, confidence interval.

7. Practical Clinical Implications

For current practice, the clearest candidates for IV iron are symptomatic patients with HFrEF or HF with mildly reduced ejection fraction (HFmrEF) and TSAT below 20%. Coexisting anemia, which is common in this subgroup, strengthens the clinical rationale but is not required for benefit. Patients with TSAT ≥20% who meet guideline criteria only because ferritin is below 100 µg/L probably have a lower likelihood of response. This does not mean they can never benefit; rather, it means that the available evidence is less persuasive, and the risk-benefit discussion should be more cautious [18,19].

Patients with ferritin above 400 µg/L and TSAT below 20% represent a difficult and clinically important group. They were excluded from several trials because of concern for overload, yet they may reflect severe inflammation-driven iron sequestration rather than excess bioavailable iron. In such patients, TSAT suggests restricted circulating iron availability, while ferritin may reflect inflammation or tissue storage. Because prospective trial evidence is limited, treatment outside guideline-based criteria should not be routine. The point is that future trials should deliberately address this phenotype instead of excluding it by default [7,8].

HFpEF requires a separate and more conservative position. All of the outcome evidence, and almost all of the randomized evidence, comes from patients with reduced or mildly reduced ejection fraction. The two randomized trials conducted in HFpEF were small, one was terminated early, and neither was powered for clinical outcomes or for safety [15,16]. Routine extension of the TSAT-based framework to HFpEF is therefore not recommended here. A TSAT below 20% does not by itself constitute an HF-specific indication for IV iron in HFpEF, and the modest functional signal observed in FAIR-HFpEF should be treated as hypothesis-generating while adequately powered trials are awaited. Where treatment is considered in an individual patient with HFpEF, the decision should rest on a recognized indication for iron repletion other than extrapolation from the HFrEF and HFmrEF trials—for example symptomatic iron-deficiency anemia or another established hematological or gastrointestinal indication—and on the applicable local regulatory and reimbursement framework. Table 3 summarizes this position.

Timing is another practical issue. AFFIRM-AHF and IRONMAN support assessment and treatment around the vulnerable post-discharge period in patients hospitalized for HF with reduced or mildly reduced ejection fraction and ID [13,14]. In ambulatory patients, routine review provides an opportunity to screen, treat, and monitor without waiting for decompensation. Hemoglobin and iron indices should be reassessed 4–6 weeks after the first infusion and then once or twice yearly. Re-dosing is reasonable when TSAT falls again below 20%, particularly if symptoms, anemia, or recurrent HF events are present [7].

A recurrent or rapidly relapsing iron deficit should not be considered automatically as a need for repeated infusion. It should prompt assessment for blood loss and reversible contributors, especially gastrointestinal and urinary tract sources. Active uncontrolled infection remains a reasonable reason to defer infusion. Table 3 provides a practical approach that is consistent with the evidence base while acknowledging the unresolved diagnostic questions.

8. Safety of Intravenous Iron Therapy

Modern IV iron formulations have a reassuring safety profile across the HF trial program. Hypersensitivity reactions occur but are uncommon, in the order of 0.1–1% of patients [49]. Serious anaphylactic reactions are rare with contemporary preparations, although infusion should still occur in a setting able to recognize and manage acute reactions. Most reactions are mild and self-limited, but prior infusion reactions, multiple drug allergies, and active inflammatory states may justify additional caution.

Hypophosphatemia is the most formulation-specific concern. It is more closely associated with FCM than with FDI. FCM can increase fibroblast growth factor 23 (FGF23), which suppresses renal phosphate reabsorption and increases urinary phosphate loss [50]. In many patients, the reduction in phosphate is mild and transient. The clinical relevance increases when repeated infusions are given, when baseline vitamin D deficiency or malnutrition is present, or when symptoms such as weakness, bone pain, or unexplained fatigue occur. Periodic phosphate measurement is therefore reasonable in patients receiving repeated FCM, even though systematic monitoring is not uniformly mandated.

Concerns about iron overload, oxidative stress, and infection have not been confirmed in HF trials. A 2023 meta-analysis of 12 trials including 4376 patients with HFrEF and ID found a comparable rate of infection-related adverse events with IV iron and standard care (risk ratio 0.86, 95% CI 0.74–1.00) [51]. IRONMAN, with the longest follow-up among the large outcome trials, found no association between IV iron and adverse events over a median of 2.7 years [14].

The absence of a safety signal in trials does not eliminate the need for individualized caution. Trial populations are selected, and patients with active infection, very high ferritin, or other complex inflammatory states are often under-represented. The safest clinical approach is to avoid infusion during uncontrolled infection, avoid treatment when TSAT is already adequate unless there is a specific reason, and reassess biomarkers before repeat dosing.

9. Current Guideline Recommendations

The 2021 ESC HF guidelines recommended routine screening for ID in all HF patients (Class I, Level C) and IV iron for symptomatic HFrEF with ID (Class IIa, Level A) [1]. The 2023 focused update strengthened the treat-

Table 3. Practical approach to patient selection, timing, monitoring, and safety.

Domain	Practical approach	Rationale/caveat
Screening	Check hemoglobin, ferritin, and TSAT in symptomatic HF and around hospitalization for acute HF	Guidelines support screening; TSAT should not be overlooked when ferritin is low or high
Most likely responders	Symptomatic HFrEF or HFmrEF with TSAT <20%, particularly with anemia, recent hospitalization, or impaired functional capacity	Low TSAT best enriches for risk and treatment response in pooled analyses
Lower-probability responders	Patients qualifying only by ferritin <100 µg/L with TSAT ≥20%	Available analyses show little average benefit in this phenotype; avoid automatic retreatment
Uncertain high-risk phenotype	TSAT <20% with ferritin >300–400 µg/L	May represent inflammation-driven sequestration; under-represented in trials; future studies needed
HFpEF with low TSAT	Do not extend the TSAT-based framework routinely. Treat only when a recognized indication for iron repletion exists other than extrapolation from HFrEF/HFmrEF trials, and within the applicable local regulatory framework	Randomized HFpEF data are limited to two small trials, one stopped early; TSAT <20% alone is not currently an HF-specific indication for intravenous iron in HFpEF
Formulation and dose	FCM or FDI according to local availability, dosing logistics, and patient factors; use weight- and hemoglobin-based tables where appropriate	FCM has the largest HF trial base; FDI has outcome evidence from IRONMAN and lower hypophosphatemia tendency
Timing	Consider treatment before discharge after acute HF when criteria are met; treat ambulatory patients during routine review if symptomatic and low TSAT	Post-discharge period is vulnerable; ambulatory treatment may improve symptoms and reduce events
Monitoring	Reassess hemoglobin, ferritin, TSAT and clinical response 4–6 weeks after infusion, then once or twice yearly; interpret ferritin together with TSAT, hemoglobin, time since infusion and clinical response	Biomarker recurrence and clinical recurrence may not coincide. A rise in ferritin alone does not prove successful repletion and may partly reflect macrophage iron handling; do not repeat dosing blindly on the basis of a single marker
Re-dosing	Repeat treatment when TSAT again falls below 20% and the clinical context supports iron restriction	Persistent or recurrent ID should prompt search for blood loss and reversible causes
Safety	Avoid infusion during uncontrolled active infection; consider phosphate monitoring with repeated FCM; be cautious when TSAT is adequate	Trial safety is reassuring, but selected populations do not eliminate real-world caution

FCM, ferric carboxymaltose; FDI, ferric derisomaltose; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; TSAT, transferrin saturation.

ment recommendation to Class I, Level A for symptomatic HFrEF or HFmrEF with ID, with the aim of relieving symptoms and improving quality of life. It also supported assessment of iron status before discharge or at the first review after an acute HF admission [22].

North American guidance has historically been more conservative, acknowledging potential benefit in selected patients without adopting the same strength of operational recommendation. The Heart Failure Society of America scientific statement provides a detailed appraisal of the diagnostic and therapeutic evidence [23]. The divergence between guideline traditions should not be overstated. Both European and North American perspectives recognize that ID is clinically relevant in HF. The difference lies more in how confidently treatment criteria are operationalized.

10. Unresolved Issues and Future Directions

The optimal definition of ID in HF remains unsettled. A shift toward TSAT, with less reliance on ferritin, appears biologically and clinically defensible but still requires prospective validation. Serum iron correlates closely with TSAT and performs well in observational cohorts, yet it has never been used to select patients into a randomized trial, and its incremental predictive value over TSAT is unknown [7,8]. Future trials should test biomarker-defined phenotypes rather than repeat broad guideline-based inclusion. A biomarker-stratified design would use TSAT below 20% as the principal and currently supported eligibility criterion; measure serum iron prospectively in all participants; prespecify concordant and discordant TSAT and serum-iron strata; formally test the interaction between treatment and serum iron at or below 13 µmol/L; and treat ferritin as a stratification and safety variable rather than as evidence of bioavailable iron. A trial of this design would establish whether serum iron adds predictive information beyond TSAT, instead of assuming that the two criteria are already equivalent.

HFpEF is the largest remaining gap. FAIR-HFpEF and IRON-HFpEF together randomized fewer than 90 patients and were designed for functional and mechanistic endpoints [15,16]. An adequately powered randomized trial in HFpEF with objectively documented restriction of circulating iron availability, using recurrent HF hospitalization and patient-reported outcomes, is required before the selection framework proposed here can reasonably be extended beyond reduced and mildly reduced ejection fraction.

Myocardial iron imaging remains a research tool. Cardiac magnetic resonance T2* and T1 mapping can track myocardial iron content, and the randomized Myocardial-IRON study documented measurable myocardial iron repletion after IV FCM in HF with ID [52]; rapid and sustained changes in myocardial T1 after FCM have also been reported [40]. Direct tissue studies show discordance between serum iron indices and myocardial iron content, which supports the view that current biomarkers may not fully capture tissue-level iron availability [53]. The practical obstacles are substantial. These studies are expensive, available in a minority of centres and dependent on dedicated expertise; measured values vary with field strength, pulse sequence, scanner platform and local protocol, and multicentre standardization is insufficient. T2* is far better validated for iron overload than for quantifying iron deficiency, and native T1 is also influenced by edema, fibrosis and other tissue characteristics, so a change in signal is not necessarily a change in iron. No validated cut-off defines treatment-responsive myocardial iron deficiency, and no study has shown that a change in myocardial iron content predicts functional improvement or a reduction in clinical events. Imaging may eventually help future trials connect systemic biomarkers, tissue repletion, and clinical response, but it is not ready for routine diagnostic use.

The sex-specific signal from recent pooled analyses also requires careful investigation. It may reflect biological differences in iron metabolism, baseline risk, body size, absolute iron dose, menopausal status, or statistical instability within subgroup analyses. It should not lead to withholding treatment from women who meet current criteria. It does, however, justify prespecified sex-stratified analyses in future trials and may eventually inform dosing or monitoring strategies [20,48]. Beyond stratified analysis, an adequately powered randomized trial conducted specifically in women appears justified. Such a trial would enroll women with symptomatic HFrEF or HFmrEF and TSAT below 20%; stratify by menopausal status or age, anemia, baseline TSAT, ferritin and inflammatory status, body weight and absolute iron dose; compare IV iron with placebo or usual care according to the applicable regulatory context; and assess recurrent HF hospitalization, cardiovascular death, Kansas City Cardiomyopathy Questionnaire score, six-minute walk distance and safety, including hypophosphatemia and the consequences of repeated dosing. It should be designed to distinguish genuine effect modification from the limited power of earlier subgroup analyses. The present signal is hypothesis-generating and is not evidence that IV iron is ineffective in women.

Newer high-absorption oral preparations, including sucrosomial iron, have shown preliminary promise and may suit selected patients, although HF-specific evidence remains limited [54,55]. They should not be considered substitutes for IV iron where IV iron is evidence-based, but they may become relevant for maintenance strategies, mild deficiency, or settings where infusion access is difficult. The optimal frequency of re-dosing, duration of maintenance therapy, and threshold for retreatment remain unresolved.

Finally, the conceptual boundary between iron deficiency, iron restriction, and iron overload deserves refinement. HF is an inflammatory and metabolic syndrome in which circulating availability, tissue storage, cellular demand, and myocardial utilization may diverge. The next phase of research should integrate TSAT, serum iron, ferritin, hepcidin, soluble transferrin receptor, CRP, myocardial imaging, and patient-reported outcomes into a more coherent treatment-response model.

11. Limitations of This Review

This review has the limitations inherent to a narrative design. It was not based on a registered protocol, formal risk-of-bias assessment, or original quantitative pooling. Trial results and pooled analyses are interpreted in light of mechanistic plausibility and biomarker biology, but such interpretation cannot replace prospectively designed comparative studies. Some conclusions about TSAT, sex-specific response, and possible upper thresholds for benefit are based on subgroup or meta-regression analyses and should therefore be considered hypothesis-generating.

A further limitation concerns ejection fraction phenotype. Almost all of the available evidence, and all of the outcome evidence, comes from patients with reduced or mildly reduced ejection fraction. In HFpEF the randomized data are confined to two small trials, one of which was stopped early for slow recruitment, and neither was powered for clinical outcomes or for safety [15,16]; the conclusions of this review about patient selection should not be extended to that population. Similarly, patients with very high ferritin and low TSAT, active inflammatory conditions, advanced kidney disease, or repeated infusion needs are incompletely represented in randomized data. These gaps should be made explicit when applying trial evidence to complex real-world patients.

12. Conclusions

ID is a frequent and clinically meaningful comorbidity in HF, with effects on functional capacity, symptoms, hospitalization, and survival that are independent of anemia and linked to cardiomyocyte, skeletal muscle, and mi-

tochondrial energy metabolism. The current guideline definition has supported trial design and implementation, but it has limited diagnostic and prognostic precision. Ferritin, as an acute-phase reactant, may reflect inflammation more than usable iron; TSAT identifies higher-risk patients and likely responders more reliably, and serum iron is a promising but not yet prospectively validated complement.

Across FAIR-HF, CONFIRM-HF, AFFIRM-AHF, IRONMAN, HEART-FID, FAIR-HF2, and pooled analyses, IV iron with FCM or FDI reduces HF hospitalizations and improves symptoms, exercise capacity, and quality of life. A mortality benefit has not been established. The most plausible interpretation of the current evidence is not that IV iron is broadly ineffective, but that benefit is concentrated in patients with a biologically relevant restriction of circulating iron availability.

The future of IV iron therapy in HF will depend on the ability to distinguish treatment-responsive iron restriction from a nonspecific abnormality of iron biomarkers. Refining diagnostic criteria, validating TSAT-based selection and testing whether serum iron adds predictive value, clarifying sex differences, generating adequately powered evidence in HFpEF, improving safety monitoring, and linking systemic biomarkers to myocardial and skeletal muscle iron biology are the priorities that follow from the evidence assembled here.

Author Contributions

LBel, MG, and LBon: conceived and designed the review, performed the literature selection and synthesis, drafted the manuscript, and revised it critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used the AI-assisted grammar and language-editing tools built into Microsoft Word for grammar checking and language editing, and used ChatGPT (OpenAI) to generate the conceptual schematic shown in Fig. 1. No artificial-intelligence tool was used to generate, analyze, or interpret study data or to draft the scientific content of the manuscript. Fig. 1 is a conceptual illustration and does not represent primary or experimental data. The authors reviewed and edited all AI-assisted output, including the figure, and take full responsibility for the content of the manuscript.

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