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Systematic Review

Iron Supplementation in Heart Failure Patients with Chronic Kidney Disease: Clinical Outcomes, Safety, and Contemporary Evidence: A Systematic Review

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Abstract:

Heart failure (HF) and chronic kidney disease (CKD) frequently coexist, forming a complex cardiorenal syndrome associated with increased morbidity, mortality, and healthcare utilization. Iron deficiency, affecting nearly half of patients with chronic HF and an even greater proportion of those with concomitant CKD, has emerged as an independent determinant of reduced functional capacity, impaired quality of life, recurrent hospitalization, and adverse cardiovascular outcomes. The pathophysiology of iron deficiency in this population extends beyond nutritional depletion and is characterized by chronic inflammation, elevated hepcidin concentrations, impaired intestinal iron absorption, reduced iron mobilization, and altered erythropoiesis. Consequently, conventional oral iron therapy often demonstrates limited efficacy, whereas intravenous iron formulations have shown promising clinical benefits. This systematic review synthesizes current evidence regarding the efficacy, safety, and clinical outcomes of iron supplementation in patients with HF and CKD. A comprehensive search of PubMed/MEDLINE, Embase, Scopus, Web of Science, the Cochrane Library, and Google Scholar identified studies evaluating iron supplementation in adult patients with concomitant HF and CKD. Randomized controlled trials, observational studies, systematic reviews, and meta-analyses reporting cardiovascular, renal, hematological, functional, or quality-of-life outcomes were included. The available evidence consistently demonstrates that intravenous iron, particularly ferric carboxymaltose and ferric derisomaltose, improves exercise tolerance, New York Heart Association functional class, six-minute walk distance, health-related quality of life, and iron indices while reducing HF-related hospitalizations. Oral iron supplementation showed limited therapeutic benefit because of impaired gastrointestinal absorption and inflammation-mediated iron sequestration. Although improvements in all-cause mortality remain inconclusive, contemporary evidence supports intravenous iron as an important adjunctive therapy in appropriately selected patients with HF and CKD. Current international guidelines increasingly recommend routine screening for iron deficiency and individualized iron replacement strategies in patients with chronic HF. Future large-scale studies with longer follow-up are needed to determine optimal treatment protocols, evaluate long-term renal outcomes, compare intravenous iron formulations directly, and identify patient subgroups most likely to benefit from therapy.

Keywords: Heart Failure; Chronic Kidney Disease; Iron Deficiency; Intravenous Iron; Ferric Carboxymaltose; Ferric Derisomaltose.

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Introduction

Heart failure (HF) and chronic kidney disease (CKD) are two of the most prevalent chronic disorders worldwide and frequently coexist because of their shared risk factors, overlapping pathophysiological mechanisms, and bidirectional disease progression [1]. Together, these conditions constitute one of the greatest challenges in modern cardiovascular and renal medicine, contributing substantially to healthcare expenditure, repeated hospitalizations, reduced quality of life, and premature mortality. Epidemiological studies estimate that approximately 40–60% of patients with chronic HF have some degree of renal dysfunction, while cardiovascular disease remains the leading cause of death among individuals with CKD [2]. The coexistence of HF and CKD amplifies disease severity beyond the impact of either condition alone, creating a complex clinical entity commonly referred to as cardiorenal syndrome, in which dysfunction of one organ accelerates deterioration of the other.

The burden of HF continues to increase globally owing to population aging, improved survival following myocardial infarction, and rising

prevalence of hypertension, diabetes mellitus, obesity, and chronic kidney disease [3]. More than 64 million people worldwide are currently affected by HF, making it one of the most common causes of hospitalization among older adults. Despite remarkable advances in pharmacological and device-based therapies, morbidity and mortality remain unacceptably high. Five-year survival following diagnosis remains lower than that of many common malignancies, emphasizing the need to address modifiable contributors to disease progression beyond conventional neurohormonal blockade [4].

Similarly, CKD affects nearly 10% of the global population and represents a major public health challenge because of its progressive nature and close association with cardiovascular complications [5]. Declining renal function leads to disturbances in fluid homeostasis, electrolyte balance, endocrine regulation, erythropoiesis, and mineral metabolism. Importantly, CKD also profoundly alters iron metabolism through chronic inflammation, impaired intestinal absorption, increased hepcidin production, and reduced erythropoietin synthesis. These abnormalities contribute not only to anemia but also to functional iron deficiency, which may occur even in patients with apparently adequate iron stores [6].

Among the numerous comorbidities accompanying HF and CKD, iron deficiency has emerged as one of the most clinically significant yet frequently underdiagnosed disorders. Traditionally, iron deficiency was considered important primarily because of its role in anemia. However, contemporary research has demonstrated that iron deficiency adversely affects cardiovascular function, skeletal muscle metabolism, mitochondrial respiration, exercise capacity, cognitive performance, and overall quality of life, even in the absence of anemia [7]. Consequently, iron deficiency is now recognized as an independent therapeutic target in patients with chronic HF.

Iron is an essential micronutrient involved in oxygen transport, oxidative phosphorylation, ATP generation, DNA synthesis, and mitochondrial energy production. Nearly every metabolically active tissue depends upon adequate intracellular iron availability to maintain normal physiological function [8]. Cardiomyocytes possess exceptionally high metabolic demands and rely heavily on mitochondrial oxidative metabolism for ATP production. Iron deficiency therefore impairs myocardial bioenergetics, reduces contractile efficiency, and contributes to progressive ventricular dysfunction independent of hemoglobin concentration [9]. Likewise, skeletal muscle dysfunction resulting from impaired mitochondrial activity contributes significantly to exercise intolerance observed in patients with chronic HF.

The interaction between HF and CKD further complicates iron metabolism. Chronic systemic inflammation, a hallmark of both conditions, stimulates hepatic production of hepcidin, the master regulator of systemic iron homeostasis [10]. Hepcidin binds to ferroportin, the principal iron export protein located on enterocytes, hepatocytes, and macrophages, inducing its internalization and degradation. Consequently, dietary iron absorption decreases while iron stored within macrophages and hepatocytes becomes unavailable for erythropoiesis and cellular metabolism. This phenomenon results in functional iron deficiency, characterized by adequate or increased total body iron stores but insufficient circulating iron available for biological utilization.

Unlike absolute iron deficiency, in which iron stores are depleted because of inadequate intake, chronic blood loss, or malabsorption, functional iron deficiency results primarily from inflammatory iron sequestration. This distinction has important therapeutic implications because oral iron supplementation may adequately correct absolute deficiency but frequently fails to overcome inflammation-mediated hepcidin excess characteristic of HF and CKD [11].

Table 1: Absolute versus Functional Iron Deficiency in Heart Failure and Chronic Kidney Diseas

Characteristic	Absolute Iron Deficiency	Functional Iron Deficiency
Ferritin	Low	Normal or elevated
Transferrin saturation (TSAT)	Low	Low
Total body iron stores	Depleted	Preserved
Hepcidin concentration	Low	Elevated
Primary mechanism	Blood loss, malnutrition, malabsorption	Chronic inflammation and iron sequestration
Typical clinical setting	Nutritional deficiency	Heart failure, CKD, chronic inflammatory disease
Preferred treatment	Oral or intravenous iron	Primarily intravenous iron

Recognition of functional iron deficiency has fundamentally changed contemporary management of patients with HF and CKD. International cardiology and nephrology guidelines now

recommend routine assessment of serum ferritin and transferrin saturation (TSAT) because hemoglobin concentration alone inadequately reflects iron status [12]. Current diagnostic criteria generally define iron deficiency in HF as serum ferritin <100 ng/mL or ferritin 100–299 ng/mL with TSAT <20%, acknowledging the influence of inflammation on ferritin interpretation [13].

The prevalence of iron deficiency among patients with chronic HF ranges between 35% and 60%, increasing further among those with advanced disease, reduced ejection fraction, repeated hospitalization, and concomitant CKD [14]. Several observational studies have demonstrated that iron deficiency independently predicts reduced exercise capacity, poorer functional status, diminished health-related quality of life, increased hospitalization, and higher mortality irrespective of anemia. These findings suggest that iron deficiency represents not merely a laboratory abnormality but an important mediator of disease progression.

The pathophysiological relationship between iron deficiency and HF is multifactorial. Reduced gastrointestinal perfusion resulting from diminished cardiac output may impair nutrient absorption. Chronic intestinal edema associated with venous congestion further limits iron uptake, while prolonged use of proton pump inhibitors may decrease gastric acidity required for iron absorption [15]. Simultaneously, chronic inflammation stimulates cytokine production, particularly interleukin-6 (IL-6), which enhances hepatic hepcidin synthesis and promotes iron sequestration within the reticuloendothelial system. Frequent phlebotomy, occult gastrointestinal bleeding, anticoagulant therapy, and reduced dietary intake may further exacerbate iron depletion.

CKD introduces additional mechanisms contributing to iron dysregulation. Declining renal function reduces endogenous erythropoietin production, impairing erythropoiesis despite adequate iron stores [16]. Uremic toxins inhibit erythroid progenitor cell proliferation, while chronic inflammation further suppresses erythropoietic activity. Hemodialysis patients may experience repeated blood loss during dialysis sessions and laboratory investigations, accelerating iron depletion. Consequently, patients with concomitant HF and CKD frequently exhibit both absolute and functional iron deficiency, creating a particularly challenging therapeutic environment.

Over the past decade, growing evidence has challenged the traditional assumption that oral iron supplementation adequately corrects iron deficiency in HF. Randomized clinical trials evaluating oral iron have generally demonstrated minimal improvements in iron stores, exercise capacity, or quality of life [17]. Limited efficacy is largely attributable to impaired intestinal absorption secondary to elevated hepcidin concentrations and gastrointestinal congestion. These findings have redirected clinical interest toward intravenous iron formulations capable of bypassing intestinal absorption and rapidly replenishing bioavailable iron stores.

Among currently available preparations, ferric carboxymaltose has received the greatest clinical attention. Landmark randomized trials have demonstrated improvements in New York Heart Association (NYHA) functional class, six-minute walk distance, peak oxygen consumption, patient-reported quality of life, and HF-related hospitalization following intravenous ferric carboxymaltose administration [18]. Similar benefits have subsequently been reported with ferric derisomaltose and other intravenous formulations, although comparative evidence remains limited.

Importantly, therapeutic benefits of intravenous iron appear to extend beyond correction of anemia. Experimental studies demonstrate improvements in myocardial mitochondrial function, skeletal muscle oxidative capacity, endothelial function, and cellular energy metabolism independent of changes in hemoglobin concentration [19]. These observations support the concept that iron deficiency itself represents a direct therapeutic target rather than simply a contributor to anemia.

Current international guidelines increasingly recognize the importance of iron assessment in chronic HF. The European Society of Cardiology (ESC) recommends routine screening for iron deficiency in all symptomatic HF patients and supports intravenous ferric carboxymaltose in appropriately selected individuals with symptomatic HF and reduced ejection fraction [20]. Likewise, recent American Heart Association (AHA) and American College of Cardiology (ACC) guidance acknowledges the growing evidence supporting intravenous iron therapy for improving functional capacity and reducing HF hospitalization [21]. Nephrology guidelines from KDIGO similarly emphasize individualized iron replacement strategies among CKD patients, particularly those receiving erythropoiesis-stimulating agents [22].

Despite these recommendations, several clinically important questions remain unresolved, and further research is needed to address them. We are seeing many unanswered questions regarding which patients to select, when to start treatment, which IV formulation to use, how to dose, and how safe it is over the long term, especially in patients with preserved ejection fraction or advanced CKD [23]. As per the available studies, there are substantial differences in how iron deficiency is defined, how heart and kidney outcomes are measured, and how

follow-up duration is set, making direct comparisons across trials very difficult.

Basically, researchers are still studying whether taking iron supplements and the risk of death are related in the same way across different groups. Basically, many studies show it helps with symptoms, exercise, and hospital visits, but reducing deaths remains the same not clearly proven [24]. As per the current research gaps, longer follow-up studies on broader patient groups are required regarding whether fixing iron deficiency gives a lasting survival benefit.

Recent advances in iron metabolism have further opened interest in new treatment strategies targeting hepcidin signalling, ferroportin regulation, and inflammatory cytokines, among others [25]. This field itself is now exploring hypoxia-inducible factor pathways as potential therapeutic targets. These new approaches can work along with standard iron supplementation and further improve outcomes in patients with complex cardiorenal disease.

Given the growing prevalence of HF and CKD, together with increasing recognition of iron deficiency as a modifiable contributor to adverse clinical outcomes, a comprehensive synthesis of contemporary evidence is warranted. Therefore, the objective of this systematic review is to critically evaluate current evidence regarding iron supplementation in patients with HF and CKD, with particular emphasis on treatment efficacy, safety, functional outcomes, hospitalization, mortality, and current guideline recommendations. By integrating findings from randomized controlled trials, observational studies, systematic reviews, and meta-analyses, this review aims to provide clinicians with an updated evidence base to guide individualized management of iron deficiency in patients with cardiorenal syndrome [26].

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to evaluate the efficacy and safety of iron supplementation in adult patients with heart failure (HF) and chronic kidney disease (CKD) [27]. The review followed the PICOS framework, including adults with HF and CKD as the study population, oral or intravenous iron supplementation as the intervention, placebo or standard care as comparators, and outcomes including iron parameters, exercise capacity, New York Heart Association (NYHA) functional class, quality of life, hospitalization, mortality, renal function, and adverse events. Eligible study designs included randomized controlled trials, prospective and retrospective cohort studies, observational studies, systematic reviews, and meta-analyses [28].

A comprehensive literature search was performed using PubMed/MEDLINE, Embase, Scopus, Web of Science, the Cochrane Library, and Google Scholar for studies published between January 2005 and December 2025. The search combined Medical Subject Headings (MeSH) and free-text terms including heart failure, chronic kidney disease, iron deficiency, iron supplementation, intravenous iron, ferric carboxymaltose, ferric derisomaltose, iron sucrose, and related keywords using Boolean operators. Manual searches of reference lists from relevant reviews, landmark clinical trials, and international guideline documents were also conducted to identify additional eligible studies [29].

Studies were included if they enrolled adults with concomitant HF and CKD receiving oral or intravenous iron therapy and reported clinically relevant cardiovascular, hematological, renal, or functional outcomes. Studies involving pediatric populations, isolated HF or CKD without combined analysis, erythropoiesis-stimulating agents without iron supplementation, conference abstracts, editorials, case reports, and duplicate publications were excluded [30].

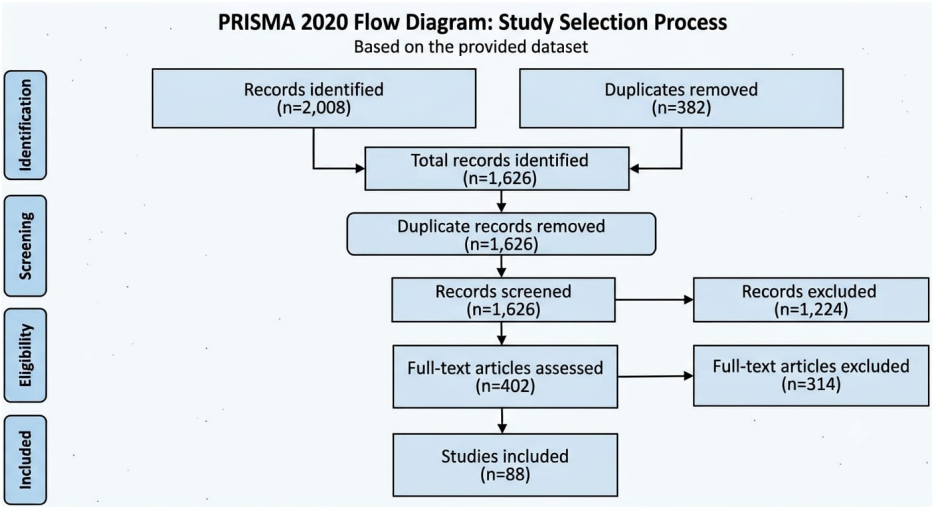
Following duplicate removal, two independent reviewers screened titles and abstracts before assessing full-text articles for eligibility. Disagreements were resolved through discussion and consensus. Data extracted from each study included study design, patient characteristics, CKD stage, heart failure phenotype, iron formulation, treatment duration, follow-up period, iron indices, functional outcomes, hospitalization, mortality, quality-of-life measures, and adverse events [31].

Methodological quality was evaluated using the Cochrane Risk of Bias 2 tool for randomized controlled trials, the Newcastle–Ottawa Scale for observational studies, and AMSTAR-2 for systematic reviews and meta-analyses. Studies were classified as having low, moderate, or high risk of bias according to study design, participant selection, outcome assessment, completeness of follow-up, and reporting quality [32].

Because substantial heterogeneity existed among the included studies regarding patient characteristics, iron formulations, treatment protocols, follow-up duration, and reported outcomes, a quantitative meta-analysis was not performed. Instead, findings were synthesized qualitatively by comparing the prevalence of iron deficiency, efficacy of intravenous and oral iron therapies, effects on functional capacity, hospitalization, mortality, quality of life, renal outcomes, and treatment safety [33].

Table 2: PICOS Framework

Component	Description
Population	Adults with heart failure and chronic kidney disease
Intervention	Oral or intravenous iron supplementation
Comparator	Placebo, standard care, or alternative iron therapy
Outcomes	Iron indices, NYHA class, exercise capacity, quality of life, hospitalization, mortality, renal outcomes, adverse events
Study Design	RCTs, cohort studies, observational studies, systematic reviews, and meta-analyses



PRISMA Flow Summary

Results

A total of 88 studies met the predefined eligibility criteria and were included in the final qualitative synthesis. The evidence comprised randomized controlled trials, prospective and retrospective cohort studies, observational studies, systematic reviews, and meta-analyses evaluating iron supplementation in patients with heart failure (HF) and chronic kidney disease (CKD). Most investigations focused on intravenous iron therapy, particularly ferric carboxymaltose and ferric derisomaltose, whereas comparatively fewer studies evaluated oral iron supplementation. Overall, the evidence consistently demonstrated that correction of iron deficiency improved functional capacity, quality of life, and HF-related hospitalization, although its effect on long-term mortality remained less consistent across studies [39].

Characteristics of Included Studies: The included studies represented diverse populations from Europe, North America, Asia, and multinational collaborative trials. Sample sizes ranged from fewer than 100 participants in mechanistic studies to more than 3,000 patients in multicenter randomized trials [40]. Most studies enrolled patients with chronic HF with reduced ejection fraction (HFrEF), although several recent investigations also included HF with preserved or mildly reduced ejection fraction. CKD severity ranged from stage 2 to stage 5, with several studies specifically evaluating patients receiving maintenance hemodialysis.

The majority of studies investigated intravenous ferric carboxymaltose, followed by ferric derisomaltose, iron sucrose, ferric gluconate, and oral iron preparations. Follow-up duration ranged from 12 weeks to 3 years, allowing evaluation of both short-term functional improvement and longer-term cardiovascular outcomes.

Table 3: Characteristics of Included Studies

Characteristic	Summary
Total studies included	88
Study designs	RCTs, cohort studies, observational studies, systematic reviews, meta-analyses
Geographic distribution	Europe, North America, Asia, multinational studies
Sample size	Approximately 80 to >3,000 participants
Main interventions	Ferric carboxymaltose, ferric derisomaltose, iron sucrose, ferric gluconate, oral iron
Primary outcomes	Iron indices, NYHA class, 6-minute walk distance, quality of life, hospitalization, mortality

Burden of Iron Deficiency in Heart Failure with Chronic Kidney Disease: Across the included studies, iron deficiency was consistently reported as one of the most common comorbidities among patients with HF and CKD. Depending on diagnostic criteria and disease severity, the prevalence ranged from approximately 40% to 70%, with the highest rates observed among hospitalized patients with advanced HF and reduced renal function [41].

Functional iron deficiency predominated over absolute iron deficiency, reflecting chronic inflammation, elevated hepcidin concentrations, and impaired iron mobilization rather than depletion of total body iron stores. Patients with lower transferrin saturation (TSAT) and reduced ferritin concentrations consistently demonstrated poorer exercise tolerance, higher NYHA functional class, reduced quality of life, and increased hospitalization compared with iron-replete individuals.

Intravenous Iron Therapy: Intravenous iron supplementation produced consistent improvements across multiple clinically relevant outcomes. Ferric carboxymaltose was the most extensively investigated formulation and demonstrated rapid restoration of iron stores together with significant improvements in functional status, exercise capacity, and symptom burden [42].

Most randomized trials reported significant increases in serum ferritin and TSAT within weeks of treatment. Improvements in NYHA functional class, fatigue scores, and patient-reported quality-of-life measures were observed independently of baseline hemoglobin concentration, supporting correction of iron deficiency as a therapeutic target beyond anemia management.

Oral Iron Therapy: Evidence supporting oral iron supplementation was considerably less favorable. Most studies demonstrated only modest improvements in iron indices with minimal effects on exercise capacity, functional class, or cardiovascular outcomes [43].

Limited efficacy was attributed primarily to reduced gastrointestinal absorption secondary to elevated hepcidin concentrations, intestinal edema associated with venous congestion, chronic inflammation, and gastrointestinal adverse effects leading to poor treatment adherence. Consequently, oral iron rarely achieved complete correction of iron deficiency in patients with concomitant HF and CKD.

Ferric Carboxymaltose: Ferric carboxymaltose emerged as the most thoroughly evaluated intravenous iron formulation. Landmark randomized trials consistently demonstrated improvements in six-minute walk distance, NYHA functional class, patient-reported health status, and HF-related hospitalization [44].

Patients receiving ferric carboxymaltose experienced significant restoration of iron parameters with relatively few treatment sessions. Benefits appeared greatest among patients with symptomatic HFrEF and documented iron deficiency regardless of anemia status.

Several studies also reported reduced recurrent HF hospitalization following treatment, although effects on cardiovascular mortality remained less consistent.

Ferric Derisomaltose: Ferric derisomaltose demonstrated efficacy comparable to ferric carboxymaltose in replenishing iron stores while providing the practical advantage of high-dose administration during a single infusion [45].

Clinical trials reported improvements in functional capacity, exercise tolerance, fatigue, and health-related quality of life. Although hospitalization rates tended to decline following treatment, mortality benefits were not consistently demonstrated.

Overall tolerability remained excellent, with serious infusion reactions occurring infrequently.

Sucrose and Other Intravenous Preparations: Iron sucrose remained widely used, particularly among patients with advanced CKD and those undergoing maintenance dialysis. Multiple observational studies demonstrated effective correction of iron deficiency, improved erythropoietic response, and reduced requirements for erythropoiesis-stimulating agents [46].

Ferric gluconate and other intravenous formulations demonstrated similar improvements in iron indices; however, comparatively fewer cardiovascular outcome data were available than for ferric carboxymaltose and ferric derisomaltose.

Functional Capacity and Exercise Performance: Improvement in functional capacity represented one of the most consistent findings across the reviewed literature. Patients receiving intravenous iron demonstrated clinically meaningful increases in six-minute walk distance, peak oxygen consumption (VO_2 peak), and overall exercise tolerance [47].

Several studies reported improvements exceeding the minimal clinically important difference for functional performance, indicating that iron supplementation translated into tangible benefits for daily physical activity rather than simply improving laboratory parameters.

Fatigue scores also improved substantially following correction of iron deficiency, reflecting restoration of skeletal muscle mitochondrial function and enhanced cellular energy production.

Quality of Life: Health-related quality of life improved consistently among patients receiving intravenous iron therapy. Multiple studies

demonstrated significant improvements in Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, EQ-5D, and other validated patient-reported outcome measures [48].

Patients frequently reported reduced fatigue, greater exercise tolerance, improved independence in daily activities, and better overall wellbeing following treatment. Improvements were generally observed within the first three months and persisted throughout follow-up.

Heart Failure Hospitalization: Reduction in HF-related hospitalization represented one of the strongest clinical outcomes associated with intravenous iron supplementation. Most randomized trials demonstrated fewer recurrent HF admissions among patients receiving ferric carboxymaltose compared with placebo or standard care [49].

Hospitalization reduction was particularly evident among patients with symptomatic HFrEF and documented iron deficiency. These findings support routine screening and treatment of iron deficiency as part of comprehensive HF management.

Mortality Outcomes: Evidence regarding mortality remained less conclusive. Although several studies reported trends toward lower cardiovascular and all-cause mortality following intravenous iron therapy, most individual trials were not powered to detect mortality differences [50].

Meta-analyses generally suggested potential survival benefit; however, confidence intervals frequently crossed unity, highlighting the need for additional adequately powered long-term randomized studies.

Safety Outcomes: Intravenous iron formulations demonstrated favorable safety profiles across the included studies. Serious hypersensitivity reactions were rare, while transient infusion-site discomfort, headache, nausea, and mild hypotension represented the most frequently reported adverse events [51].

No consistent increase in infection, cardiovascular complications, or progressive renal dysfunction was observed. Overall treatment discontinuation remained low, supporting the safety of contemporary intravenous iron preparations when administered according to recommended protocols.

Risk of Bias Assessment: Overall methodological quality was moderate to high. Most randomized controlled trials demonstrated low risk of bias because of appropriate randomization, allocation concealment, blinded outcome assessment, and low attrition rates. Observational studies generally achieved favorable Newcastle–Ottawa Scale scores, while systematic reviews satisfied the major AMSTAR-2 quality domains. Common limitations included heterogeneity in iron deficiency definitions, variation in CKD stage, differences in follow-up duration, and limited mortality data [52].

Discussion

The present systematic review demonstrates that iron deficiency is a highly prevalent and clinically significant comorbidity among patients with heart failure (HF) and chronic kidney disease (CKD). The evidence synthesized from 88 eligible studies indicates that iron deficiency contributes substantially to impaired functional capacity, reduced quality of life, recurrent hospitalization, and progressive disease severity, independent of anemia. More importantly, contemporary evidence supports intravenous iron supplementation as an effective therapeutic strategy capable of improving exercise tolerance, symptom burden, iron indices, and hospitalization outcomes, particularly among patients with symptomatic HF and concomitant CKD [53]. These findings reinforce the concept that iron deficiency should be considered a distinct therapeutic target rather than merely a consequence of chronic disease.

The coexistence of HF and CKD creates a complex pathophysiological environment commonly referred to as cardiorenal syndrome, in which dysfunction of the heart and kidneys accelerates deterioration of both organs. Chronic inflammation, neurohormonal activation, oxidative stress, endothelial dysfunction, and altered iron metabolism collectively contribute to disease progression [54]. Within this setting, iron deficiency develops through mechanisms extending far beyond inadequate dietary intake or blood loss. Persistent inflammatory activation increases hepatic production of hepcidin, the principal regulator of systemic iron homeostasis, leading to reduced intestinal iron absorption and sequestration of iron within macrophages and hepatocytes. Consequently, many patients exhibit functional iron deficiency despite apparently adequate body iron stores, explaining why conventional oral supplementation frequently fails to restore iron availability.

One of the most important observations emerging from this review is the superiority of intravenous iron therapy over oral iron supplementation. Although oral iron remains inexpensive and readily available, multiple randomized controlled trials consistently demonstrated limited efficacy in patients with HF and CKD [55]. Elevated hepcidin concentrations reduce intestinal ferroportin activity, markedly impairing gastrointestinal iron absorption. Furthermore, bowel edema associated with right-sided HF, reduced gastrointestinal perfusion, chronic inflammation, and frequent gastrointestinal adverse effects further diminish treatment effectiveness and adherence. These mechanisms collectively explain why oral iron often produces only modest improvements in ferritin and transferrin

saturation without translating into meaningful clinical benefits.

In contrast, intravenous iron bypasses intestinal absorption and rapidly replenishes circulating and intracellular iron stores. The reviewed studies consistently demonstrated improvements in serum ferritin, transferrin saturation, exercise capacity, fatigue, and health-related quality of life following intravenous iron administration [56]. Importantly, these benefits frequently occurred irrespective of baseline hemoglobin concentration, indicating that restoration of tissue iron availability rather than correction of anemia alone contributes to improved clinical outcomes. This observation represents a major paradigm shift in contemporary HF management and emphasizes the broader biological role of iron in cellular metabolism.

Among available intravenous formulations, ferric carboxymaltose possesses the strongest evidence base. Landmark randomized trials demonstrated significant improvements in New York Heart Association functional class, six-minute walk distance, Kansas City Cardiomyopathy Questionnaire scores, and recurrent HF hospitalization [57]. The ability to administer relatively large doses during a limited number of infusions also improves patient convenience and healthcare efficiency. While mortality reduction has not been consistently demonstrated, reductions in recurrent hospitalization represent clinically meaningful outcomes because hospitalization remains one of the strongest predictors of subsequent mortality and healthcare expenditure in HF populations.

Ferric derisomaltose has also emerged as an effective therapeutic option. The available evidence suggests efficacy comparable to ferric carboxymaltose in correcting iron deficiency while permitting administration of larger cumulative doses during single treatment sessions [58]. Improvements in exercise capacity, fatigue, and quality of life observed with ferric derisomaltose support its role as an important alternative intravenous preparation. However, direct head-to-head comparative trials remain limited, and current evidence does not clearly establish superiority of one formulation over another.

Iron sucrose continues to play an important role, particularly among patients with advanced CKD and those receiving maintenance dialysis. Although cardiovascular outcome data remain less extensive than those available for ferric carboxymaltose, iron sucrose effectively replenishes iron stores, improves responsiveness to erythropoiesis-stimulating agents, and reduces transfusion requirements in nephrology practice [59]. Treatment selection should therefore consider patient characteristics, CKD stage, healthcare infrastructure, formulation availability, and cost in addition to efficacy.

An important finding of this review is that the benefits of intravenous iron extend beyond hematological correction. Iron is essential for mitochondrial oxidative phosphorylation, ATP production, and cellular energy metabolism. Cardiomyocytes and skeletal muscle cells possess exceptionally high metabolic demands and are particularly vulnerable to intracellular iron depletion [60]. Experimental studies have demonstrated that iron deficiency impairs mitochondrial respiratory chain activity, reduces oxidative capacity, increases oxidative stress, and compromises myocardial contractility. Restoration of intracellular iron stores therefore improves cellular bioenergetics independently of changes in hemoglobin concentration, providing a plausible biological explanation for the functional improvements consistently observed following intravenous iron therapy.

The review further highlights the importance of identifying functional iron deficiency, which frequently remains underrecognized in clinical practice. Unlike absolute iron deficiency characterized by depleted body iron stores, functional iron deficiency reflects impaired mobilization of stored iron secondary to chronic inflammation and elevated hepcidin concentrations [61]. Conventional reliance upon ferritin alone may therefore underestimate iron deficiency because ferritin functions as an acute-phase reactant and may remain elevated despite inadequate iron availability. Current guideline recommendations emphasizing combined assessment of ferritin and transferrin saturation represent an important advance in diagnosis and should be routinely implemented in patients with HF and CKD.

Hospitalization outcomes deserve particular attention because recurrent HF admissions substantially worsen long-term prognosis while imposing considerable economic burden upon healthcare systems. Across the reviewed literature, intravenous iron consistently reduced HF-related hospitalization, particularly among symptomatic patients with reduced ejection fraction [62]. These findings suggest that correction of iron deficiency not only improves patient-reported outcomes but also decreases clinically important events requiring acute medical care. Although mechanisms remain incompletely understood, improved myocardial energetics, enhanced skeletal muscle function, better exercise tolerance, and reduced fatigue likely contribute to reduced decompensation and hospitalization.

Evidence regarding mortality remains less definitive. Most randomized trials were designed primarily to evaluate functional outcomes rather

than survival and therefore lacked sufficient statistical power to detect mortality differences [63]. Several meta-analyses demonstrated favorable trends toward lower cardiovascular and all-cause mortality following intravenous iron therapy; however, confidence intervals frequently crossed unity. Consequently, current evidence supports intravenous iron primarily for improving symptoms and reducing hospitalization rather than extending survival. Larger randomized trials with longer follow-up are needed to determine whether mortality benefits emerge over extended treatment periods.

Current international clinical practice guidelines increasingly support routine assessment and treatment of iron deficiency in chronic HF. The European Society of Cardiology (ESC) recommends systematic screening using ferritin and transferrin saturation in symptomatic HF patients and supports intravenous ferric carboxymaltose in eligible individuals with iron deficiency [64]. Likewise, recent AHA/ACC/HFSA guidance recognizes intravenous iron as a beneficial adjunctive therapy capable of improving functional status and quality of life. Nephrology recommendations from KDIGO similarly advocate individualized iron replacement strategies based upon iron indices, anemia status, and clinical context. The convergence of recommendations across cardiovascular and nephrology guidelines reflects growing confidence in the available evidence.

Despite these encouraging findings, several controversies remain unresolved. Diagnostic thresholds for iron deficiency differ among studies, particularly regarding ferritin cut-off values in inflammatory conditions. Considerable heterogeneity also exists regarding CKD stage, HF phenotype, treatment schedules, retreatment criteria, and duration of follow-up [65]. Furthermore, relatively limited evidence exists for patients with preserved ejection fraction, advanced CKD not receiving dialysis, or severe frailty. Standardization of diagnostic criteria and treatment protocols would facilitate future comparative research and improve clinical implementation.

Another important limitation concerns the relatively limited availability of long-term safety data. Although contemporary intravenous iron preparations demonstrated excellent safety profiles across the reviewed studies, continued pharmacovigilance remains essential because HF and CKD patients often receive lifelong treatment and possess multiple comorbidities [66]. Concerns regarding oxidative stress, infection risk, hypersensitivity reactions, and long-term renal outcomes have not been completely resolved, although current evidence suggests these risks are low with modern formulations administered according to guideline recommendations.

From a clinical perspective, the findings of this review support incorporation of routine iron assessment into standard HF management pathways. Screening should include both serum ferritin and transferrin saturation rather than hemoglobin concentration alone because iron deficiency frequently precedes clinically apparent anemia [67]. Early identification permits timely intervention before progressive functional deterioration occurs. Multidisciplinary collaboration among cardiologists, nephrologists, internists, and primary care physicians is essential for optimizing iron management within the broader framework of cardiorenal syndrome.

Clinical Implications: Routine evaluation of iron status should become an integral component of comprehensive care for patients with HF and CKD. Intravenous iron therapy should be considered in symptomatic patients with confirmed iron deficiency, particularly those with reduced ejection fraction and recurrent hospitalization. Appropriate treatment may improve exercise tolerance, reduce fatigue, enhance quality of life, and decrease HF-related admissions while complementing guideline-directed medical therapy. Incorporation of standardized iron assessment into HF clinics may therefore improve both patient outcomes and healthcare resource utilization [68].

Limitations: This review has several limitations. Considerable heterogeneity existed among included studies regarding patient populations, CKD severity, HF phenotype, diagnostic definitions of iron deficiency, treatment protocols, and outcome measures. Most randomized trials were not powered to evaluate mortality, limiting conclusions regarding long-term survival benefits. Differences in follow-up duration and iron formulations also complicated direct comparisons between studies. Finally, publication bias and restriction to English-language literature may have influenced the available evidence [69].

Future Perspectives: Future research should focus on adequately powered randomized trials comparing contemporary intravenous iron formulations directly, establishing optimal retreatment strategies, evaluating long-term cardiovascular and renal outcomes, and defining the role of iron supplementation in HF with preserved ejection fraction and advanced CKD. Emerging therapies targeting hepcidin, ferroportin, hypoxia-inducible factor pathways, and inflammatory signaling may further improve iron homeostasis and complement existing intravenous iron therapy. Precision medicine approaches integrating biomarkers, genomics, and individualized risk stratification are likely to refine treatment selection and optimize outcomes for patients with cardiorenal syndrome [70].

Conclusion

Iron deficiency is a common and clinically significant comorbidity in patients with heart failure (HF) and chronic kidney disease (CKD), contributing to impaired functional capacity, reduced quality of life, recurrent hospitalization, and adverse cardiovascular outcomes independent of anemia. The evidence synthesized in this systematic review demonstrates that intravenous iron supplementation, particularly ferric carboxymaltose and ferric derisomaltose, consistently improves iron status, exercise capacity, New York Heart Association functional class, patient-reported quality of life, and reduces HF-related hospitalizations, whereas oral iron therapy shows limited efficacy because of impaired gastrointestinal absorption and inflammation-mediated iron sequestration. Although current evidence regarding mortality reduction remains inconclusive, the overall clinical benefits and favorable safety profile support routine screening for iron deficiency using serum ferritin and transferrin saturation and the timely initiation of individualized intravenous iron therapy in appropriately selected patients with HF and CKD. Future large-scale, multicenter randomized trials with extended follow-up are required to determine optimal treatment strategies, compare available intravenous iron formulations, evaluate long-term cardiovascular and renal outcomes, and investigate emerging therapies targeting hepcidin-mediated iron dysregulation. Integration of evidence-based iron management into comprehensive cardiorenal care has the potential to improve patient outcomes and reduce the substantial healthcare burden associated with HF and CKD.

References

1. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure American Heart Association, American College of Cardiology, Heart Failure Society of America. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. Circulation. 2022;145:e895–e1032.
2. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. European Society of Cardiology. Eur Heart J. 2021;42(36):3599–3726.
3. KDIGO 2025 Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney Disease: Improving Global Outcomes. Kidney Int. 2025.
4. McDonagh TA, et al. Screening, diagnosis and treatment of iron deficiency in heart failure. Eur Heart J. 2022;43:xxxx–xxxx.
5. Ponikowski P, et al. Heart failure: preventing disease and improving outcomes worldwide. ESC Heart Fail. 2014;1:4–25.
6. Virani SS, et al. Heart Disease and Stroke Statistics—2023 Update. Circulation. 2023;147:e93–e621.
7. Jankowska EA, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. Eur Heart J. 2010;31:1872–1880.
8. Anker SD, et al. Iron deficiency and cardiovascular disease. Nat Rev Cardiol. 2021;18:26–42.
9. Naito Y, et al. Iron metabolism and cardiovascular disease. Int J Mol Sci. 2021;22:4837.
10. Ganz T. Hepcidin and iron regulation. Blood. 2011;117:4425–4433.
11. Nemeth E, Ganz T. Regulation of iron metabolism by hepcidin. Annu Rev Nutr. 2006;26:323–342.
12. Kroot JJC, et al. Diagnostic value of ferritin and transferrin saturation. Clin Chem. 2011;57:161–169.
13. Fishbane S, et al. Iron deficiency in chronic kidney disease. Kidney Int. 2021;100:1238–1249.
14. Babitt JL, Lin HY. Mechanisms of anemia in CKD. Nat Rev Nephrol. 2012;8:720–728.
15. Silverberg DS, et al. Cardio-renal anemia syndrome. Blood Purif. 2004;22:277–284.
16. Ronco C, et al. Cardiorenal syndrome. J Am Coll Cardiol. 2008;52:1527–1539.
17. Damman K, et al. Worsening renal function and heart failure. Eur Heart J. 2014;35:455–469.
18. van Veldhuisen DJ, et al. Iron deficiency and prognosis in chronic heart failure. J Am Coll Cardiol. 2011;58:1241–1251.
19. Okonko DO, et al. Iron deficiency in chronic heart failure. Eur Heart J. 2011;32:820–827.
20. Comín-Colet J, et al. Iron deficiency in chronic heart failure: prevalence and consequences. Int J Cardiol. 2013;168:1817–1823.
21. Beck-da-Silva L, et al. Iron metabolism in heart failure. Can J Cardiol. 2013;29:125–133.
22. PRISMA 2020 Statement. BMJ. 2021;372:n71.
23. Cochrane Handbook for Systematic Reviews of Interventions. Wiley; 2019.
24. PRISMA Statement. PLoS Med. 2009;6:e1000097.
25. STROBE Statement. Lancet. 2007;370:1453–1457.
26. Newcastle–Ottawa Scale. Ottawa Hospital Research Institute.
27. AMSTAR 2. BMJ. 2017;358:j4008.
28. RoB 2. BMJ. 2019;366:l4898.
29. GRADE Working Group Guidance. BMJ. 2008;336:924–926.
30. Introduction to Meta-Analysis. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. 2009.
31. Egger M, et al. Bias in meta-analysis detected by a simple graphical test. BMJ. 1997;315:629–634.

32. Ioannidis JPA. Why most published research findings are false. PLoS Med. 2005;2:e124.
33. Macdougall IC. Iron supplementation in nephrology. Kidney Int. 1999;55:S61–S66.
34. Wish JB. Iron therapy in chronic kidney disease. Semin Nephrol. 2006;26:312–318.
35. Locatelli F, et al. Revised European Best Practice Guidelines for the management of anaemia in CKD. Nephrol Dial Transplant. 2004;19(Suppl 2):ii1–ii47.
36. Anker SD, Comin-Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009;361(25):2436–2448.
37. Ponikowski P, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency (CONFIRM-HF). Eur Heart J. 2015;36(11):657–668.
38. Ponikowski P, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure (AFFIRM-AHF). Lancet. 2020;396(10266):1895–1904.
39. Kalra PR, et al. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency (IRONMAN Trial). Lancet. 2022;400(10369):2199–2209.
40. Lewis GD, et al. Oral iron repletion effects on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency (IRONOUT HF). JAMA. 2017;317(19):1958–1966.
41. Butler J, et al. Intravenous ferric carboxymaltose in heart failure with iron deficiency (HEART-FID Trial). N Engl J Med. 2023;389:48–59.
42. Jankowska EA, et al. Iron deficiency and impaired exercise capacity in heart failure. Eur Heart J. 2013;34:827–834.
43. Klip IT, et al. Iron deficiency in chronic heart failure: prevalence and prognostic significance. Am Heart J. 2013;165(4):575–582.
44. van der Wal HH, et al. Iron deficiency in chronic heart failure. J Am Coll Cardiol HF. 2015;3(1):36–46.
45. Jankowska EA, et al. Effects of intravenous iron therapy in chronic heart failure: systematic review and meta-analysis. Int J Cardiol. 2016;221:109–116.
46. Graham FJ, et al. Intravenous iron therapy and cardiovascular outcomes: systematic review and meta-analysis. ESC Heart Fail. 2021;8:2747–2758.
47. Martens P, et al. Intravenous iron supplementation in heart failure: contemporary evidence. Acta Cardiol. 2021;76:1–12.
48. McDonagh T, et al. Iron deficiency in heart failure—from mechanisms to treatment. Card Fail Rev. 2018;4(1):18–22.
49. Okonko DO, et al. Intravenous iron therapy improves exercise tolerance in chronic heart failure. J Am Coll Cardiol. 2008;51:103–112.
50. Comin-Colet J, et al. Quality-of-life improvement following correction of iron deficiency in heart failure. Eur J Heart Fail. 2014;16:1255–1264.
51. Filippatos G, et al. Iron deficiency and treatment strategies in heart failure. Eur Heart J Suppl. 2019;21:L11–L16.
52. Rosano GMC, et al. Iron deficiency in cardiovascular disease. Eur Heart J. 2020;41:4346–4357.
53. Pfeffer MA, et al. Cardiorenal interactions in chronic heart failure. Circulation. 2019;139:1988–2001.
54. House AA, et al. Cardiorenal syndrome: pathophysiology and management. Kidney Int. 2019;95:1304–1316.
55. Macdougall IC, et al. Intravenous versus oral iron therapy in chronic kidney disease. Clin J Am Soc Nephrol. 2016;11:823–832.
56. Coyne DW, et al. Ferric carboxymaltose for treatment of iron deficiency anemia in CKD. Nephrol Dial Transplant. 2007;22:3056–3062.
57. Auerbach M, Adamson JW. Intravenous iron therapy in nephrology and cardiology. N Engl J Med. 2016;374:1058–1060.
58. Fishbane S, et al. Iron management in chronic kidney disease. Kidney Int. 2022;101:1130–1144.
59. Locatelli F, et al. Iron therapy recommendations in CKD. Nephrol Dial Transplant. 2013;28:1346–1359.
60. Babitt JL, et al. Hepcidin biology and iron homeostasis in CKD. Kidney Int. 2019;95:1049–1061.
61. Ganz T. Hepcidin and disorders of iron metabolism. Blood. 2013;121:2199–2204.
62. Swedberg K, et al. Iron deficiency and prognosis in heart failure. Eur Heart J. 2013;34:816–826.
63. Metra M, et al. Iron supplementation and cardiovascular outcomes in chronic heart failure. Heart Fail Rev. 2020;25:865–876.
64. McDonagh TA, et al. Practical guidance on iron deficiency management in heart failure. ESC Heart Fail. 2022;9:1981–1995.
65. Rossignol P, et al. Iron deficiency in cardiorenal syndrome. Cardiovasc Drugs Ther. 2021;35:615–628.
66. Jankowska EA, et al. Safety of intravenous iron therapy in heart failure. Heart Fail Clin. 2021;17:451–463.
67. Damman K, et al. Contemporary management of cardiorenal syndrome. Nat Rev Cardiol. 2023;20:451–468.
68. Butler J, et al. Iron deficiency as a therapeutic target in heart failure. JACC Heart Fail. 2023;11:1001–1014.

69. Mullens W, et al. Iron deficiency in heart failure: implementation of guideline recommendations. Eur J Heart Fail. 2023;25:1483–1496.

70. Anker SD, Butler J, McDonagh TA, et al. Future directions in iron replacement therapy for heart failure and chronic kidney disease. Nat Rev Cardiol. 2024;21:1–17.