



Iron Deficiency in Cardiovascular Disease

— Diagnosis, Clinical Implications, and Future Directions —

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Iron is an essential requirement for normal cellular function and oxygen transport. Deficiency of iron, due to suboptimal intake, blood loss, malabsorption or maldistribution is the most common nutrient deficiency worldwide. Iron deficiency (ID) has traditionally been ignored until anemia develops. Amongst patients with cardiovascular (CV) disease, ID is common and is associated with worse symptoms, poorer quality of life, and a worse prognosis. However, the criteria used to define ID in studies and international guidelines are inconsistent and lack universal acceptance. Accordingly, we review the various criteria used to define ID in patients with CV disease, discuss how these might have influenced the results of observational studies and randomized trials and suggest areas for future research.

Key Words: Anemia; Cardiovascular disease; Iron deficiency

Iron is required for oxygen transport (by hemoglobin (Hb)) and storage (by myoglobin), electron transport (in the mitochondrial electron transport chain) and many enzymatic functions.¹⁻⁴ Iron deficiency (ID) is the most common nutrient deficiency worldwide,⁵ and although the commonest cause is low dietary intake, physiological (e.g., menstruation in young women) or pathological conditions (e.g., gastrointestinal (GI) bleeding or malabsorption due to diseases or medicines) can also induce ID. Anemia, as currently defined by the World Health Organization (WHO),⁶ is a common but late manifestation of ID. However, the consequences of ID extend beyond iron-deficient erythropoiesis. Alone or in combination with anemia, ID is associated with fatigue and lethargy, poorer quality of life (QOL),⁷⁻¹⁰ impaired physical performance^{11,12} and cognitive function,¹³ and with a poorer prognosis in patients with cardiovascular disease (CVD).¹⁴⁻¹⁸ ID in skeletal and cardiac muscle has also been demonstrated at a cellular level in some CVDs and is probably functionally important.^{1,2,4,19}

Patients with CVD may be at increased risk of ID due to increased GI and genitourinary (GU) blood loss secondary to antiplatelet or anticoagulant medications, reduced GI absorption and impaired mobilization after absorption due to increased secretion of hepcidin and widespread use of agents that reduce gastric acidity.²⁰

Investigations of ID are rarely done in the absence of anemia.²¹ If they are done, and they do suggest ID, oral

iron supplements are often not prescribed.²² Iron can be also replaced intravenously (IV), which will correct ID rapidly and reliably. However, in the absence of any iron-excretory pathways, some caution in administering IV iron is required because it bypasses the complex homeostatic systems that have evolved to prevent iron overload.²³

Iron Metabolism

Iron uptake occurs in the duodenum and proximal jejunum.²⁴ Most dietary iron is in an oxidized ferric form (Fe^{3+}), which requires chelation by organic acids or reduction to ferrous iron (Fe^{2+}) to be absorbed.^{25,26} Gastric acidity promotes iron absorption by gut enterocytes,^{25,27} which import iron via ferroportin into the circulation where it binds to plasma transferrin. The iron-transferrin complex binds to transferrin receptors on the surface of target cells.²⁵ The complex is then internalized and conveyed to mitochondria for formation of iron-sulfur clusters or heme.²⁸ All cells of the body can store excess iron for future needs, first as ferritin and eventually as hemosiderin.²⁶ Hepatocytes, reticuloendothelial macrophages and Kupffer cells are specialized cells that contain an abundance of ferritin, which stores iron that can be rapidly mobilized to meet systemic demands. Iron can also be trapped inside cells as hemosiderin, caused by defective ferritin degradation. The iron in hemosiderin has poor availability. Very little ferritin escapes into the circulation, unless cells are damaged, for

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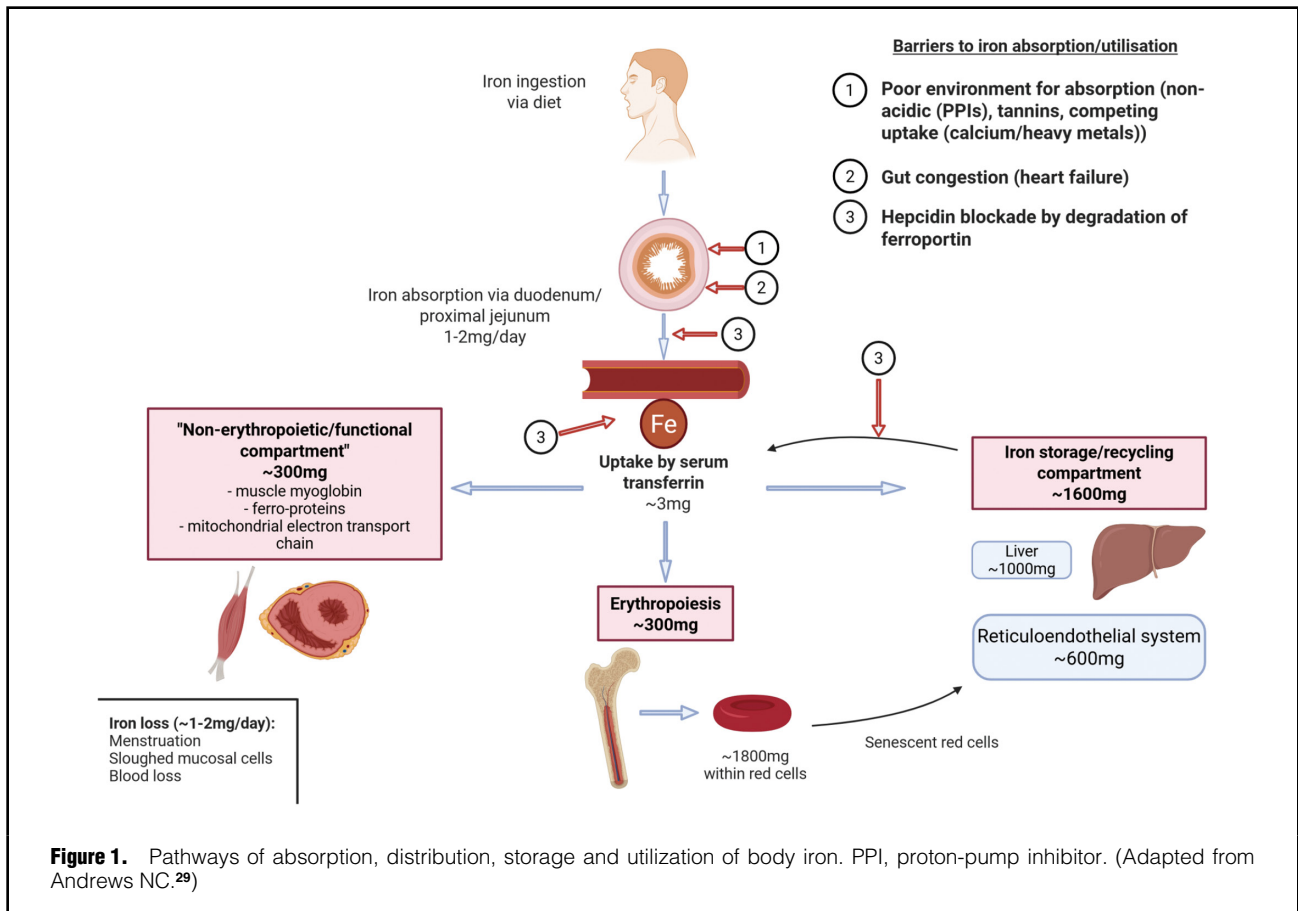
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instance, due to inflammation or infection. Plasma ferritin is iron-poor and reflects the spillover of ferritin from storage sites.

Daily absorption of iron ($\approx 1-2$ mg when someone is healthy and iron replete but increasing 10-fold if there is ID and normal absorption) is similar to daily losses of iron, mainly from subtle GI blood loss or menstruation.²⁵ At any time, there is between 4 and 6 g of iron in the body²⁹ (Figure 1). Absorption, storage, and recovery of iron are under tight control to avoid deficiency or overload. Hepcidin, produced and released from the liver, has a key role in iron uptake and availability. It binds to and blocks ferroportin,³⁰ preventing iron absorbed by enterocytes or stored in the reticuloendothelial system from entering the circulation and locking iron inside enterocytes,³⁰ which are continuously sloughed into the feces.²⁵ Plasma concentrations of hepcidin fall (increasing iron absorption) in response to low transferrin saturation (TSAT) or hypoxia, and increase (reducing available iron) in response to infection, inflammation, elevated TSAT or liver iron overload.^{26,28,31}

Prevalence of ID

The prevalence of ID (defined by serum biomarkers) in men and postmenopausal women increases with age, even in the absence of overt disease, as does the prevalence of anemia.¹⁶ To what extent this indicates occult disease (cancer or CVD) or physiological changes with age is uncertain, but it is associated with greater all-cause and cardiovascular

death.¹⁸ Patients with CVD probably have a higher prevalence of ID even after adjusting for age, either due to the disease or its treatment. In people with established CVD, the prevalence of ID ranges widely, from 15% to >80%, depending on the CVD and definition of ID (Table 1).^{7,8,10,15,17,32-43} Bone marrow histology is considered the "gold standard" for diagnosing ID,⁴⁴ but is seldom done because it is invasive and painful. It also requires special expertise in sampling and assessment, which can be subjective and operator-dependent.⁴⁵

Diagnostic Criteria for ID

There is no international consensus as to which biomarker/s, and which diagnostic threshold of these biomarker/s, should be used to define ID. For example, criteria differ considerably between guidelines intended for the general population compared with patients with heart failure (HF) (Table 2). Currently, for patients with HF, the ESC and ACC definitions of ID (Table 2) are popular, but this may change in the light of new information from observational studies,⁴³ meta-analyses of trials of intravenous iron therapy,^{46,47} and subsequent expert opinion.^{48,49}

The arguments for and against available biomarkers are summarized in Figure 2 and discussed below.

The Standard Hematology Profile Epidemiological studies indicate that the mean Hb concentration declines only a little with age. For healthy men, it is ≈ 14.5 g/dL and for healthy women ≈ 13.5 g/dL between 65 and 79 years of age.^{50,51} There is a large difference between these mean

Table 1. Definitions and Prevalence of ID for Different Cardiovascular Conditions (Serum and BM Criteria for ID Are Investigator Defined)

Study	Year	Study design	N	Women (%)	Age (years)	Prevalence of ID (%)	Definition of ID
Stable CAD							
Bozzini C et al.	2002	PC	546	26	61	15*	Ferritin <55µg/L men, <24µg/L women
ACS							
Zeller T et al.	2018	PC	836	24	63	29*	Ferritin <100µg/L or 100–299µg/L + TSATs <20%
Meroño O et al.	2017	PC	244	27	≈65	57*	Ferritin <100µg/L or TSAT <20% when ferritin <800µg/L
HFrEF							
Klip T et al.	2013	PC	1,506	26	64	50*	Ferritin <100µg/L or 100–299µg/L + TSAT <20%
Grote Beverborg et al.	2018	PC	42	24	68	40	BM: Gale scale 0–1 + ≤10% erythroblasts containing iron
Okonko DO et al.	2011	PC	157	28	71	43	TSAT <20%
Jankowska EA et al.	2010	PC	546	12	55	37*	Ferritin <100µg/L or 100–300µg/L + TSAT <20%
Tkaczyszyn M et al.	2017	PC	1,821	29	66	52*	Ferritin <100µg/L or 100–299µg/L + TSAT <20%
Sierpinski et al.	2020	PC	30	7	63	83	BM: Gale scale 0–1
HFpEF							
Bekfani T et al.	2019	PC	190	33	71	58*	Ferritin <100µg/L or 100–299µg/L + TSAT <20%
Beale A et al.	2019	MA	1,877	42–70	54–80	59*	Ferritin <100µg/L or 100–299µg/L + TSAT <20%
HFrEF or HFpEF							
Masini G et al.	2022	PC	4,422	40	75	48	Serum iron ≤13µmol/L
						46	TSAT ≤20%
						57*	Ferritin ≤100µg/L
						68*	Ferritin <100µg/L or 100–299µg/L + TSATs<20%
Moliner P et al.	2017	PC	1,821	21–39	62–70	46	TSAT <20%
						33*	Ferritin <100µg/L
						52*	Ferritin <100µg/L or 100–299µg/L + TSAT <20%
Hospitalized HF							
Jankowska EA et al.	2014	PC	165	19	65	65*	Ferritin <100µg/L or 100–299µg/L + TSAT <20%
						37	Hepcidin <14.5ng/mL+sTfR ≥1.59 mg/L
Núñez J et al.	2016	PC	626	48	73	74*	Ferritin <100µg/L or 100–299µg/L + TSAT <20%
Cohen-Solal A et al.	2014	PC	832	51	78	72*	Ferritin <100µg/L or 100–299µg/L + TSAT <20%
Cardiac surgery							
Rössler J et al.	2019	PC	730	26	68	21*	Ferritin <100µg/L
Miles LF et al.	2018	RC	266	24	64	39*	Ferritin <100µg/L or 100–300µg/L + TSATs <20%±CRP >5mg/L
Piednoir P et al.	2011	PC	100	32	67	37*	Ferritin <80µg/L or Ferritin 80–150µg/L + TSAT <20% + CRP<5 mg/L or sTfR-F index >0.7 if CRP >5 mg/L
Jankowska EA et al.	2015	PC	65	9	64	48	BM: Gale scale 0–1+≤10% erythroblasts containing iron

*Definitions including ferritin with prevalence. ACS, acute coronary syndrome; BM, bone marrow; CAD, coronary artery disease; CRP, C-reactive protein; ID, iron deficiency; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; PC, prospective cohort; MA, meta-analysis; TSATs, transferrin saturations; sTfR, soluble transferrin receptor.

population values and the WHO definition of anemia.⁶ Healthy adults with a normal Hb value rarely have other biomarkers indicating ID. Patients with ID are more likely to have abnormalities in red cell indices (e.g., low mean corpuscular volume and high red cell distribution width), which may increase the suspicion that a low Hb is due to ID.¹⁶ However, for reasons that are unclear, patients with HF may not have these classical changes and yet have evidence of ID.³⁷

Ferritin Intracellular iron is stored in ferritin, with large amounts found in the liver, spleen, and bone marrow. In the absence of inflammation, serum ferritin correlates with hepatic ferritin content.⁵² Most clinical laboratories can measure serum ferritin. The WHO defines a low serum ferritin as <15 µg/L in the absence of infection or inflam-

mation or, if either is present, <70 µg/L.⁵³ However, many clinical laboratories use a threshold of 30 µg/L.^{54–58} Values <15 µg/L and perhaps <30 µg/L are specific for ID.⁵⁹

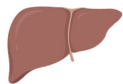
Plasma volume expansion might transiently reduce serum ferritin by a small amount.⁶⁰ Some have defined ID as a serum ferritin <100 µg/L, but values between 30 and 100 µg/L appear common in patients who have normal amounts of iron on bone marrow histology.^{17,61} Cell damage due to infection or inflammation releases ferritin into the circulation,^{23,62,63} and therefore serum ferritin may be normal or increased in the presence of ID.²³ For patients with HF, there is a weak relationship between serum ferritin and anemia.^{16,64} Reports vary about diurnal variations in serum ferritin.⁶⁵ Importantly, in patients with HF, lower serum ferritin is associated with a better prognosis, probably

Table 2. International Recommended Diagnostic Definitions and Gold-Standard BM Validation of Serum Markers of ID for Various Cardiovascular Conditions and in the General Population

	Recommended in international guideline?	Diagnostic recommendation	Evidence base for recommendation?	Assessed in BM?	Suggested tests and thresholds based on BM data
Stable CAD/ cardiac surgery	No	N/A	N/A	Yes (n=65) ³³ Age (years)=64±8 Women (%)=9%	sTfR >1.32 mg/L/ TSAT <32%
ACS	No	N/A	N/A	No	N/A
HFrEF	Yes ESC 2021 ¹²⁷	Ferritin <100 µg/L or TSAT <20% if ferritin 100–299	Yes (Table 3)	Yes (n=42) ¹⁷ Age (years)=68±10 Women (%)=24%	TSAT <20% or serum iron ≤13 µmol/L
	Yes ACC/AHA/HFSA 2022 ¹²⁸	Ferritin <100 µg/L or TSAT <20% if ferritin 100–300	Yes (Table 3)		
HFpEF	Yes ESC 2021 ¹²⁷	Ferritin <100 µg/L or TSAT <20% if ferritin 100–299	No	No	N/A
	Yes ACC/AHA/HFSA 2022 ¹²⁸	Ferritin <100 µg/L or TSAT <20% if ferritin 100–300	No		
Hospitalized HF	No	N/A	N/A	No	N/A
General population	Yes WHO ⁵⁶	Ferritin <15 µg/L	Yes ⁵⁷	Yes (n=54) ⁵⁸ Age (years)=Unknown Women (%)=Unknown	Ferritin <30 µg/L

ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; FSA, Heart Failure Society of America. Other abbreviations as in Table 1.

Possible markers of reduced intra-cellular iron

**Ferritin**Pros:

- Inexpensive
- Widely available
- Specific for ID if <15µg/L

Cons:

- Poor specificity if >30µg/L
- Increased in inflammation including:
 - Infection
 - CV disease (incl. heart failure)
 - Renal disease
- May be affected by volume status

**sTfR**Pros:

- Direct marker of cellular ID
- Not directly affected by inflammation

Cons:

- Expensive
- Limited clinical experience and validation
- Not widely available

Possible markers of reduced plasma iron availability

**Serum iron**Pros:

- Inexpensive
- Widely available
- Less affected by inflammation than ferritin

Cons:

- Diurnal variation in healthy people - less obvious with disease/ID
- Acute increase after ingestion of iron supplements in healthy people

TSATPros:

- Inexpensive
- Widely available
- Less affected by inflammation than ferritin

Cons:

- Requires measuring two indices
- May vary diurnally and be affected by volume status

Typical results of common iron biomarkers during various clinical conditions			
Condition \ Biomarker	Iron deficiency - Yes Inflammation - No	Iron deficiency - Yes Inflammation - Yes	Iron deficiency - No Inflammation - Yes
Ferritin	↓	Highly variable	↑
Serum iron	↓	↓	~↓
Transferrin	↑	↓	↓
TSAT	↓	↓	~↓
sTfR	↑	↑	Normal
Haemoglobin	↓ / Normal	↓ / Normal	↓ / Normal

(~↓) = little or no decline
(↓) = small decline

Abbreviations: Fe: iron; ID: iron deficiency; TSAT: transferrin saturation;
sTfR: soluble transferrin receptor

Figure 2. Characteristics of available serum iron biomarkers including pros and cons of each and typical findings of each during various clinical conditions (±iron deficiency, ±inflammation). Fe, iron; ID, iron deficiency; TSAT, transferrin saturation; sTfR, serum soluble transferrin receptor.

because it reflects low inflammatory activity, and not ID, in the setting of CVD.^{16,43}

Serum Iron Iron in serum is almost exclusively transferrin bound, unless transferrin saturation is >40% (e.g., in the hours and days after IV iron therapy), in which case iron is also present as non-transferrin bound iron (NTBI). Measuring serum iron is an inexpensive test and widely available. In those without CVD, there is diurnal variation of 8–15%,^{66,67} which is of little to no significance in clinical practice. Concentrations may increase transiently after oral iron ingestion.^{68,69} Low serum iron ($\leq 13 \mu\text{mol/L}$) is associated with bone marrow iron depletion.¹⁷ In contrast to ferritin, there is an inverse relationship between serum iron and markers of inflammation and infection,¹⁶ probably due to hepcidin-mediated reduction in iron absorption (leading to absolute ID) and sequestration in the reticulo-endothelial system (leading to functional ID).⁷⁰

Transferrin and Total Iron Binding Capacity (TIBC) Transferrin is secreted by liver cells, binds iron in the blood and transports it to cells.²⁵ Serum transferrin increases in response to ID, but declines in line with liver iron content, liver injury, and chronic inflammation, although it may transiently increase with infection.⁷¹ Serum ferritin and transferrin are usually inversely correlated. TIBC is the amount of iron that is required to saturate serum transferrin fully.⁷² It is a surrogate measure of transferrin. High transferrin concentrations suggest ID, although it is not considered sufficient alone to diagnose ID.

Transferrin Saturation (TSAT) TSAT is the percentage of transferrin that is bound to iron. The WHO suggests values <16% indicate ID,⁷³ although values <20% are widely used in practice. Measurement of TSAT requires measurement of both serum iron and serum transferrin or TIBC. A fall in the availability of iron is a major stimulus to the secretion of transferrin.⁵ Serum iron and TSAT are highly correlated (*r* values >0.9) in patients with chronic stable HF and probably in other clinical settings.¹⁶ The diurnal variation in TSAT shadows that of serum iron, as does the increase after consuming oral iron.⁶⁵ Lower values of both TSAT and serum iron are associated with lower Hb.¹⁶ TSAT, like serum iron, is inversely related to serum markers of inflammation,^{70,74} and therefore serum ferritin. In the presence of inflammation (often accompanied by a high ferritin), serum transferrin may be low and easily saturated by serum iron. Consequently, TSAT may be normal despite a low serum iron.⁷⁵ This may lead to ID being missed due to a falsely normal TSAT, and thus serum iron may be a better marker of ID than TSAT. Conversely, transferrin may be high when ferritin is low or normal and TSAT may be <20% even when serum iron is in the normal range.

Soluble Transferrin Receptor (sTfR) Cellular uptake of iron occurs when the transferrin receptor binds transferrin-bound iron. Intracellular ID leads to intensified expression of TfR on the cell surface to increase iron avidity. This is particularly true in developing erythrocytes, which are responsible for most of the sTfR shed into the circulation. High concentrations reflect both intracellular iron depletion and expansion of the erythroid compartment.^{15,76} sTfR may be unaffected by inflammation.^{28,77} In anemic patients with chronic non-CV inflammatory disease (e.g., rheumatoid arthritis), it discriminates between anemia due to ID and other causes of defective erythropoiesis associated with chronic disease.⁷⁸ A high ratio between sTfR and log-ferritin has also been used to indicate ID.^{23,79} More research is

required to establish values for sTfR that are diagnostic of ID in clinical practice. However, based on physiological function, a low ratio of serum iron to sTfR might be the best marker of iron deficiency.

Others Zinc protoporphyrin, reticulocyte Hb content, percentage of hypochromic red cells and hepcidin have also been used to assess ID,^{15,55,80–82} but have rarely been applied to populations with CVD.²³ The increase in Hb in response to iron supplements might also be considered as a marker of ID, although the response may be blunted in the presence of inflammation.⁶⁴

Absolute or Functional ID

ID may be absolute, in which case both serum ferritin and TSAT should be low. However, in the presence of inflammation, tumor necrosis factor (TNF)- α stimulates an increase in ferritin, which acts like a sponge, soaking up iron and rendering it unavailable for metabolic purposes (particularly for invading micro-organisms), causing functional ID.⁸³ If sufficient iron is given rapidly enough, functional ID may be overwhelmed but oral iron may fail. Treatment with agents such as sodium-glucose cotransporter 2 inhibitors (SGLT2i) may reduce the inflammatory stimulus to ferritin, releasing iron. This may partially account for the longer-term increase in Hb with SGLT2i therapy, and for some of their prognostic benefits. Serum iron or TSAT may be the best measure of ID, whether functional or absolute.

Iron Replacement Therapy

By the time someone develops anemia due to ID, the iron deficit is likely to exceed 1,000 mg.⁸⁴ Oral iron therapy is currently the first-line treatment of ID in primary care. In otherwise healthy individuals, absorption of iron can increase to 20 mg/day in the context of ID.⁸⁵ Accordingly, assuming no further loss of iron, it takes ≥ 2 months for supplements to achieve repletion.⁸⁶ Iron absorption is reduced by some foodstuffs, such as tea and coffee, by commonly prescribed medicines, such as proton-pump inhibitors and H₂ antagonists,^{20,86} and by any inflammatory disease that increases hepcidin, especially perhaps GI disease. Some studies suggest that oral iron absorption is reduced in HF, but others find increased absorption in patients with concomitant ID.⁶⁹ Up to one-third of patients have GI side effects with oral iron,⁸⁷ which may reduce adherence and therefore the success of therapy.

Intravenous iron quickly replenishes iron stores, leading to rapid correction of ID.⁸⁷ Adverse events were common with first-generation formulations of intravenous iron, attributed to the rapid release of free iron into the circulation. Modern preparations use carbohydrate-encapsulated iron that is taken up by macrophages, which gradually release the iron, avoiding large amounts of free, non-transferrin-bound iron.⁸⁸ Single doses of IV iron can be given over 15–30 min. Third-generation formulations of IV iron used in clinical trials (iron sucrose (IS), ferric carboxymaltose (FCM), iron isomaltoside (aka ferric derisomaltose (FDI)) and ferrumoxytol) are safe, with a very low risk of severe adverse reactions.⁸⁹

No instances of anaphylaxis have been reported in any large HF trial.^{90–95} There were 2 angioedema events with IV FCM in HEART-FID, although neither was deemed severe.⁹⁵ FCM may cause serum phosphate concentrations to fall,⁹⁶ with adverse consequences for bone metabolism⁹⁷

when given repeatedly to people with normal renal function (impaired renal function prevents phosphate wasting). This side-effect appears specific to FCM. It is unclear whether it is relevant to patients with HF. FDI appears to be associated with fewer hypersensitivity reactions than IS or FCM, and has a more rapid hematological response than IS.⁹⁸ There do not appear to be any other clinically important differences between formulations.^{98,99}

Chronic iron overload is toxic, augmenting oxidative stress,⁸⁶ and potentially predisposing to infection.¹⁰⁰ IV iron increases myocardial iron, in a potentially irreversible manner, which raises the potential for cumulative build-up with repeated dosing.¹⁰¹ The longer-term effect of repeated doses of IV iron on body tissues, including the myocardium, is unclear.¹⁰² Guidance in this area is lacking, particularly on what constitutes a safe maximal cumulative dose. Importantly, IV FDI is associated with a lower risk of serious infections and hospitalizations of any cause in patients with HF.^{103,104}

Iron Deficiency in Specific CV Conditions

Chronic Coronary Syndromes

Background and Prevalence Research from >20 years ago suggested that higher iron was associated with a greater risk of heart disease,⁹³ accounting for the low cardiovascular risk of premenopausal women. In contrast, recent large observational studies show that ID is associated with a higher risk of CV events and death. A meta-analysis of prospective studies and a Mendelian randomization analysis, both comprising >150,000 people, suggested that being iron replete was associated with a lower incidence of coronary artery disease (CAD),^{105,106} but another found no association between genetically determined iron status and CAD after adjusting for CV risk factors.¹⁰⁷ In a study comparing patients with (n=1,480) and without (n=682) CAD, lower Hb and iron indices were associated with the presence of CAD.¹⁰⁸

One study (n=546) reported a 15% prevalence of ID in patients with stable, angiographically proven CAD, defined as a serum ferritin <55 µg/L in men and <24 µg/L in women.³² A study comprising 65 patients with CAD reported ID in 48% using staining of bone marrow.³³ sTfR ≥1.32 mg/L was the best predictor of bone-marrow ID with TSAT (<32%) a close second, and serum ferritin having little predictive value.³³

Iron Biomarkers and Outcomes In people with type 2 diabetes (T2DM) and CAD (n=287), higher concentrations of sTfR, lower TSAT, and both low or high ferritin are associated with a higher risk of CV hospitalizations and death at 5 years.¹⁰⁹ ID may worsen the prognosis of CAD by impairing the biochemical cardioprotective response to ischemia/hypoxia, inducing negative post-ischemic cardiac remodeling. In a large population of patients with coronary or peripheral arterial disease or risk factors for heart disease, a low serum ferritin (<100 or <30 µg/L) was not associated with a greater mortality rate, but a low TSAT (<20%) was.²¹ Potential biochemical mechanisms, diagnostic challenges and the therapeutic implications of ID in patients with CAD are reviewed elsewhere.¹¹⁰

Effect of Iron Therapy No trial has assessed the effect of exogenous iron on outcomes in patients with stable CAD. A post-hoc analysis of the PIVOTAL trial comparing proactive high dose IV iron vs. reactive low-dose IV iron in patients with ID on maintenance hemodialysis found 31%

lower rate of myocardial infarction (MI) in those in the high-dose arm.¹¹¹ This finding was limited to first events. We are unaware of ongoing trials in this patient population.

Acute Coronary Syndromes (ACS)

Background and Prevalence In patients presenting with ACS, the prevalence of biomarker-defined ID ranges from 29% (n=836; ESC definition)³⁴ to 51% (n=1,156; serum iron ≤13 µmol/L).¹¹²

Cardiac magnetic resonance (CMR) imaging shows that IV iron is taken up by infiltrating macrophages within 24 h at the site of a MI (n=30, 83% ST-segment elevation MI (STEMI)).¹¹³ However, in those with intra-myocardial hemorrhage post STEMI, an increase in peri-infarction iron persists for several months,^{114,115} which correlates with adverse left ventricular (LV) remodeling¹¹⁴ and may be pro-inflammatory.¹¹⁴

Iron Biomarkers and Outcomes In a meta-analysis of prospective studies in patients not previously known to have CAD (n=156,427), there was an inverse relationship between both TSAT and serum iron and incident ACS or CAD (fatal and non-fatal) between 3 and 15 years of follow-up.¹⁰⁵ ID defined either by ESC criteria or TSAT <20%, correlated with a larger infarct area and more extensive microvascular obstruction in 125 patients with STEMI undergoing percutaneous coronary intervention.¹¹⁶ In another study of 115 patients following an ACS, serum iron ≤13 µmol/L and TSAT <20% were associated with lower LV ejection fraction but not larger infarct size, defined by extent of troponin rise.¹¹⁷ Beyond the index event, serum iron ≤13 µmol/L was associated with higher all-cause deaths (n=1,156) over 3 years.¹¹² There was a stronger relation between a combination of low serum iron (≤12.8 µmol/L) and high sTfR (≥3 mg/L) and subsequent death.¹¹²

Contrasting evidence also exists; in 237 patients undergoing intervention for STEMI, ID (TSAT <20% or ferritin <100) was associated with a lower mortality rate and less clinical HF.¹¹⁸

Effect of Iron Therapy There are no randomized trials of exogenous iron for ACS. An observational study of 39 patients reported that IV iron (ferumoxytol) given within a few days of an ACS, was associated with a smaller infarct size and a lower LV systolic volume at 3 months, assessed by CMR, compared with a matched control group.¹¹⁹

Ongoing Research One trial is currently investigating the effect of IV iron in patients with ID (n=480) after MI (ESC criteria) on LV function and recovery using CMR (NCT03991000); another trial will evaluate the effects of IV iron on QOL, morbidity, and death in ≈2,000 patients with a recent ACS and ID (TSAT <20%, or ferritin <100 µmol/L) (NCT05759078).

Chronic HF With Reduced Ejection Fraction (HFrEF)

Background and Prevalence Anemia is common (~30%) in patients with HFrEF, and associated with worse symptoms, exercise capacity, and prognosis.^{16,120,121} The reported prevalence of ID (ESC definition; n=3,327) is approximately 50%,^{35,37} and even higher if patients are anemic.^{7,35,37} The prevalence of ID on bone marrow histology may be ≈40%, but this is based on a study of many fewer patients (n=42).¹⁷

ID is also associated with fatigue, poor quality of life and exercise intolerance as well as higher mortality, even in the absence of anemia.^{7,14,35,36} Trials of erythropoietin stim-

Table 3. Completed Outcome Trials of Iron Therapy Including >200 Patients With Heart Failure and ID

	FAIR-HF	CONFIRM-HF	IRON-OUT	AFFIRM-AHF	IRONMAN	HEART-FID
Year	2009	2014	2017	2020	2022	2023
Country	10 countries in Europe and Argentina	9 European countries	USA	15 countries (international)	UK	14 countries (international)
No. of patients	459 (2:1 IV FCM vs. placebo)	301 (1:1 FCM vs. placebo)	225 (1:1 oral iron vs. placebo)	1,108 (1:1 FCM vs. placebo)	1,137 (1:1 FDI vs. SoC)	3,065 (1:1 FCM vs. placebo)
Definition of ID	Ferritin <100 µg/L or 100–299 µg/L if TSAT <20%	Ferritin <100 µg/L or 100–300 µg/L if TSAT <20%	Ferritin 15–100 µg/L or 100–299 µg/L with TSAT <20%	Ferritin <100 µg/L or 100–299 µg/L if TSAT <20%	TSAT <20% + ferritin <400 µg/L or ferritin <100 µg/L	Ferritin <100 µg/L or 100–300 µg/L if TSAT <20%
Inclusion criteria	• NYHA II & LVEF ≤40% • NYHA III & LVEF ≤45% • Hb 9.5–13.5 g/dL	• NYHA II or III • LVEF ≤45% • Hb <15 g/dL • BNP >100 pg/mL / NT-proBNP >400 pg/mL	• NYHA II–IV • LVEF ≤40% • Hb 9–13 g/dL (women); 9–15 g/dL (men)	• LVEF <50% • HF hospitalization • NT-proBNP ≥1,600 pg/mL (SR) or ≥2,400 pg/mL (AF) • ≥40 mg IV furosemide or equivalent • Hb 8–15 g/dL	• LVEF ≤45% • HF hospitalization within 6/12 or NT-proBNP >250 pg/mL (SR) or >1,000 pg/mL (AF) • Hb 9–14 g/dL	• LVEF ≤40% • Hb 9–13.5 g/dL (women); Hb 9–15 g/dL (men) • HF hospitalization within 12/12 or NT-proBNP >600 pg/mL (SR) or >1,000 pg/mL (AF)
Age (years, mean, unless otherwise stated)	67	69	63 (median)	71	73	69
Sex (women)	244 (53%)	141 (47%)	80 (36%)	494 (45%)	300 (26%)	1,037 (34%)
Form of iron therapy; dose (mean or dosage)	IV FCM; N/A	IV FCM; 1,500 mg	Oral iron polysaccharide; 150 mg BD for 16 weeks	IV FCM; 1,352 mg	IV FDI; 1,978 mg	IV FCM; 2,317 mg
Follow-up (weeks)	24	52	16	52	140	99
Primary endpoint	PGA and NYHA class at week 24	Change in 6MWT from baseline to week 24	Change in pVO ₂ from baseline to week 16	Composite of total HF hospitalization and CV death	Composite of recurrent HF hospitalization and CV death	Hierarchical composite of death within 12/12, HF hospitalization or change in 6MWT
TSAT (%)*	18±13	20±18	18 (15–22)	15±8	18.8±6	23.9±11.2
TSAT <20%	NR	NR	NR	83%	76%	~40%
Hb (g/dL)/anemia	11.9/51%	12.4/NR	12.6/NR	12.2/52%	12.1/68%	12.6/58%
Ferritin (µg/L)*	53	57	69	84	49	56
Outcome	• Improvement in PGA: OR 2.51 (1.75–3.61); P<0.001 • Improvement in NYHA (by 1 class: OR 2.40; 1.55–3.71; P<0.001)	• Increase in 6MWT distance at week 24 (33±11 m, P<0.002) • Extending out to week 52 (P<0.001)	• No significant difference in pVO₂ at 16 weeks (21 mL/min) P=0.46	• Trend to improvement: RR 0.79 (0.62–1.01); P=0.059 • Reduction in total HF hospitalizations with (RR 0.74 (0.58–0.94); P=0.013)	• No significant reduction in primary outcome: RR 0.82 (0.66–1.02); P=0.07 • Reduction in primary outcome in C-19 sensitivity analysis: RR 0.76 (0.58–1.00); P=0.047 • Fewer SACEs in FDI group vs. control (P=0.016)	• No significant improvement in win ratio for primary outcome HR 1.10 (0.99–1.23); P=0.02 - using 2-sided significance level of P=0.01

*Presented as mean (SD) or median (1st–4th quartile). If not available for whole population, results presented are those for the treatment group. 6MWT, 6-minute walk test; BD, twice daily; BNP, B-type natriuretic peptide; C-19, Covid-19; FCM, ferric carboxymaltose; Hb, hemoglobin; LVEF, left ventricular ejection fraction; NR, not reported; NYHA, New York Heart Association class; NT-proBNP, N-terminal pro-BNP; OR, odds ratio; PGA, Patient Global Assessment; pVO₂, peak volume of oxygen utilization; RR, relative risk; SACE, serious adverse cardiac event. Other abbreviations as in Table 1.

ulating agents that aimed to correct anemia showed little evidence of clinical benefit,¹²² whereas trials of IV iron have shown improvements in symptoms and well-being and reduced hospitalizations for heart failure.^{90–92}

On a cellular level, myocardial iron depletion can be present in patients with HFrEF,^{1,2,4,123} and will exacerbate mitochondrial dysfunction,^{2,124} leading to impaired muscle contractility,¹²⁴ which may contribute to the progression of the HF syndrome.¹²⁵ Correcting iron depletion can reverse both mitochondrial structural and functional defects

improving contractility in human cardiomyocytes in vitro,¹²⁴ and skeletal muscle mitochondrial energy production in vivo.¹²⁶

The European Society of Cardiology (ESC) and American College of Cardiology (ACC) define ID as a serum ferritin <100 µg/L or TSAT <20% if ferritin 100–299 (ESC) or 100–300 (ACC) µg/L.^{127,128} These criteria, originally used to define iron repletion in patients with chronic renal disease,¹²⁷ were arbitrarily applied to patients with HF to facilitate recruitment into clinical trials of IV iron therapy. They

form the inclusion criteria for several completed trials of IV iron described next.^{90,91,93} These definitions of ID have not been validated: serum iron $\leq 13 \mu\text{mol/L}$, TSAT $\leq 19.8\%$ or sTfR $\geq 1.25 \text{ mg/L}$ more accurately reflect bone marrow ID.^{17,130}

Iron Biomarkers and Outcomes In patients with HF, among potential measures of ID, serum iron and TSAT are highly correlated ($r > 0.9$) and, together with anemia, strong predictors of prognosis.^{16,43} For patients with ID, controversy exists about the importance of anemia as a marker of response. A low Hb might simply be an index of more severe ID that might show a larger response to IV iron. Alternatively, correction of anemia might be a key mediator of the response to IV iron. Anemic patients have a worse prognosis, so even if the relative benefits of IV iron are the same, the absolute benefit will be larger for those with anemia.

In contrast to low Hb, serum iron or TSAT, a low serum ferritin is generally associated with a better prognosis.^{16,17,43,131} The association between ID using the ESC/ACC definitions and prognosis is less clear.^{14,35,131} In a multivariable analysis, 1 study found that a serum sTfR $\geq 1.25 \text{ mg/L}$ was the only marker of ID that predicted all-cause death.¹³⁰

Effect of Iron Therapy

Intravenous Iron For patients with HF and ID (ESC definition), early trials showed that IV iron improved symptoms and QOL.^{90,91} Outcome trials, namely IRONMAN⁹⁴ and HEART-FID,⁹⁵ did not show that IV iron reduced recurrent hospitalizations for HF and CVD deaths. In IRONMAN, the primary endpoint was “nearly” significant (hazard ratio 0.82; 95% confidence interval: 0.66–1.02), but the study was particularly affected by the COVID-19 pandemic, which reduced recruitment and re-dosing of IV iron and resulted in fewer events than expected.⁹⁴ Many patients in HEART-FID may not have been truly iron deficient (mean TSAT 24%) and out-of-protocol dosing of IV iron in both trials may have diluted any benefit. In aggregate meta-analyses, however, IV iron does appear to reduce CVD hospitalizations, particularly those for HF.^{46,47} The benefit seems to be limited to those with lower TSAT, particularly if there is concomitant anemia,^{46,47,64} with some potential harm if TSAT $> 24\%$.⁴⁶ Uncertainty remains about the effect of IV iron on CV or all-cause death.^{46,47} Importantly, if the correct patients are treated (low TSAT; anemic), the magnitude of benefit of IV iron in terms of reducing hospitalizations and deaths may match, or even exceed, that of the benefit obtained from SGLT2i.^{102,132}

In a randomized trial of 75 patients with ID (ACC-defined) and persistently reduced LVEF ($< 45\%$) despite cardiac resynchronization device implantation (≥ 6 months), IV FCM improved LVEF and cardiac contractility compared with placebo.¹³³

Taken together, the data available do not support the continued use of the current guideline criteria to define ID, based heavily on serum ferritin $< 100 \mu\text{g/L}$. Applying this criterion, over one-third of patients do not have true ID (TSAT $< 20\%$), whereas up to 20% of patients not captured by this criterion do have ID (TSAT $< 20\%$ or serum iron $\leq 13 \mu\text{mol/L}$),⁴³ diluting any potential benefit in trials of IV iron repletion. In line with recent publications,^{48,83,134} the current criteria may be outdated and should be replaced by TSAT $< 20\%$.

Oral Iron In a study of 225 patients with HFpEF, oral

iron was not effective in replenishing iron stores or improving QOL or exercise tolerance over 16 weeks⁸² (Table 3). This result may be due to low absorption of oral iron, perhaps related to a combination of increases in hepcidin and low gastric acidity due to prescription of proton-pump inhibitors.^{20,25,28} However, many of the patients enrolled may not have had ID;⁸² the median TSAT was 19% and one-quarter of patients had TSAT $> 24\%$; the median serum iron was $13 \mu\text{mol/L}$, with one-quarter having values $\geq 16 \mu\text{mol/L}$. Oral sucrosomal iron shows promise, given its lower GI side-effect profile and alternative route of enteric absorption compared with standard oral iron therapy,¹³⁵ but as yet there are only data from a pilot study.¹³⁶

Ongoing Research Only very recently reported, the FAIR-HF2 trial of 1,105 participants with ID (ESC criteria) and LVEF $\leq 45\%$ showed a non-significant reduction in total hospitalizations for HF, or cardiovascular death or first heart failure hospitalization in patients with a TSAT $< 20\%$.¹³⁷ There was, however a reduction in CV deaths and first hospitalizations for HF in those treated with IV iron. A subsequent Bayesian meta-analysis of over 7,000 patients confirmed significantly lower rates of the composite endpoint of hospitalizations for HF and CVD (rate ratio 0.81; 95% confidence interval 0.63–0.97).¹³⁸ This was driven by reductions in both endpoints.

Chronic Heart Failure With Preserved Ejection Fraction (HFpEF)

Background and Prevalence Patients with HFpEF are typically older and more likely to be women than those with HFrEF; a substantial proportion have comorbidities such as chronic kidney disease and atrial fibrillation, which increase the likelihood of anemia and ID.^{139,140} ID is associated with poorer QOL and exercise capacity³⁸ in HFpEF.

A meta-analysis of studies in 1,877 patients with HFpEF reported a prevalence of ID (ESC/ACC-definitions) of 42–70%.¹⁰ A large cohort study showed that 41% of those without, and up to 71% of those with, anemia had a TSAT $< 20\%$.¹⁶

Many of the comorbidities common in HFpEF, such as diabetes, are associated with abnormalities of skeletal muscle function and mitochondrial metabolism.¹⁹ In 8 patients with HFpEF and ID, concentrations of cellular TfR, obtained from endomyocardial biopsies, were higher than in a control group without ID.³

Based on very limited evidence, the most recent ESC guidelines suggest that patients with HFpEF be screened for ID, adopting the definition used for those with HFrEF: ferritin $< 100 \mu\text{g/L}$ or TSAT $< 20\%$ if ferritin 100–299 $\mu\text{g/L}$.¹²⁷ Similarly, the most recent update to the 2013 ACC guidelines does not discriminate between HFrEF and HFpEF, and suggests adopting the same cutoff points as for HFrEF: ferritin $< 100 \mu\text{g/L}$ or TSAT $< 20\%$ if ferritin 100–300 $\mu\text{g/L}$.¹⁴¹

No criteria for ID based on serum biomarkers have been validated against bone marrow histology in this group of patients.

Iron Biomarkers and Outcomes There is conflicting evidence of an association between ID and higher mortality or HF hospitalization rates in patients with HFpEF.¹⁰ A meta-analysis of 4 studies comprising only 711 patients with HFpEF found no significant association between ID and death or hospitalization.¹⁰ However, analyses of large cohorts, including $> 1,000$ patients with HFpEF, found that a low serum iron and low TSAT were associated with

higher mortality rates irrespective of HF phenotype.^{16,43}

Effect of Iron Therapy In the only randomized trial in patients with HFpEF (mean LVEF 55%) and ID (ESC criteria), there was an improvement in 6-minute walk test distance with IV FCM at 24 weeks, but it did not persist at 52 weeks.¹⁴² Despite the greater prevalence ID in HFpEF than in HFrEF (as well as the fact that it is purportedly more common), trial recruitment was slow and terminated early. Only 39 out of a target of 200 patients were randomized.

Ongoing Research The IRONMET-HFpEF trial aims to assess the effect of IV FDI on exercise capacity (LVEF $\geq 50\%$) by change in peak $\dot{V}O_2$ between baseline and 12 weeks (NCT04945707).

Hospitalized HF

Background and Prevalence Among patients hospitalized for HF, the prevalence of ID using the ESC definition varies from 65% in younger patients, mostly with HFrEF,¹⁵ to 72–74% in older patients, many of whom have HFpEF.^{39,40} A study using an alternative definition (hepcidin <14.5 ng/mL and sTfR ≥ 1.59 mg/L) reported a lower prevalence of 37%.¹⁵ Iron indices, as well as Hb concentration, can be low due to plasma volume expansion in patients with severe congestion.¹⁴³ In the placebo arm of the AFFIRM-AHF trial, serum ferritin and TSAT increased by ≈ 25 ng/mL and $\approx 5\%$, respectively, within 6 weeks of discharge,⁹³ which may reflect resolution of congestion.⁶⁰

The new ESC guidelines use the same criteria for ID in both the acute and chronic setting. The ACC guidelines do not comment.^{125,126} Unsurprisingly, no definition has been validated against a bone marrow gold standard.

Iron Biomarkers and Outcomes In a study of 832 patients, low serum ferritin (<100 μ g/L) was associated with a higher risk of early readmission³⁰ following an episode of hospitalized HF.³⁹ Among the potential measures of ID, only the novel definition of a low hepcidin/high sTfR ratio predicted death in a study of 165 patients, most of whom had HFrEF.¹⁵

Effect of Iron Therapy In a study of 49 patients with ID (serum ferritin <300 μ g/L if TSAT $<20\%$), a single dose of IV FCM (1,000 mg) given prior to discharge did not improve 6-minute walk distance compared with placebo at 12 weeks.¹⁴⁴ In the AFFIRM-AHF trial ($n=1,108$, mean age 71 years, 56% men, mean LVEF 33%), patients randomized to IV FCM (mean total dose 1,352 mg) prior to discharge had 26% fewer re-admissions for HF over the following year ($P=0.013$) but with no effect on CV or all-cause deaths. The trial narrowly missed its primary endpoint, a composite of recurrent HF hospitalizations and CV death (relative risk 0.79; (0.62–1.01); $P=0.059$)⁹³ (Table 3). QOL also improved by a small amount.⁹³ IRONMAN found no difference in the effect of IV FDI on the primary outcome, or its components, in those enrolled during hospitalization vs. outpatients.¹⁴⁵

Ongoing Research We are not aware of other outcome trials of oral or IV iron in acute HF. There are 2 small trials are investigating if IV FDI improves QOL and exercise capacity in patients with LVEF $<50\%$ ($n=146$) (NCT05971732) and $\geq 50\%$ ($n=170$) (NCT05991128). Many admissions for HF ($\leq 25\%$) are caused or complicated by infection,¹⁴⁶ which may confound interpretation of serum ferritin and cause concern about the safety of IV iron (contra-indicated in acute infection); further analyses are required to identify optimal criteria for ID in this setting.

Cardiac Surgery

Background and Prevalence Cardiac surgery is accompanied by a high probability of blood loss and use of blood products.¹⁴⁷ Higher perioperative blood loss correlates with worse surgical outcomes.¹⁴⁸ Although blood transfusions can correct anemia, they are associated with worse outcomes.¹⁴⁹ ID is the leading cause of preoperative anemia.¹⁵⁰ Postoperative anemia and/or ID may prolong hospital stay and reduce the benefits of postoperative rehabilitation.¹⁵¹

The prevalence of ID (ACC definition) in 277 patients, mostly undergoing coronary artery bypass graft (CABG) surgery, was 39%.⁴¹ A similar prevalence (37%) was reported in 100 patients, mostly having valve surgery, using a novel and rather complex definition of ID (including ferritin, TSAT, CRP and/or sTfR).⁴² In a study of 65 patients, predominantly men, with CAD undergoing cardiac surgery, the prevalence of bone marrow ID was 48%.³³ Another study of 42 patients scheduled for CABG with a history of HFrEF found bone marrow ID in 40%.¹⁷ Consensus documents about the management of perioperative anemia and iron deficiency in cardiac surgery recommend varying definitions of ID. In a recently published document, the authors recommend assessing ID in all surgical candidates. They defined ID as ferritin <30 μ g/L or, in presence of inflammation (not defined by the authors), as either ferritin 30–100 μ g/L, reticulocyte Hb <25 pg or sTfR/log serum ferritin >2 .¹⁵² In an earlier document, not specific to cardiac surgery, ID was defined as ferritin <30 μ g/L or, in those with C-reactive protein >5 mg/L, as ferritin <100 μ g/L and/or TSAT $<20\%$.¹⁵³

One study of 65 patients, all of whom had CAD, found that sTfR ≥ 1.32 mg/L was the most sensitive and specific biomarker for ID on bone marrow biopsy.³³

Iron Biomarkers and Outcomes ID is associated with longer hospital stay, greater postoperative fatigue and use of more blood products perioperatively compared with no ID.^{41,42,154}

Effect of Iron Therapy The only randomized trial of IV iron prior to cardiac surgery included patients with serum ferritin <100 μ g/L ($n=252$) or anemia ($n=253$). A combination of IV iron, recombinant erythropoietin, vitamin B12 and folic acid was used. Patients were randomized within 3 days prior to elective cardiac surgery. Hb increased and red cell transfusions were reduced during the first 7 postoperative days compared with standard care.¹⁵⁵ There was no difference in mortality rates. No trial has assessed IV iron alone in patients with ID prior to cardiac surgery.

Ongoing Research Three trials investigating IV iron are currently recruiting patients undergoing elective cardiac surgery. Only 1, which is non-randomized and unblinded, is specifically assessing its preoperative use in patients with ID ($n=900$) (NCT04040023). One randomized, double-blind trial is examining its use in anemic patients preoperatively ($n=1,000$) (NCT02632760), and the other is assessing its preoperative use in patients irrespective of iron status or the presence of anemia (NCT03574311).

Other Conditions

Severe Aortic Stenosis Just over 50% of patients referred for surgery or transcatheter aortic valve implantation (TAVI) had ID (ESC definition) in 2 observational cohorts ($n=959$).^{156,157} In a study of patients assessed primarily for suitability for TAVI ($n=495$), ID was associated with a combined primary endpoint of all-cause death, unplanned

HF hospitalization or blood transfusion in the first year after TAVI.¹⁵⁷ No interventional trials using IV iron have yet been completed in this population.

Pulmonary Arterial Hypertension (PAH) In 693 patients with PAH, ID defined by serum iron $<14\mu\text{mol/L}$ and TSAT $<21\%$ ($n=430$; 62%) predicted worse symptoms and exercise capacity while definitions using ferritin did not.¹⁵⁸ TSAT $<21\%$ was independently associated with higher all-cause death at mean follow-up of 36 months. Smaller studies have also demonstrated associations between various non-ferritin-based ID definitions and higher pulmonary artery pressures, lower cardiac index,¹⁵⁹ and worse symptoms and functional capacity.^{159,160} A study of 20 patients with PAH and ID (serum iron $<10\mu\text{mol/L}$ + ferritin $<150\mu\text{g/L}$ + TSAT $<15\%$ + C-reactive protein $<25\text{mg/L}$) suggested that IV FCM improved the 6-minute walk test distance and QOL.¹⁶¹ Preclinical models suggest that iron depletion may contribute to the development of PAH.¹⁶²

Future Directions

Clinical trials and meta-analyses have shown that, for patients with HFrEF and ID defined largely by the ESC/ACC criteria, IV iron improves symptoms and reduces the risk of hospitalization for HF. Effects on mortality rates are uncertain. The COVID-19 pandemic interfered with the conduct of some trials, particularly in relation to maintaining iron repletion with repeated iron dosing. Inclusion of patients with a TSAT $>20\%$, as well as those who were not anemic, diluted the proportion of patients with ID who could possibly benefit. Indeed, patients with high TSATs might have been harmed by administration of IV iron.

We should strive for precision, or more precisely “accurate” medicine – after all, you can be consistently wrong and still be precise. There is little evidence to support the continued use of serum ferritin as a clinically useful marker of ID in patients with CVD. More data are required on the optimal timing, dose and frequency of repeat IV iron administration to determine whether full replenishment of iron leads to the best results for patients. Validating serum biomarkers against bone marrow iron stores to improve accuracy of ID diagnosis in larger populations is feasible in those undergoing cardiac surgery.

The long-term (years) impact of repeated iron infusions should be examined given the known risks of iron overload, especially in the myocardium.¹⁰¹

Further research on oral iron supplements is warranted, either to correct ID when IV iron is either not available or unaffordable, or to prevent recurrent ID after correction with IV iron. Newer preparations of oral iron may be better tolerated and absorbed (e.g., ferric maltol or sucrosomial iron). Better understanding of the effects of iron supplements on hepcidin and iron absorption may improve efficacy (e.g., alternate day dosing).

Current evidence for iron repletion for patients with CVD and ID is mainly for patients with HFrEF. There is little evidence to support iron repletion in other groups of patients with CVD. However, both CVD and ID are common in older people. Correction of ID may reduce frailty and increase resilience in frail patients.¹⁰⁴

Perhaps most importantly, there is a widespread lack of education and awareness among clinicians on the importance of ID in CVD and the benefits of treatment in appropriately selected patients.¹⁶³

Conclusions

Many older people, especially those who also have CVD, have evidence of ID, which may cause or exacerbate fatigue and breathlessness, impair QOL and exercise capacity, and is associated with a worse prognosis. For some groups of patients, there is evidence that correction of ID improves each of these problems, but many more people might benefit from iron repletion, even in the absence of overt HF. Diagnostic criteria for ID in patients with CVD should be re-evaluated, to improve both efficacy and safety in future clinical trials and in clinical practice, for those receiving IV iron. For the moment, the strongest evidence is for TSAT $<20\%$, especially for patients with anemia. Whether sTfR alone or as a ratio with serum iron adds further value is unknown. Serum ferritin is neither a useful marker of ID nor of the response to IV iron in patients with CVD.

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