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REPLY to a letter regarding the article “**Natural history and prognostic significance of iron deficiency and anaemia in ambulatory patients with chronic heart failure**”

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We thank Drs Zeng and Jiang for their interest (1). They raise an important question: how should iron deficiency (ID) be defined for patients with heart failure (HF)? Current guidelines define ID by the inclusion criteria in the FAIR-HF trial (2). These criteria were based on expert opinion when the trial was planned, more than 15 years ago and, pragmatically, balanced the need for broad inclusion criteria to facilitate recruitment but exclude patients at risk of iron overload.

Serum ferritin binds intra-cellular iron, which is otherwise highly toxic. In health, only a small fraction is shed into the blood, but this increases in response to cell-damage, for instance, severe COVID infection (3). Inflammation, albeit at much lower intensity, is part of the heart failure syndrome (4), where serum ferritin is more closely related to inflammation and ongoing cell damage than to ID (5).

Transferrin saturation (TSAT) (<20%) and serum iron ( $\leq 13 \mu\text{mol/L}$ ) are better markers of ID than the FAIR-HF criteria when compared with the gold-standard of bone-marrow biopsy (6). TSAT and serum iron are highly correlated, with lower levels strongly related to anaemia and poorer outcomes. In contrast, lower serum ferritin is associated with a lower likelihood of anaemia and better prognosis (5). In our analysis, of those with prevalent ID defined by the FAIR-HF criteria at baseline ( $n = 568$ ), 81% had a serum ferritin  $< 100 \mu\text{g/L}$ , but 42% of these patients had a serum iron  $> 13 \mu\text{mol/L}$ . When defined by the FAIR-HF criteria, we found that outcomes were similar amongst those in whom ID persisted, resolved or developed over the following year compared to those who never had ID. However, when defined by a serum iron  $\leq 13 \mu\text{mol/L}$ , persistent ID was associated with higher mortality whilst recovery of ID was associated with better survival.

The clinical ‘acid-test’ of the utility of markers of ID is whether they help predict a greater response to intervention with IV iron. An individual patient-data meta-analysis of trials of

ferric carboxymaltose (FCM) in patients with stable HF, suggested that **higher** serum ferritin but **lower** TSAT might be associated with a greater response to IV iron (7). However, AFFIRM-AHF found that both lower serum ferritin and TSAT were associated with trends to greater benefit (8). Similar analyses of ongoing trials are planned.

Novel biomarkers of ID, such as serum soluble transferrin receptor (sTfR), may identify bone marrow ID more accurately in patients with heart failure (9). Unfortunately, this test was not available for our analysis. Assay heterogeneity, lack of an accepted diagnostic threshold and high costs have restricted clinical application of sTfR.

Patients taking antiplatelets and anticoagulants, and those receiving oral iron, were not excluded from our study. However, prescriptions of antithrombotic agents at baseline were not higher in those with a serum iron  $\leq 13$   $\mu\text{mol/L}$ , nor was their use independently associated with incident ID at 1 year. Oral iron is commonly prescribed for ID, but compliance may be poor due to side effects, absorption may be low, and it might take longer than a year for oral iron supplements to correct the total iron deficit.

Further research is required to confirm or refute our proposed markers and threshold values for ID but we think it is unlikely that the FAIR-HF criteria will stand the test of time. This is an important issue, because inclusion of patients who do not have ID in trials of IV iron will dilute benefit and might increase risk. Fortunately, or unfortunately depending on your perspective, ID is very common in patients with HF and, consequently, an inaccurate definition will still be correct a lot of the time. However, the greatest benefit is likely to be found in those with the greatest iron deficit. The question may not be whether our patients with HF have ID but rather how severe it is?

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