Redefining both iron deficiency and anaemia in cardiovascular disease.

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It ain't what you don't know that gets you into trouble.

It's what you know for sure that just ain't so (Mark Twain).

There is no such uncertainty as a sure thing (Robert Burns).

Word count without quotes above 1517 and 15 references

Anaemia is common in older people, appears mainly due to iron deficiency and is associated with loss of well-being, reduced exercise capacity and increased all-cause and cardiovascular morbidity and mortality (1, 2). Whether iron deficiency is a physiological function of getting older or reflects the growing prevalence of cardiovascular and non-cardiovascular disease in an ageing population is uncertain; both might be true. The adverse prognosis associated with anaemia and iron deficiency might also reflect greater age and underlying disease rather than direct effects of anaemia or iron deficiency. However, randomised trials are required to show that correcting iron deficiency is beneficial and that it is indeed a driver of poor health and outcomes.

Randomised trials designed to correct iron deficiency, predominantly with intravenous (IV) rather than oral supplements, have been conducted for a variety of diseases, including chronic kidney disease (CKD) (3), inflammatory bowel disease (4), chronic lung disease (5) and pulmonary hypertension (6) with varying degrees of success. IV iron has become standard of care despite the scarcity of randomised placebo-controlled trials for patients with CKD or inflammatory bowel disease. The strongest evidence-base is for patients with reduced left ventricular ejection fraction (LVEF) and heart failure (HFrEF), where IV iron has improved symptoms and reduced hospitalisations for heart failure and, possibly, mortality (2, 7). Further substantial trials are underway that should confirm or refute the effects of IV iron on mortality in this population and determine whether patients with heart failure and preserved LVEF (HFpEF) also benefit (2).

However, many patients with heart failure who are thought to be iron deficient appear to gain little benefit from IV iron. This may be because the current definition of iron deficiency adopted by heart failure guidelines (serum ferritin <100 ng/mL or, if ferritin is between 100 and 299 ng/mL, transferrin saturation (TSAT) <20%) is poor (2). It is certainly radically different from

either the World Health Organisation (W.H.O.) definition (serum ferritin <15 ng/mL in the absence of inflammatory disease) or common laboratory practice (serum ferritin <30 ng/mL) (8, 9). If the definition of iron deficiency lacks specificity, then clinical trials will include many patients without iron deficiency who are unlikely to benefit from and might be harmed by IV iron. Inclusion of such patients will dilute the benefit observed in clinical trials leading, at best, to an underestimation of benefit and, at worst, a neutral outcome (8). Conversely, if the definition of iron deficiency lacks sensitivity, then, in clinical practice, many patients with iron deficiency may be denied a simple and effective treatment (8).

In this issue, Martens et al investigate, in a broad spectrum of patients with pulmonary vascular disease, the relationship between both symptom severity and exercise capacity and the presence of iron deficiency according to the current guideline-definition or according to the serum concentrations of ferritin, iron or TSAT (10). Serum iron and TSAT were highly correlated. Serum iron <14 μmol/L or TSAT <21% predicted more severe symptoms and poorer exercise capacity but serum ferritin or the current guideline-definition did not. Analysis of large cohorts of patients with heart failure and of populations with a broad range of cardiovascular disease show, paradoxically, that higher serum ferritin but lower TSAT are associated with worse outcomes (8, 11). Further analysis suggests that both relationships might be U-shaped, with a nadir of risk for serum ferritin below 30 ng/mL and for TSAT between 30% and 40% (9). Despite the divergent associations with mortality, serum ferritin and TSAT are correlated and most patients with a serum ferritin <30 ng/mL will have a TSAT <20%. Although TSAT and serum iron are highly correlated (11), low serum transferrin is also associated with a worse prognosis. Consequently, patients with both a low serum iron and low transferrin may have a normal TSAT but still have a bad prognosis and those with a normal serum iron and a high

transferrin may have a low TSAT but a good prognosis. Ultimately, serum iron might be better than TSAT as a marker of iron deficiency in patients with cardiovascular disease, although blood samples should not be taken shortly after ingesting oral iron which may cause a temporary increase in serum concentrations.

Adding further complexity is the concept of functional iron deficiency, in other words iron trapped by ferritin inside cells that is not available for other functions. A high serum ferritin is supposed to identify such patients. However, serum ferritin may just reflect increased leakage from cells damaged by inflammation and intra-cellular ferritin may actually be depleted. In the context of patients with cardiovascular disease, it might be best to abandon measuring serum ferritin altogether as it is both confusing and unhelpful.

However, rather than trying to use symptoms or prognosis to define how blood tests should be used to define iron deficiency, perhaps it is better to look at the bone marrow iron depletion. One study suggested that TSAT (AUC: 0.93) or serum iron (AUC: 0.92) might be better markers of iron deficiency than haemoglobin (AUC: 0.82), ferritin (AUC: 0.67) or soluble transferrin receptor concentration (STfR AUC: 0.68) (12). Other studies suggest that STfR may be a better predictor (13); disparities may reflect differences amongst assays and populations.

However, it is naïve to think of iron deficiency as an all or nothing phenomenon. A spectrum of severity exists. Setting strict criteria for iron deficiency is appropriate for clinical trials trying to prove that iron replacement is effective. However, if the treatment is simple, safe and affordable then, in clinical practice, it may be appropriate to relax the criteria for iron deficiency in order to benefit as many people as possible (Figure 1).

The findings of Martens et al. have important repercussions. Firstly, iron deficiency may be somewhat less common than previous estimates. Using the heart failure guidelines definition, Martens et al found that iron deficiency was present in >70% of patients but if a definition of serum iron <14 µmol/L or TSAT <21% was applied, then the prevalence of iron deficiency dropped to about 55%. Inclusion of patients believed erroneously to be iron deficient may account for the lack of benefit of a previous RCT of IV iron for pulmonary hypertension (6). Clinical trials in heart failure may also have underestimated the true effect of IV iron by including patients who did not have iron deficiency ("you can't fix what's not 'broken"; variously attributed).

Ultimately, it is the therapeutic response to iron that really matters, which can be measured in several ways; a rise in haemoglobin or an improvement in well-being or prognosis. Most patients with iron deficiency are anaemic and iron replacement will increase haemoglobin. The increase in haemoglobin could simply be a marker of success but could also be the key mediator of benefit. If the latter is true, then patients with a lower haemoglobin should obtain greater benefit in either relative or absolute terms. So far, the data are inconclusive. In the FAIR-HF and CONFIRM-HF trials, neither haemoglobin nor ferritin predicted improvement in symptoms or exercise capacity (7). An individual-patient-data meta-analysis of smaller RCTs suggested that TSAT but neither haemoglobin nor ferritin predicted the reduction in hospitalisation for heart failure (7). Two recent substantial trials showed trends for a greater benefit of IV iron on heart failure hospitalisation in patients with a low TSAT but one also found a similar trend for low serum ferritin (7). None of these trials has reported the effects of IV iron in patients sub-grouped by serum iron.

And what of oral iron? One small, short-term trial, before the advent of SGLT2i, suggested no effect (2). However, longer-term, oral iron might be effective. Perhaps patients with iron deficiency and heart failure need only one IV shot, topped-up each year with a few weeks of oral iron?

Interestingly, analysis of a large population with cardiovascular disease suggests that morbidity and mortality begin to climb when haemoglobin drops below 14 g/dL for men or 13 g/dL for women (1 g/dL above the W.H.O. definition of anaemia) (9). Almost all patients with iron deficiency might be anaemic if the threshold for defining anaemia was raised. Interestingly, iron replacement alone often does not normalise haemoglobin in patients with heart failure. The increase in haemoglobin with SGLT2 inhibitors is similar in the presence and absence of iron deficiency, suggesting that both impaired erythropoiesis and iron deficiency contribute to the anaemia of heart failure (14). SGLT2i stimulate erythropoiesis and improve iron absorption and it is unclear whether a beneficial synergy exists between SGLT2i and IV iron or whether a rapid increase in haematocrit might increase the risk of vascular events (15). Should everyone with cardiovascular disease get iron supplements unless there is evidence of iron overload (Figure 1)? Or perhaps everyone without evidence of iron overload soon after their 70th birthday? (1).

Martens et al now have the information and opportunity to conduct a large RCT to assess the effects of intervention on well-being and prognosis. Perhaps a novel approach would be valid? Treat all patients without evidence of iron overload and identify the criteria that best predict response. Showing who does and does not benefit from iron supplements are both important.

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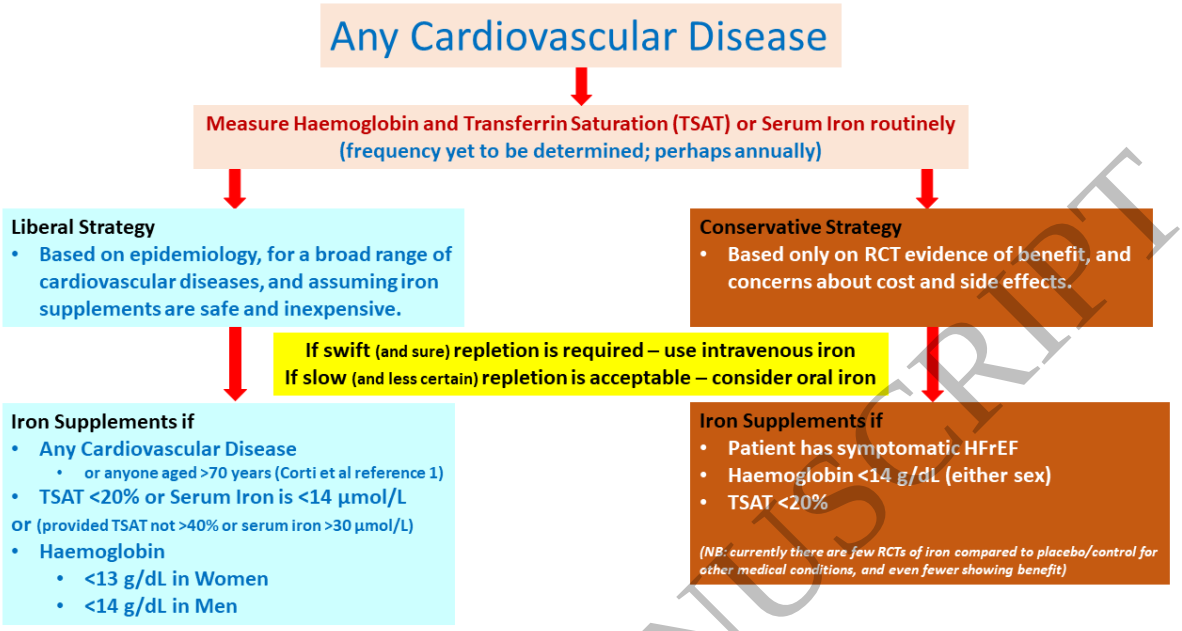

Graphical Abstract
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