



IRON DEFICIENCY IN HEART FAILURE AND CARDIOVASCULAR DISEASES – FROM PATHOPHYSIOLOGY TO MODERN STRATEGIES

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Abstract

Iron deficiency affects 40-80% of heart failure patients – across reduced, mid-range, and preserved ejection fraction subtypes – worsening exercise intolerance, frailty, quality of life, hospitalization rates, and mortality, regardless of anemia presence. This review examines iron deficiency's central role in oxygen metabolism, mitochondrial energy production (adenosine triphosphate), and cellular respiration; its strong links to coronary artery disease (around 60% prevalence, raising ischemic events and impairing heart muscle remodeling after infarction) and pulmonary hypertension (40-60% prevalence, shortening six-minute walk distance, elevating pulmonary pressures, and harming right heart function); diagnostic hurdles during inflammation; and evidence-driven treatment strategies. Inflammation boosts hepcidin, a hormone that traps iron inside cells by breaking down ferroportin, starving heart muscle cells of energy and forcing reliance on inefficient anaerobic metabolism. Intravenous iron, such as ferric carboxymaltose, consistently delivers gains: better left ventricular ejection fraction, New York Heart Association symptom class, six-minute walk distance (plus 45 meters versus placebo), and quality-of-life scores (EQ-5D or Minnesota questionnaires), alongside 20-30% drops in heart failure hospitalizations from major trials like FAIR-HF, IRONMAN, HEARTFID, and FAIR-HF2. Oral iron falls short due to poor uptake in inflamed conditions. European Society of Cardiology 2023 guidelines urge routine screening and intravenous iron for symptomatic reduced or mid-range ejection fraction heart failure (strongest recommendation, high-quality evidence), with growing support for preserved ejection fraction and pulmonary hypertension cases.

Running title: Iron deficiency: cardiovascular disease

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Introduction

Iron plays a crucial role in the uptake, transport, storage and metabolism of oxygen in humans. It does this by accepting and donating electrons as it shifts between its ferrous (Fe^{2+}) and ferric (Fe^{3+}) forms. It is also responsible for erythropoiesis and immune cell functions. Furthermore, iron is involved in cellular respiration, oxidative phosphorylation, vascular homeostasis, and the citric acid cycle (Krebs cycle) in the mitochondria. The levels of iron in the body depend on how much we eat, how our bodies use it, and how much we excrete. Having enough iron is essential for producing ATP in mitochondria, especially in energy-demanding cells like heart muscle cells and skeletal muscle cells [1,2].

Iron deficiency (ID) is one of the most common nutritional shortages worldwide, impacting up to a one-third of people globally. Infants, young children, the elderly, and women are the most affected groups [3,4]. A notable aspect of ID is that inflammation can cause it, which is important for chronic diseases. When the immune system activates, it releases proinflammatory cytokines that raise plasma hepcidin levels. This inhibits red blood cell production and shortens their lifespan. Increased hepcidin production leads to functional ID by degrading ferroportin, which traps iron in intestinal cells, the spleen, liver cells, and macrophages [5,6].

In cardiology, ID in patients with heart failure (HF) is defined as a serum ferritin concentration <100 ng/mL, or $100 - 299$ ng/mL if the transferrin saturation (TSAT) is $<20\%$. In contrast, the cut-off values for the general population are lower (ferritin <30 ng/mL or TSAT $<20\%$) [7,8].

However, these criteria are still debated. Inflammation significantly interferes with the interpretation of serum ferritin level. Alternative cut-off points have been proposed, such as a TSAT $\leq 19.8\%$ or a serum iron concentration ≤ 13 $\mu\text{mol/L}$, as these may better reflect the risk of mortality. Conflicting definitions hinder the recognition, prevention, and management of this deficiency, potentially leading to the exclusion of patients who could benefit from iron therapy [9–11].

Both ID and anemia come with their own risks and lead to lower exercise capacity, higher hospitalization rates among HF patients, greater cardiovascular risk, and increased overall mortality. Notably, patients with both ID and anemia tend to experience more severe symptoms [7,12].

ID affects about 50% of those with chronic heart failure (CHF) and limits the clinical benefits from standard treatment [1,13]. A similar pattern is seen in acute heart failure (AHF) patients, with prevalence as high as 80% [14]. It was also reported that there is a higher rate of iron deficiency (ID) in patients who have heart failure with preserved ejection fraction (HFpEF), and this is especially common

among women. In this group, ID is linked to longer hospital stays, a connection that does not appear in patients with heart failure with reduced ejection fraction (HFrEF). Further, ID in patients with HFpEF worsens their prognosis and reduces physical performance compared to those without the deficiency, suggesting a potentially critical role for iron status screening in HFpEF [11,15].

In coronary artery disease (CAD), ID affects about 60% of patients and is linked to a higher risk of ischemic events and increased cardiovascular mortality in both CAD patients and those without it. This correlation is partly due to the negative effects on heart remodeling after a myocardial infarction (MI) [16]. ID is a major yet often neglected contributing factor to the progression of pulmonary hypertension (PH). It also affects around 60% of PH patients, worsening prognosis, reducing exercise capacity, and impairing right heart function [17,18].

The worsened prognosis, frequent hospitalizations, and heightened risk of cardiovascular and all-cause mortality linked to ID in HF stem from iron's essential physiological functions and go beyond just the presence of anemia. Another important factor is how ID impacts the quality of life (QoL) for HF patients by causing frailty and hindering skeletal muscle function [3,7]. This has a very significant effect on their physical potential as demonstrated by tests like the 6-minute walk test (6MWT) and it leads to a reduction of the daily self-sufficiency. The treatment of this deficiency is associated with the use of intravenous ferric carboxymaltose (FCM), which enhances the performance of the patients, reduces the symptoms and the probability of hospitalization and improved the quality of life [19–21].

The effectiveness of intravenous FCM has also been seen in HFrEF patients, with improvements in heart function, especially left ventricular ejection fraction (LVEF) and left ventricular end-systolic volume (LVESV) [22]. In contrast, oral iron supplements did not effectively improve exercise capacity in HFrEF patients, as shown in the IRONOUT-HF trial [2,18].

However, one study indicated that oral sucroso-mial iron was as effective as intravenous treatments in HFrEF patients with ID. While this suggests potential, it has not yet been incorporated into clinical guidelines. This shows that the success of treatment may depend on how well the specific iron formulation is absorbed and tolerated [23]. Despite the high prevalence of ID among HF patients, routine screening is not adequately performed in clinical settings, limiting the potential to improve outcomes for many patients [18].

This review aims to give a thorough overview of ID in HF and related cardiovascular issues, focusing on the changing diagnostic criteria and the best ways to provide iron therapy while highlighting areas where clinical practice can improve.

Pathophysiology

Iron plays a fundamental role in cardiovascular physiology that extends far beyond oxygen transport. Iron deficiency is a common comorbidity in heart failure, affecting 40% to 70% of patients and worsening symptoms, exercise capacity, and prognosis [24]. Up to 60% of patients with coronary artery disease, and an even higher proportion of those with heart failure or pulmonary hypertension have iron deficiency; the prevalence increases with the severity of cardiac and renal dysfunction [16]. The following section discusses the primary pathophysiological pathways, a graphical summary of which is provided in **figure 1**.

Iron absorption, transport, and storage

Iron homeostasis is tightly regulated through the coordinated action of transport proteins and regulatory hormones. There is no known pathway for iron excretion from the human body, with the only loss of iron occurring through desquamation or blood loss; iron homeostasis is therefore highly dependent on intake, uptake, and storage [24]. Iron absorption into the gut mucosa occurs for heme-bound iron via the heme transporter and for non-heme-bound iron after reduction of ferric to ferrous iron through the divalent metal transporter 1 (DMT1) [25]. In the circulation, iron is transported to target organs bound to the serum iron binding protein transferrin. Individual cells modulate their uptake of transferrin-bound iron depending on their iron requirements, using both transferrin receptor 1-dependent and independent pathways [26]. Iron influx into cells

from transferrin-bound serum iron occurs mainly through binding to transferrin receptor 1 (TFR1), a transmembrane glycoprotein, with subsequent receptor mediated endocytosis and iron release. The only known pathway for cellular efflux is through transmembrane protein ferroportin 1 (FPN1) [24].

Inflammation and hepcidin-mediated iron dysregulation

The liver-derived peptide hormone hepcidin serves as the master regulator of systemic iron homeostasis. When hepcidin binds to ferroportin, the complex is internalized and degraded in lysosomes, resulting in intracellular iron sequestration and reduced iron availability to tissues [24]. Inflammation greatly increases hepcidin synthesis, predominantly through interleukin-6, which acts through the JAK2–STAT3 pathway to increase the transcription of the hepcidin gene in hepatocytes. Serum hepcidin levels may increase by a factor of more than 10 in patients with sepsis compared with healthy persons [27]. In heart failure, the erythropoietin-erythroferrone-hepcidin axis becomes activated as disease worsens. Erythropoietin stimulates the production of erythroferrone, which by suppressing the hepatic synthesis of hepcidin promotes the reabsorption of iron from the gastrointestinal tract and the release of iron from stores [28]. Inflammation in heart failure may confer resistance to the actions of erythroferrone, thus explaining why heart failure is not characterized by polycythemia. Inflammation promotes both hepcidin and ferritin, and serum hepcidin and serum ferritin levels were highly correlated at baseline in heart failure patients [28].

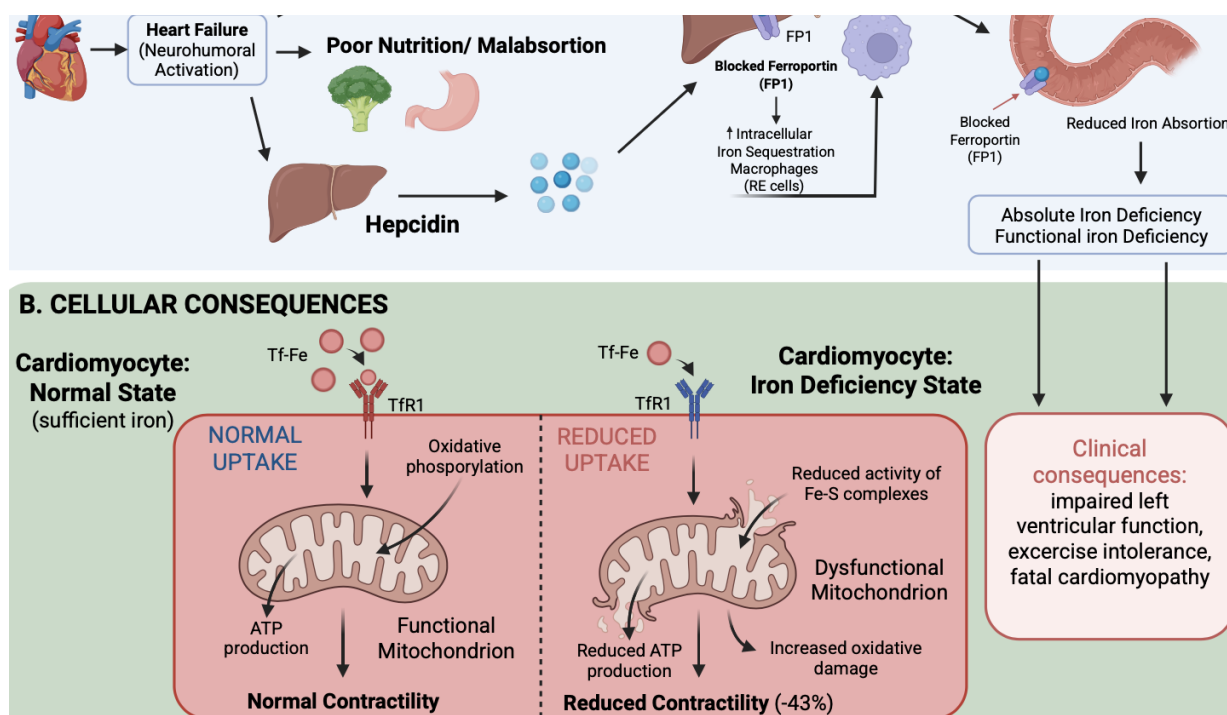


FIGURE 1 Pathophysiology of Iron Deficiency in Heart Failure: from systemic dysregulation to cardiomyocyte energetic failure

Iron's critical role in cardiomyocyte metabolism

Iron is indispensable for mitochondrial function and energy production in cardiomyocytes. Mitochondrial oxidative phosphorylation provides over 90% of the heart's adenosine triphosphate (ATP), and iron is critical for this process [29]. Studies using human embryonic stem cell-derived cardiomyocytes demonstrated that iron depletion affected mitochondrial function through reduced activity of the iron-sulfur cluster containing complexes I, II and III, but not complexes IV and V. Iron deficiency reduced cellular ATP levels by 74% and reduced contractile force by 43% [30]. In a mouse model, iron deficiency without anemia was responsible for decreased left ventricular function through a reduction in mitochondrial complex I activity, probably secondary to a decrease in complex I quantity. These abnormalities were reversed after iron treatment [31]. Myocardial iron deficiency in animal models leads to severe mitochondrial dysfunction, alterations of mitophagy, and mitochondrial biogenesis, with profound alterations in cardiac mechanics and the occurrence of a fatal cardiomyopathy all effects prevented by intravenous administration of iron [32]. The mRNA-binding protein tristetraprolin is induced by iron deficiency and degrades mRNAs of mitochondrial Fe/S-cluster-containing proteins to match the decrease in Fe/S cluster availability; in the absence of tristetraprolin, iron deficiency results in nonfunctional complex III, electron leakage, and oxidative damage [33].

Consequences of iron deficiency on cardiac contractility and exercise capacity

The metabolic consequences of iron deficiency directly translate into impaired cardiac contractile function through multiple pathways. Mice with cardiomyocyte-targeted deletion of IRP1 and IRP2 were unable to increase left ventricular systolic function in response to an acute dobutamine challenge, and after myocardial infarction developed more severe left ventricular dysfunction with increased heart failure mortality [34]. Recent evidence identifies three distinct mechanistic pathways for iron-deficient heart failure: Type 1 involves marked hypoferrae-mia driving cardiomyocyte iron depletion; Type 2 involves intracellular skeletal myocyte iron depletion disproportionate to systemic biomarkers; and Type 3 involves myocardial-specific iron depletion in advanced heart failure [35]. Iron deficiency in the heart failure population, independently from anemia, is associated with changes in bioenergetic metabolisms with a shift toward anaerobic glycolysis and lactate production, contributing to skeletal muscle myopathy and exercise intolerance [36]. Phosphorus magnetic resonance spectroscopy demonstrated that the phosphocreatine to ATP ratio was lower in heart failure patients with iron deficiency (1.03) compared to those without iron deficiency (1.72), irrespective of anaemia and cardiac structure and function [29].

Diagnostics and clinical assessment

According to WHO guidelines, the recommended marker for iron deficiency (ID) is ferritin, an iron-storage protein, measured in plasma, serum, or other biological fluids. In apparently healthy individuals (without inflammation or infection) measurements of this marker reflect the amount of stored iron with values below 15 ng/mL in adults and below 12 ng/mL in children (aged 0 to 59 months). As ferritin is an acute-phase protein, its concentration increases in response to inflammation. In such cases, the diagnostic value of ferritin becomes limited and additional markers are recommended (such as hemoglobin and soluble transferrin receptor – sTfR) with simultaneous measurement of C-reactive protein (CRP) and/or α -1 acid glycoprotein (AGP) [37]. Although hemoglobin measurement is useful in detecting anemia, iron deficiency can be present independently [7].

Conditions such as heart failure, associated with inflammation, can elevate ferritin levels, leading to the use of higher cut-off values for defining iron deficiency. In cardiological guidelines ID is considered when a serum ferritin is below 100 ng/mL or transferrin saturation (TSAT) below 20% if ferritin is between 100-299 ng/mL (ESC) or 100-300 ng/mL (ACC) in patients with HF. The guidelines were originally established for patients with heart failure with reduced ejection fraction (HFrEF) and the same thresholds are now applied to patients with heart failure with preserved ejection fraction (HFpEF). Routine testing of such patients using a complete blood count, serum ferritin concentration, and TSAT is recommended, whereas bone marrow biopsy is not suggested as a standard diagnostic method. Recent guidelines do not emphasize the terms absolute and functional iron deficiency, but they correspond and are still used in clinical practice: absolute ID – ferritin below 100 ng/mL, and functional ID – ferritin between 100-299 ng/mL with TSAT below 20% [7,38–40].

The co-occurrence of heart failure (HF) with iron deficiency is associated with worse HF outcomes [41] and requires special diagnosis and treatment. In an international cohort of heart failure patients, iron deficiency was found in approximately 50% of cases. It was associated with lower hemoglobin or albumin levels and higher CRP concentration [42]. Another study shows that iron deficiency was more frequent among women, patients with more severe symptoms and specified HF phenotypes other than HFrEF [10].

Measurement of transferrin saturation (fraction of transferrin that is saturated with iron – TSAT) is commonly used to indicate iron deficiency, with values below 20% applied in clinical practice. To determine this marker, both serum iron and serum transferrin or total iron binding capacity (TIBC) must be measured. There is a correlation between serum iron and TSAT, especially in stable HF populations. However, inflammation can affect TSAT

leading to false results [43]. Among iron metabolism biomarkers – including high sTfR, low hepcidin, and low serum iron – low TSAT level demonstrates the strongest relationship with all-cause mortality and long-term HF hospitalizations. Recent findings indicate that assessing ID solely through TSAT <20% may detect more patients with decompensated heart failure than when ESC criteria are used [42]. Moreover, patients with HF demonstrate a greater tendency to have a TSAT index < 20% than a ferritin level < 100 ng/mL, which may highlight the value of transferrin saturation [40]. Serum iron concentration may reflect iron availability, including bone marrow iron stores. The value of this marker is affected by inflammatory processes, although it is a better predictor of ID than TSAT or ferritin. Transferrin, a protein that carries iron through the blood and total iron binding capacity (TIBC), a surrogate measure of transferrin, also can be used in the diagnostic process, but alone they are insufficient [43]. In HF patients with mid-range to preserved left ventricular ejection fraction (LVEF), low serum iron may indicate a higher risk of adverse cardiovascular events [42].

In chronic coronary syndromes and acute coronary syndromes, sTfR was the best predictor, less sensitive to inflammation; transferrin saturation was also useful, whereas ferritin had little predictive value. ID frequently affects patients undergoing transcatheter aortic valve implantation (TAVI) for aortic stenosis and patients with pulmonary arterial hypertension. In these populations, TSAT may be a more sensitive marker than ferritin [43].

Iron deficiency remains largely underdiagnosed [40]. Evaluation based on serum ferritin is limited. Therefore, ID in HF patients may require additional diagnostic tests such as TSAT, serum iron or sTfR to ensure accurate diagnosis and appropriate treatment [10].

Clinical evidence and therapeutic outcomes of iron supplementation in heart failure

Patients with heart failure experience reduced physical capacity, which in severe cases may impair all aspects of daily functioning, ultimately leading to a significant deterioration in quality of life. This section reviews the results of randomized clinical trials evaluating the effects of iron supplementation on physical performance, quality of life and symptom burden in adult patients with heart failure.

Physical capacity and quality of life

The findings regarding the impact of iron supplementation on physical capacity in patients with heart failure are not entirely consistent; however, most studies suggest an improvement in exercise tolerance (**Tab. 1**). In the FAIR-HFpEF trial, a significant improvement in the 6- minute walk test (6MWT) was observed in the iron-treated group compared with placebo (increase of 45 ± 62 m vs. -7.8 ± 60.6 m). The HEART-FID trial demonstrated a modest increase in 6MWT distance [44]. A similar trend was reported in the FAIR-HF2 trial, where iron supplementation was associated with improvements in both physical capacity and quality of life, although these effects were mainly evident in selected patient subgroups [45].

Analysis of secondary endpoints revealed a statistically significant improvement in the EQ-5D questionnaire score (mean difference: +0.055) as well as in a patient-assessed well-being after 12 months. Similarly, in the IRONMAN trial, patients reported improved quality of life after 4 months of follow-up, as assessed by the Minnesota Living with Heart Failure Questionnaire [46]. Notably, improvements in quality of life were primarily observed in the short term, while the effect appeared to attenuate over longer follow-up periods, suggesting a potential need for optimization of supplementation regimens.

TABLE 1 Summary of findings on Iron Supplementation in Heart Failure patients: impact on physical capacity, quality of life, hospitalization, and cardiac mortality

Trial	Year of publication	Population	Intervention	Effect on physical capacity	Effect on quality of life	NYHA Scale	Hospitalization/ cardiac mortality
<i>FAIR-HF2</i>	2025	HF, EF<45% + ID	IV ferric carboxymaltose	↑ (in subgroups)	↑	Not significant	↓ (in men)
<i>FAIR-HFpEV</i>	2024	HF, EV>50% + ID	IV ferric carboxymaltose	↑ (6MWT)	↑	Not significant	Not significant
<i>HEART-FID</i>	2023	HF, EF<40% + ID	IV ferric carboxymaltose	↑ (small increase in 6MWT)	Not significant	Not significant	Not significant
<i>IRONMAN</i>	2022	HF, EF<45% + ID	IV ferric derisomaltose	↑	↑	Not significant	↓ (in COVID-19-adjusted analysis)

ID – Iron Deficiency, HF – Heart Failure, EF – Ejection Fraction, 6MWT – 6-Minute Walk Test

At the same time, some studies did not demonstrate significant changes in functional capacity parameters [18]. These discrepancies may be attributed to differences in study populations, severity of heart failure and the type of intervention applied. Overall, the available evidence suggests that iron supplementation may improve physical capacity and quality of life in patients with heart failure; however, its precise impact requires further investigation.

New York Heart Association (NYHA) classification

The NYHA classification is a four-stage scale used to assess the severity of heart failure symptoms based on limitations in daily physical activity. The findings across studies were relatively consistent. Most trials did not demonstrate a significant improvement in NYHA class, suggesting a limited effect of iron supplementation on symptom severity in heart failure [18,44–46].

Hospitalizations and mortality

The results concerning hospitalization rates and cardiovascular mortality remain inconclusive. Some studies did not demonstrate a reduction in either hospital admissions or mortality among patients with heart failure. However, the IRONMAN trial (2022) and FAIR-HF2 (2025) suggest a different trend [45,46].

In the IRONMAN study, a reduction in the rate of heart failure hospitalizations and cardiovascular deaths was observed; however, this difference did not reach statistical significance ($p = 0.07$). In a sensitivity analysis accounting for the impact of the COVID-19 pandemic, the primary endpoint achieved statistical significance ($p = 0.047$).

An interesting observation was reported in the FAIR-HF2 trial. In a subgroup analysis stratified by sex, no statistically significant reduction in the risk of first hospitalization for heart failure or death was observed in women (25 events in the treatment group vs. 33 in the placebo group; $p = 0.80$). In contrast, among men, a significant reduction in heart failure hospitalizations and mortality was noted (108 vs. 141 events; $p = 0.016$). The authors emphasized the need for further research on sex-related differences in response to intravenous iron therapy.

In summary, the available evidence is inconsistent regarding the effect of iron supplementation on reducing hospitalizations and mortality in heart failure patients. The observed effects appear to depend on patient characteristics, including heart failure severity, sex, and the specific supplementation strategy employed.

Clinical implications and outcomes of iron deficiency in other cardiovascular diseases

Iron is an essential element involved in key biological processes. It plays a role in oxygen transport and storage, as well as in protein and lipid synthesis and cellular energy production [47]. Iron deficiency

(ID) is frequently seen in patients with cardiovascular diseases. It is especially present in people with coronary artery disease, pulmonary hypertension, and in those undergoing cardiac surgery, and becomes more common as heart and kidney function decline. This condition is often linked to chronic inflammation and problems with iron absorption [16]. In chronic inflammation, hepcidin levels increase, which makes it harder to absorb iron and release it from cells. As a result, less iron is available for red blood cell production [48].

Iron plays an important role in mitochondrial function. Its deficiency leads to reduced energy production in cardiomyocytes [30]. The current understanding of the relationship between acute coronary syndromes and ID remains limited and is still evolving [49]. Studies show that coronary artery disease (CAD) may affect as many as 60% of people with confirmed ID [16]. It was associated with poorer physical performance, reflected by lower exercise capacity (7.9 vs. 9.3 METs) and a shorter distance in the 6-minute walk test (277 vs. 423 m). No clinical trials have yet evaluated iron supplementation in patients with acute coronary syndrome (ACS) and confirmed iron deficiency. However, in patients after STEMI, intravenous iron was associated with improvement left ventricular ejection fraction ($53 \pm 10\% \rightarrow 59 \pm 9\%$ vs $54 \pm 6\% \rightarrow 57 \pm 10\%$) and reduced infarct size ($27 \pm 8\% \rightarrow 17 \pm 9\%$ vs $27 \pm 12\% \rightarrow 20 \pm 11\%$) over 3 months [50]. The risk of coronary artery disease may decrease by up to 7–14% with higher iron levels [51]. It is important to be aware that ID may occur even without anemia in patients with CAD [16].

Pulmonary arterial hypertension (PAH) is a serious condition in which the pulmonary arteries gradually narrow, eventually leading to right ventricular failure and death [52]. Iron deficiency was observed in 33–46% of patients with PAH. It was associated with reduced exercise tolerance, impaired oxygen utilization, right ventricular dysfunction, and higher mortality [53]. An interesting phenomenon that has been scientifically proven is that patients with confirmed PAH were found to have reduced iron absorption in the gastrointestinal tract [54]. In patients with PAH, oral iron supplementation does not always effectively correct ID. One of the reasons is the increased level of hepcidin, which impairs iron absorption in the intestine [55]. Pulmonary artery pressure is higher in patients with iron deficiency (63.3 ± 12.2 vs. 38.8 ± 16.7 mmHg), and cardiac index is lower (1.4 ± 0.2 vs. 2.5 ± 0.4 L/min/m²). Additionally, the concentration of N-terminal B-type natriuretic peptide (854 ng/L vs. 136 ng/L, $p = 0.044$) is elevated [56]. An interesting finding is that PAH was diagnosed in only 17% of patients with iron deficiency anemia (IDA) [57].

Patients with confirmed ID prior to cardiac surgery have a higher risk of adverse outcomes and

are more likely to require increased red blood cell transfusions [58]. This is also associated with longer stays in the intensive care unit and hospital, as well as higher postoperative mortality [59].

“Patient blood management (PBM) is a multimodal, multidisciplinary approach to the care of patients who might need transfusion, aimed at minimising the use of blood products and improving patient outcomes.” [60] Intravenous iron administration can increase the amount of free iron in the blood, which may in turn promote the development of infections [61]. Patient blood management (PBM) can help reduce healthcare costs [60].

Iron deficiency is common among patients with cardiovascular disease and may adversely affect their clinical condition even in the absence of overt anemia. It disrupts cellular energy production in cardiomyocytes, contributing to reduced exercise capacity and an increased risk of adverse outcomes. In coronary artery disease and pulmonary hypertension, iron deficiency is associated with poorer prognosis, higher pulmonary arterial pressure, and impaired cardiac function. In patients with pulmonary hypertension, reduced gastrointestinal absorption of iron further complicates management, often limiting the effectiveness of oral supplementation. Additionally, preoperative iron deficiency in individuals undergoing cardiac surgery is linked to a higher risk of complications, an increased need for blood transfusions, and prolonged hospitalization.

Treatment

The findings of recent studies are reflected in current guidelines. Although these guidelines are continually updated with new data, the discussion of iron deficiency in the context of cardiovascular diseases focuses primarily on patients with heart failure (HF) and pulmonary arterial hypertension (PAH). All patients with HF and PAH should undergo regular screening for anemia and iron deficiency, including assessment of a complete blood count, serum ferritin concentration, and transferrin saturation (Tsat) [7,62].

Furthermore, regarding the treatment of patients with HF, the updated ESC guidelines (2023) recommend [38]:

- Intravenous iron supplementation in symptomatic patients with HFrEF or HFmrEF and iron deficiency to reduce HF symptoms and improve quality of life (QoL) (class of recommendation I, level of evidence A);
- Considering intravenous iron supplementation with iron carboxymaltose or iron deriso-maltose in symptomatic patients with HFrEF or HFmrEF and iron deficiency to reduce the risk of HF hospitalization (class of recommendation IIa, level of evidence A).

Furthermore, in the context of patients with PAH, it is recommended to correct iron deficiency

in cases of concomitant iron-deficiency anemia; in cases of severe anemia (Hb <7-8 g/dL), intravenous supplementation should be administered (class of recommendation I, level of evidence C). However, in cases of iron deficiency in patients with PAH without concomitant anemia, iron supplementation may be considered (class of recommendation IIb, level of evidence C) [62].

There are no official guidelines for other cardiovascular diseases. The results of some studies suggest that patients with other cardiovascular diseases may also benefit from iron supplementation. This group includes, among others, acute coronary syndromes (ACS) that lead to myocardial infarction (MI). However, additional studies are needed to develop official recommendations [50]. Another issue is atrial fibrillation (AF) without HF. Here, too, iron deficiency may have a potentially negative impact on the course of the disease. However, further research is necessary to develop clear recommendations regarding iron supplementation [63].

In terms of iron supplementation in patients with HF, oral and intravenous routes of administration were compared. Intravenous iron administration was associated with improved physical performance and quality of life (QoL), and after at least 12 weeks of supplementation, the rate of hospitalizations due to HF also decreased. Oral supplementation was not associated with improved physical performance or QoL; however, it may reduce the frequency of hospitalizations due to HF and all-cause mortality [64]. It should be added that although oral iron supplementation is relatively safe, it is often associated with bothersome side effects that lead patients to discontinue supplementation on their own, which further limits the effectiveness of the therapy [65]. Consequently, the ESC guidelines do not recommend oral iron supplementation in cases of iron deficiency in the context of HF [7].

Current intravenous iron preparations offer an excellent alternative when oral iron is ineffective or not tolerated. Recent studies indicate a low risk of serious adverse reactions, and side effects – particularly those affecting the gastrointestinal tract – occur less frequently than with oral administration. However, a specific side effect of iron carboxymaltose is hypophosphatemia, which occurs in up to half of patients treated with this substance [65,66].

However, one must not overlook anaphylactic reactions, which are an absolute contraindication to the continued use of intravenous iron. Nevertheless, this phenomenon is now very rare due to the introduction of new formulations [66]. On the other hand, hypersensitivity reactions that are not classic anaphylaxis – but rather activation of the complement system or an IgE-mediated immune response – are observed relatively frequently [67]. This does not constitute an absolute contraindication to continued therapy. In such cases, special pre-

cautions should be taken, and preparations should be made for the possible need for urgent intervention. A management algorithm for hypersensitivity reactions following intravenous iron administration was developed by Schaefer et al. (2020) [66].

Conclusions

Routine screening for iron deficiency and swift intravenous iron therapy mark game-changing yet underused steps in heart failure care, easing symptoms, cutting events, and boosting survival – despite vast potential to help millions. Extending proven European Society of Cardiology protocols to coronary artery disease (post-heart attack repair) and pulmonary hypertension (right heart aid) calls for immediate randomized trials, emphasizing transferrin saturation over ferritin for inflamed patients. Team-based care – blending cardiology, hematology, and nutrition – should favor intravenous over oral iron, factoring in sex differences (stronger male benefits in FAIR-HF2). Updated guidelines must require iron checks across all cardiovascular disease types to reshape heart failure outcomes.

Ethical approval

The conducted research is not related to either human or animal use.

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Conflict of interest

The authors declare they have no conflict of interest.

References

- Anker SD, Kirwan BA, van Veldhuisen DJ, Filippatos G, Comin-Colet J, Ruschitzka F, Lüscher TF, Arutyunov GP, Motro M, Mori C, Roubert B, Pocock SJ, Ponikowski P. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. *Eur J Heart Fail*. 2018;20(1):125–33; DOI:10.1002/ehf.823.
- Lewis GD, Malhotra R, Hernandez AF, McNulty SE, Smith A, Felker GM, Tang WHW, LaRue SJ, Redfield MM, Semigran MJ, Givertz MM, Van Buren P, Whellan D, Anstrom KJ, Shah MR, Desvigne-Nickens P, Butler J, Braunwald E. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: the IRONOUT HF randomized clinical trial. *JAMA*. 2017;317(19):1958–66; DOI:10.1001/jama.2017.5427.
- Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J*. 2015;36(11):657–68; DOI:10.1093/eurheartj/ehu385.
- von Haehling S, Ebner N, Evertz R, Ponikowski P, Anker SD. Iron deficiency in heart failure: an overview. *JACC Heart Fail*. 2019;7(1):36–46; DOI:10.1016/j.jchf.2018.07.015.
- Sagar P, Angmo S, Sandhir R, Rishi V, Yadav H, Singhal NK. Effect of hepcidin antagonists on anemia during inflammatory disorders. *Pharmacol Ther*. 2021;226:107877; DOI:10.1016/j.pharmthera.2021.107877.
- de las Cuevas Allende R, Díaz de Entresotos L, Conde Díez S. Anaemia of chronic diseases: pathophysiology, diagnosis and treatment. *Med Clin (Barc)*. 2021;156(5):235–42; DOI:10.1016/j.medcli.2020.07.035.
- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Piepoli MF, Price S, Rosano GMC, Ruschitzka F, Skibelund AK, ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2021;42(36):3599–726; DOI:10.1093/eurheartj/ehab368.
- Auerbach M, Deloughery TG, Tirnauer JS. Iron deficiency in adults: a review. *JAMA*. 2025;333(20):1813–23; DOI:10.1001/JAMA.2025.0452.
- Grote Beverborg N, Klip IT, Meijers WC, Voors AA, Vegter EL, Van Der Wal HH, Swinkels DW, van Pelt J, Mulder AB, Bulstra SK, Vellenga E, Mariani MA, de Boer RA, van Veldhuisen DJ, van der Meer P. Definition of iron deficiency based on the gold standard of bone marrow iron staining in heart failure patients. *Circ Heart Fail*. 2018;11(2):e004519; DOI:10.1161/CIRCHEARTFAILURE.117.004519.
- Masini G, Graham FJ, Pellicori P, Cleland JGF, Cuthbert JJ, Kazmi S, Inciardi RM, Clark AL. Criteria for iron deficiency in patients with heart failure. *J Am Coll Cardiol*. 2022;79(4):341–51; DOI:10.1016/j.jacc.2021.11.039.
- Graham FJ, Masini G, Pellicori P, Cleland JGF, Greenlaw N, Friday J, Kazmi S, Clark AL. Natural history and prognostic significance of iron deficiency and anaemia in ambulatory patients with chronic heart failure. *Eur J Heart Fail*. 2022;24(5):807–17; DOI:10.1002/ehf.2251.
- Maeder MT, Khammy O, Dos Remedios C, Kaye DM. Myocardial and systemic iron depletion in heart failure: implications for anemia accompanying heart failure. *J Am Coll Cardiol*. 2011;58(5):474–80; DOI:10.1016/j.jacc.2011.01.059.
- Graham FJ, Pellicori P, Kalra PR, Ford I, Bruzzese D, Cleland JGF. Intravenous iron in patients with heart failure and iron deficiency: an updated meta-analysis. *Eur J Heart Fail*. 2023;25(4):528–37; DOI:10.1002/ehf.2810.
- Sirbu O, Tirnoveanu A, Haliga RE, Sorodoc V, Sava M, Bologa C, Petris OR, Morarasu BC, Diaconu AD, Ceasovschi A, Lionte C, Morariu PC, Morariu BA, Stasescu C, Sascau RA, Floria M, Sorodoc L. Iron deficiency in heart failure: from ESC guidelines to clinical practice at a Romanian hospital. *Biomedicine*. 2025;13(9):2296; DOI:10.3390/biomedicine13092296.
- Barandiarán Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca HP, Henkens MTHM, Weerts J, Spanjers MHA, Knackstedt C, van Empel VPM. Iron deficiency impacts prognosis but less exercise capacity in heart failure with preserved ejection fraction. *ESC Heart Fail*. 2021;8(2):1304–13; DOI:10.1002/ehf2.13204.
- Savarese G, von Haehling S, Butler J, Cleland JGF, Ponikowski P, Anker SD. Iron deficiency and cardiovascular disease. *Eur Heart J*. 2023;44(1):14–27; DOI:10.1093/eurheartj/ehac569.
- Albulushi A, Kashoub M, Al-Saidi K, Al-Farhan H. Iron deficiency in pulmonary hypertension implications, supplementation, and future directions. *Int Heart J*. 2024;65(4):593–600; DOI:10.1536/ihj.24-055.
- Mentz RJ, Garg J, Rockhold FW, Butler J, De Pasquale CG, Ezekowitz JA, Lewis GD, O'Meara E, Ponikowski P, Troughton RW, Wong YW, She L, Harrington J, Adamczyk R, Blackman N, Hernandez AF. Ferric carboxymaltose in heart failure with iron deficiency. *N Engl J Med*. 2023;389(11):975–86; DOI:10.1056/nejmoa2304968.
- Van Veldhuisen DJ, Ponikowski P, Van Der Meer P, Metra M, Böhm M, Doletsky A, Voors AA, Macdougall IC, Anker SD, Roubert B, Zakari L, Cohen-Solal A. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. *Circulation*. 2017;136(15):1374–83; DOI:10.1161/CIRCULATIONAHA.117.027497.
- Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozd J, Fabien V, Filippatos G, Göhring UM, Keren A, Khintibidze I, Kragten H, Martinez FA, Metra M, Milicic D, Nicolau JC, Ohlsson M, Parkhomenko A, Pascual-Figal DA, Ruschitzka F, Sim D, Skouri H, van der Meer P, Lewis BS, CominColet J, von Haehling S, Cohen-Solal A, Danchin N, Dohner W, Dargie HJ, Motro M, Butler J, Friede T, Jensen KH, Pocock S, Jankowska EA. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet*. 2020;396(10266):1895–1904; DOI:10.1016/S0140-6736(20)32339-4.
- Ponikowski P, Mentz RJ, Hernandez AF, Butler J, Khan MS, Van Veldhuisen DJ, Roubert B, Blackman N, Friede T, Jankowska EA, Anker SD. Efficacy of ferric carboxymaltose in heart failure with iron deficiency: an individual patient data meta-analysis. *Eur Heart J*. 2023;44(48):5077–91; DOI:10.1093/eurheartj/ehad586.
- Martens P, Dupont M, Dauw J, Nijst P, Herbots L, Dendale P, Vandervoort P, Bruckers L, Tang WHW, Mullens W. The effect of intravenous

- us ferric carboxymaltose on cardiac reverse remodelling following cardiac resynchronization therapy—the IRON-CRT trial. *Eur Heart J*. 2021;42(48):4905–14; DOI:10.1093/eurheartj/ehab411.
23. Karavidas A, Trognan E, Lazaros G, Balta D, Karavidas IN, Polyzogopoulou E, Parisis J, Farmakis D. Oral sucrosomial iron improves exercise capacity and quality of life in heart failure with reduced ejection fraction and iron deficiency: a non-randomized, open-label, proof-of-concept study. *Eur J Heart Fail*. 2021;23(4):593–7; DOI:10.1002/ehf.2092.
 24. Cheema B, Chokshi A, Orimoloye O, Ardehali H. Intravenous iron repletion for patients with heart failure and iron deficiency: JACC state-of-the-art review. *J Am Coll Cardiol*. 2024;83(25):2674–89; DOI:10.1016/j.jacc.2024.03.431.
 25. Gao G, Li J, Zhang Y, Chang YZ. Cellular iron metabolism and regulation. *Adv Exp Med Biol*. 2019;1173:21–32; DOI:10.1007/978-981-13-9589-5_2.
 26. Frazer DM, Anderson GJ. The regulation of iron transport. *Biofactors*. 2014;40(2):206–14; DOI:10.1002/BIOF.1148.
 27. Ganz T. Anemia of Inflammation. *N Engl J Med*. 2019;381(12):1148–57; DOI: 10.1056/NEJMr1804281.
 28. Ferreira JP, Anker SD, Butler J, Filippatos G, Januzzi JL, Schueler E, Panovala-Noeva M, Wetzel K, Prochaska J, Pocock SJ, Sattar N, Sumin M, Zannad F, Packer M. Effect of empagliflozin on the mechanisms driving erythropoiesis and iron mobilization in patients with heart failure: The EMPEROR program. *J Am Coll Cardiol*. 2025;85(18):1757–70; DOI:10.1016/j.jacc.2025.03.503.
 29. Papalia F, Jouhra F, Amin-Youssef G, Shah AM, Charles-Edwards G, Okonko DO. Cardiac energetics in patients with chronic heart failure and iron deficiency: an in-vivo ³¹P magnetic resonance spectroscopy study. *Eur J Heart Fail*. 2022;24(4):716–23; DOI:10.1002/EJHF.2454.
 30. Hoes MF, Grote Beverborg N, Kijlstra JD, Kuipers J, Swinkels DW, Giepmans BNG, Rodenburg RJ, van Veldhuisen DJ, de Boer RA, van der Meer P. Iron deficiency impairs contractility of human cardiomyocytes through decreased mitochondrial function. *Eur J Heart Fail*. 2018;20(5):910–9; DOI:10.1002/EJHF.1154.
 31. Rineau E, Gaillard T, Gueguen N, Procaccio V, Henrion D, Prunier F, Lasocki S. Iron deficiency without anemia is responsible for decreased left ventricular function and reduced mitochondrial complex I activity in a mouse model. *Int J Cardiol*. 2018;266:206–12; DOI:10.1016/j.ijcard.2018.02.021.
 32. Corradi F, Masini G, Bucciarelli T, De Caterina R. Iron deficiency in myocardial ischaemia: molecular mechanisms and therapeutic perspectives. *Cardiovasc Res*. 2023;119(14):2405–20; DOI:10.1093/CVR/CVAD146.
 33. Sato T, Chang HC, Bayeva M, Shapiro JS, Ramos-Alonso L, Kouzu H, Jiang X, Liu T, Yar S, Sawicki KT, Chen C, Martínez-Pastor MT, Stumpo DJ, Schumacker PT, Blackshear PJ, Ben-Sahra I, Puig S, Ardehali H. mR-NA-binding protein tristetraprolin is essential for cardiac response to iron deficiency by regulating mitochondrial function. *Proc Natl Acad Sci U S A*. 2018;115(27):E6291–E6300; DOI:10.1073/PNAS.1804701115.
 34. Haddad S, Wang Y, Galy B, Korf-Klingebiel M, Hirsch V, Baru AM, Rostami F, Rebol MR, Heineke J, Flögel U, Groos S, Renner A, Toischer K, Zimmermann F, Engeli S, Jordan J, Bauersachs J, Hentze MW, Wollert KC, Kempf T. Iron-regulatory proteins secure iron availability in cardiomyocytes to prevent heart failure. *Eur Heart J*. 2017;38(5):362–72; DOI:10.1093/EURHEARTJ/EHW333.
 35. Packer M, Anker SD, Butler J, Cleland JGF, Kalra PR, Mentz RJ, Ponikowski P. Identification of three mechanistic pathways for iron-deficient heart failure. *Eur Heart J*. 2024;45(26):2281–93; DOI:10.1093/EURHEARTJ/EHAE284.
 36. Del Buono MG, Arena R, Borlaug BA, Carbone S, Canada JM, Kirkman DL, Garten R, RodriguezMiguel P, Guazzi M, Lavie CJ, Abbate A. Exercise intolerance in patients with heart failure: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;73(17):2209–25; DOI:10.1016/j.jacc.2019.01.072.
 37. World Health Organization. WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations. Geneva: World Health Organization; 2020. Available from: <https://www.who.int/publications/i/item/9789240000124/>.
 38. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Piepoli MF, Price S, Rosano GMC, Ruschitzka F, Skibelund AK. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2023;44(37):3627–39; DOI:10.1093/eurheartj/ehad195.
 39. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Farrow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *Circulation*. 2022;145(18):e895–e1032; DOI:10.1161/CIR.0000000000001063.
 40. Cohen-Solal A, Philip JL, Picard F, Delarche N, Taldir G, Gzara H, Kori-chi A, Trochu JN, Cacoub P. Iron deficiency in heart failure patients: the French CARENFER prospective study. *ESC Heart Fail*. 2022;9(2):874–84; DOI:10.1002/ehf2.13850.
 41. Padda I, Sebastian SA, Fabian D, Sethi Y, Johal G. The efficacy and safety of ferric carboxymaltose in heart failure with reduced ejection fraction and iron deficiency: an updated systematic review and metaanalysis of randomized controlled trials. *Diseases*. 2024;12(12):339; DOI:10.3390/diseases12120339.
 42. Dhaliwal S, Kalogeropoulos AP. Markers of iron metabolism and outcomes in patients with heart failure: a systematic review. *Int J Mol Sci*. 2023;24(6):5645; DOI:10.3390/ijms24065645.
 43. Graham FJ, Masini G, Lakhal-Littleton S, Clark AL, Cleland JGF, Pellicori P. Iron deficiency in cardiovascular disease – diagnosis, clinical implications, and future directions. *Circ J*. 2025; DOI:10.1253/circj.cj-25-0220.
 44. Von Haehling S, Doehner W, Evertz R, Garfias-Veitel T, Derad C, Diek M, Karakas M, Birkemeyer R, Filippatos G, Lainscak M, Butler J, Ponikowski P, Böhm M, Friede T, Anker SD. Ferric carboxymaltose and exercise capacity in heart failure with preserved ejection fraction and iron deficiency: the FAIRHFpEF trial. *Eur Heart J*. 2024;45(37):3789–3800; DOI:10.1093/eurheartj/ehae479.
 45. Karakas M, Friede T, Butler J, Talha KM, Placzek M, Asendorf T, Diek M, Nosko A, Stas A, Kluge S, Jarczack D, DeHeer G, Rybczynski M, Bayes-Genis A, Böhm M, Coats AJS, Edelmann F, Filippatos G, Hasenfuß G, Haverkamp W, Lainscak M, Landmesser U, Macdougall IC, Merkely B, Pieske BM, Pinto FJ, Rassaf T, Visser-Rogers JK, Rosano G, Volterrani M, von Haehling S, Anker MS, Doehner W, Ince H, Koehler F, Savarese G, Khan MS, Kröhnert UR, Gori T, Trenkwalder T, Akin I, Paitazoglou C, Kobielusz-Gembala I, Kuthi L, Frey N, Licka M, Käab S, Laugwitz KL, Ponikowski P, Anker SD. Intravenous ferric carboxymaltose in heart failure with iron deficiency (FAIR-HF2 DZHK05 trial): sexspecific outcomes. *Eur J Heart Fail*. 2025;27(11):2328–42; DOI:10.1002/ehf.3742.
 46. Kalra PR, Cleland JGF, Petrie MC, Thomson EA, Kalra PA, Squire IB, Ahmed FZ, Al-Mohammad A, Cowburn PJ, Foley PWX, Graham FJ, Japp AG, Lane RE, Lang NN, Ludman AJ, Macdougall IC, Pellicori P, Ray R, Robertson M, Seed A, Ford I. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. *Lancet*. 2022;400(10369):2199–209; DOI:10.1016/S0140-6736(22)02083-9.
 47. Alnuwaysir RIS, Grote Beverborg N, Hoes MF, Markousis-Mavrogenis G, Gomez KA, van der Wal HH, Cleland JGF, Dickstein K, Lang CC, Ng LL, Ponikowski P, Anker SD, van Veldhuisen DJ, Voors AA, van der Meer P. Additional burden of iron deficiency in heart failure patients beyond the cardio-renal anaemia syndrome: findings from the BIostat-CHF study. *Eur J Heart Fail*. 2022;24(1):192–204; DOI:10.1002/ehf.2393.
 48. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. *Blood*. 2019;133(1):40–50; DOI:10.1182/blood-2018-06-856500.
 49. Silva C, Martins J, Campos I, Arantes C, Braga CG, Salomé N, Gaspar A, Azevedo P, Álvares Pereira M, Marques J, Vieira C. Prognostic impact of iron deficiency in acute coronary syndromes. *Rev Port Cardiol (Eng Ed)*. 2021;40(8):525–36; DOI:10.1016/j.rpepce.2020.09.005.
 50. Misiewicz A, Badura K, Matuszewska-Brycht O, Krekora J, Drożdż J. Iron deficiency as a factor of worse prognosis in patients with acute myocardial infarction. *Biomedicine*. 2025;13(4):769; DOI:10.3390/biomedicine13040769.
 51. Liu Y, Clarke R, Bennett DA, Zong G, Gan W. Iron status and risk of heart disease, stroke, and diabetes: a Mendelian randomization study in European adults. *J Am Heart Assoc*. 2024;13(6):e031732; DOI:10.1161/JAHA.123.031732.
 52. Quatrederieners M, Mendes-Ferreira P, Santos-Ribeiro D, Nakhleh MK, Ghigna MR, Cohen-Kaminsky S, Perros F. Iron deficiency in pulmonary arterial hypertension: a deep dive into the mechanisms. *Cells*. 2021;10(2):477; DOI:10.3390/cells10020477.
 53. Lan M, Wu S, Fernandes TM. Iron deficiency and pulmonary arterial hypertension. *Nutr Clin Pract*. 2022;37(5):1059–73; DOI:10.1002/ncp.10884.
 54. Repsold L, Harutyunova S, Grünig E, Benjamin N, Xanthouli P, Egenlauf B, Florea A, Shaikat M, Sparla R, Mertens C, Muckenthaler MU, Eichstaedt CA. Reduced gastrointestinal iron uptake in pulmonary arterial hypertension: a prospective cross-sectional study. *Respir Res*. 2026;27(1):159; DOI:10.1186/s12931-026-03592-8.

55. Howard LSGE, He J, Watson GMJ, Huang L, Wharton J, Luo Q, Kiely DG, Condliffe R, Pepke-Zaba J, Morrell NW, Sheares KK, Ulrich A, Quan R, Zhao Z, Jing X, An C, Liu Z, Xiong C, Robbins PA, Dawes T, de Marvao A, Rhodes CJ, Richter MJ, Gall H, Ghofrani HA, Zhao L, Huson L, Wilkins MR. Supplementation with iron in pulmonary arterial hypertension two randomized crossover trials. *Ann Am Thorac Soc*. 2021;18(6):981–8; DOI:10.1513/AnnalsATS.202009-11310C.
56. Van Empel VPM, Lee J, Williams TJ, Kaye DM. Iron deficiency in patients with idiopathic pulmonary arterial hypertension. *Heart Lung Circ*. 2014;23(3):287–92; DOI:10.1016/j.hlc.2013.08.007.
57. J V, Ashwaq M, Balachandra G. Study of prevalence of pulmonary arterial hypertension in iron deficiency anaemia and vitamin B12 deficiency anemia. *Eur J Cardiovasc Med*. 2025;15(8):391–5; DOI:10.61336/EJCM/25-08-74.
58. Frei I, Gogniat AL, Buser A, Bolliger D. Anemia and iron deficiency in cardiac surgery patients: prevalence, implications, and therapeutic considerations. *J Clin Med*. 2025;14(22):8261; DOI:10.3390/jcm14228261.
59. Tibi P, McClure RS, Huang J, Baker RA, Fitzgerald D, Mazer CD, Stone M, Chu D, Stammers AH, Dickinson T, Shore-Lesserson L, Ferraris V, Firestone S, Kisson K, Moffatt-Bruce S. STS/SCA/AmSECT/SABM update to the clinical practice guidelines on patient blood management. *Ann Thorac Surg*. 2021;112(3):981–1004; DOI:10.1016/j.athoracsur.2021.03.033.
60. Franchini M, Marano G, Veropalumbo E, Masiello F, Pati I, Candura F, Profili S, Catalano L, Piccinini V, Pupella S, Vaglio S, Liumbruno GM. Patient blood management: a revolutionary approach to transfusion medicine. *Blood Transfus*. 2019;17(3):191–5; DOI:10.2450/2019.0109-19.
61. Shah A, Sugavanam A, Reid J, Palmer AJ, Dickson E, Brunskill S, Doree C, Oliver CM, Acheson A, Baikady RR, Bampoe S, Litton E, Stanworth S. Risk of infection associated with intravenous iron preparations: protocol for updating a systematic review. *BMJ Open*. 2019;9(6):e024618; DOI:10.1136/bmjopen-2018-024618.
62. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escibano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachieri JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). *Eur Heart J*. 2022;43(38):3618–731; DOI:10.1093/eurheartj/ehac237.
63. Hanna-Rivero N, Tu SJ, Elliott AD, Pitman BM, Gallagher C, Lau DH, Sanders P, Wong CX. Anemia and iron deficiency in patients with atrial fibrillation. *BMC Cardiovasc Disord*. 2022;22(1):204; DOI:10.1186/s12872-022-02633-6.
64. Mei Z, Chen J, Luo S, Jin L, Liu Q, Chen Y. Comparative efficacy of intravenous and oral iron supplements for the treatment of iron deficiency in patients with heart failure: a network meta-analysis of randomized controlled trials. *Pharmacol Res*. 2022;182:106345; DOI:10.1016/j.phrs.2022.106345.
65. DeLoughery TG. Safety of oral and intravenous iron. *Acta Haematol*. 2019;142(1):8–12; DOI:10.1159/000496966.
66. Schaefer B, Meindl E, Wagner S, Tilg H, Zoller H. Intravenous iron supplementation therapy. *Mol Aspects Med*. 2020;75:100862; DOI:10.1016/j.mam.2020.100862.
67. Rampton D, Folkersen J, Fishbane S, Hedenus M, Howaldt S, Locatelli F, Patni S, Szebeni J, Weiss G. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. *Haematologica*. 2014;99(11):1671–6; DOI:10.3324/haematol.2014.111492.