Defining iron deficiency in patients with heart failure

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For patients with heart failure and reduced left ventricular ejection fraction, intravenous iron is likely to deliver clinical and prognostic benefits for those with anaemia and transferrin saturation <20%, especially if serum ferritin exceeds 100 µg/l. A serum ferritin of <100 µg/l does not appear to be useful as a marker of iron deficiency.

Three substantial randomised trials of patients with heart failure and a reduced left ventricular ejection fraction who were thought to have iron deficiency provided inconclusive evidence on whether intravenous (IV) administration of iron reduces the rates of hospitalisation for heart failure or death(1). Perhaps iron deficiency is not an important driver of outcomes in this patient population and, therefore, iron supplements are of little benefit. Perhaps there was inadequate redosing with iron in the trials because of the COVID-19 pandemic and war in Ukraine, which disrupted many research visits, leading to recurrent iron deficiency. Perhaps the trials were underpowered. Interventions achieved similar absolute reductions in morbidity and mortality in trials of IV iron and of sodium-glucose cotransporter 2 (SGLT2) inhibitors, but the latter trials included more patients (2) (Fig. 1a). Statistical significance is not a measure of the magnitude of therapeutic effect, only of the certainty that the effect exists. Perhaps the definition of iron deficiency used to select patients for these trials (serum ferritin

<100µg/l or transferrin saturation (TSAT) of <20%), which was adapted from opinion-based guidelines for end-stage kidney disease(3), was wrong. Giving more iron to people who do not have iron deficiency is unlikely to be beneficial and could be harmful.

The World Health Organization (WHO) defines iron deficiency as a serum ferritin concentration <15 µg/l, or <70 µg/l in the presence of inflammatory disease, but many clinical laboratories define it as a serum ferritin ≤30 µg/l. The WHO places less emphasis on TSAT but suggests that values of <16% indicate iron deficiency; many laboratories recommend a TSAT of <20%. In practice, TSAT is used less widely than serum ferritin to define iron deficiency[4][5][6], but serum ferritin concentration seems inferior to TSAT as a marker of iron stores or utilisation based on analysis of bone marrow biopsy samples[4]. Serum concentrations of iron or soluble transferrin receptors might be better markers of iron deficiency but have not been used to select patients for randomized trials[4].

Anaemia is highly correlated with markers of iron deficiency and is a powerful prognostic indicator for patients with cardiovascular disease[5]. However, the WHO definition of anaemia (haemoglobin concentration <12 g/dl for women and <13 g/dl for men) might be conservative and should be reconsidered,[6] given that the mean haemoglobin concentration in women and men aged >70 years is 13.6 g/dl and 14.5 g/dl, respectively[7]. Red blood cell indices are also markers of iron deficiency, but have not been reported in randomized trials[5]. An increase in haemoglobin concentration after iron administration also reflects iron deficiency, although this increase can only be observed in retrospect and is influenced by anaemia severity, continuing blood loss, disordered erythropoiesis and changes in plasma volume.

In observational studies, low serum ferritin concentrations are associated with clinical features that suggest less severe heart failure and a fairly good prognosis[5, 8]. Serum ferritin is

derived from intracellular ferritin that is secreted by healthy cells when they are iron replete, but is also released by damaged and dying cells. A serum ferritin <15 µg/l requires the presence of both iron deficiency and healthy cells. The release of ferritin from damaged and dying cells normalizes its serum concentration, which conceals iron deficiency and renders serum ferritin misleading as a test of iron deficiency, functional or absolute, for conditions such as heart or renal failure.

Transferrin transports iron in the extracellular space and the saturation of transferrin with iron (TSAT) is a useful marker of iron availability. TSAT has a U-shaped relationship with mortality, with a nadir of risk at 20–40%, whereby higher values reflect the consequences of iron overload[6]. TSAT and serum iron concentration are highly correlated. Low serum transferrin concentrations are also associated with worse outcomes but also inflate TSAT[9], which explains why serum iron concentrations are more strongly correlated to outcomes than is TSAT. Even if the adverse prognosis associated with low haemoglobin, TSAT or serum iron concentrations might not be related to iron deficiency, they do reflect heightened risk of adverse outcomes and greater therapeutic need.

Ultimately, the therapeutic response is the best guide to selecting patients who will benefit from receiving IV iron. Several measures might be considered, including changes in haemoglobin concentration, symptoms, exercise capacity, morbidity and mortality. In landmark trials of IV iron in patients with heart failure, haemoglobin concentrations increased only modestly (by ~0.6 g/dl), which was often insufficient to correct anaemia. This modest increase might be because many patients did not actually having iron deficiency or because they had disordered erythropoiesis. The presence of anaemia predicted a greater increase in haemoglobin concentrations after giving IV iron, but whether this larger increase translates into greater effects on symptoms and exercise capacity is controversial. Patients with heart failure and more profound anaemia have more severe symptoms and worse

exercise capacity than those without anaemia and, therefore, the absolute benefits of iron supplements might be larger for those with anaemia, even if the relative benefits are similar to those without anaemia.

No significant interactions between markers of iron deficiency and the relative effects of IV iron on prognosis have been reported from analyses of the randomized trials reported so far, but strong trends for differences in absolute effects have been observed[1]. Compared to patients without anaemia, those with anaemia have a worse prognosis and appear to have a greater prognostic benefit, in absolute terms, from IV iron (Fig. 1b). However, increases in haemoglobin concentration might not be a useful surrogate for the prognostic benefits of IV iron. Patients with a serum ferritin <30 µg/l, most of whom also have TSAT <20%, have a substantial increase in haemoglobin concentrations after IV iron administration, but these patients have a fairly good prognosis whether or not they receive iron (Fig. 1c). Conversely, patients with a serum ferritin >100 µg/l but TSAT <20% have a poor prognosis and a rather small increase in haemoglobin with IV iron, but show substantial prognostic benefit (Fig. 1d). The benefits of IV iron on prognosis appear confined to patients with a TSAT <20% and might be greater when TSAT is <15%, but a worrying trend to harm is observed when TSAT is ≥24% (Fig. 1d).

In summary, TSAT, but not serum ferritin concentration, is useful for predicting the effects of IV iron on morbidity and mortality. The presence of anaemia might also be a useful marker of symptomatic and absolute prognostic benefit. Serum ferritin concentration appears more useful as a marker of heart failure severity than as a marker of iron deficiency. Provided that TSAT is <20%, IV iron is probably safe regardless of serum ferritin concentration.

More research into the therapeutic use of iron in heart failure is required. Some trials have biobanks that could help to identify better markers of therapeutic response. Pragmatic

diagnostic algorithms are needed to identify causes of iron deficiency, such as bowel cancer; frail patients might not tolerate the bowel preparation required for colonoscopy. SGLT2 inhibitors appear to improve intestinal iron absorption, increase mobilization of iron from reticuloendothelial stores, increase erythropoiesis and reduce plasma volume, amplifying the increase in haemoglobin concentration after IV iron administration, which might have attendant risks and benefits[10]. Therefore, oral iron absorption capacity needs to be reappraised for patients with anaemia and TSAT <20% who are receiving SGLT2 inhibitors, although IV iron will still be required to correct large iron deficits rapidly. Finally, when iron and SGLT2 inhibitor therapies do not normalize haemoglobin concentrations, a role for erythropoietin supplementation should be reconsidered.

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Competing interests

The University of Glasgow has received funding for research from Pharmacosmos A/S and CSL Vifor, which sell intravenous iron preparations. J.G.F.C. has received honoraria for lectures and advisory board from Pharmacosmos A/S and CSL Vifor, and was a steering committee member for the IRONMAN trial.

Fig. 1. Effect of intravenous iron on clinical outcomes. Absolute changes in the composite outcome of hospitalization for heart failure or cardiovascular death in trials of intravenous iron (IV) according to anaemia severity (a), serum ferritin concentrations (b) or TSAT (c). Mild anaemia was defined as a haemoglobin 0–1 g/dl below the WHO definition of <12 g/dl for women and <13 g/dl for men. Outcomes by anaemia severity are not available for AFFIRM-AHF and HEART-FID. Patients with serum ferritin >100 µg/l were required to have TSAT <20% to be enrolled. Patients without anaemia or with a serum ferritin <30 µg/l had lower event rates than patients with anaemia or serum ferritin >100 µg/l and derived little absolute benefit from IV iron. Patients with TSAT <20% had higher event rates and received more benefit from IV iron than those with a TSAT ≥20%. Patients with TSAT ≥20% received little benefit and those with TSAT ≥24% might have had worse outcomes with IV iron. Whether patients with TSAT <15% derive more benefit from iron than those with TSAT <20% is uncertain. The reduction in events is for rate of events in IRONMAN and patients

with an event in the individual-patient-data meta-analysis (IPD 2023)[1]. The dashed line indicates the average effect observed in trials of SGLT2 inhibitor therapy for heart failure and reduced left ventricular ejection fraction. Data are from REFs.[1,2] or from references cited in these articles. NA, not available. [a]Any anaemia.

Pullquotes

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