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EDITORIAL
Heart failure and cardiomyopathies

Intravenous iron, only for those in need

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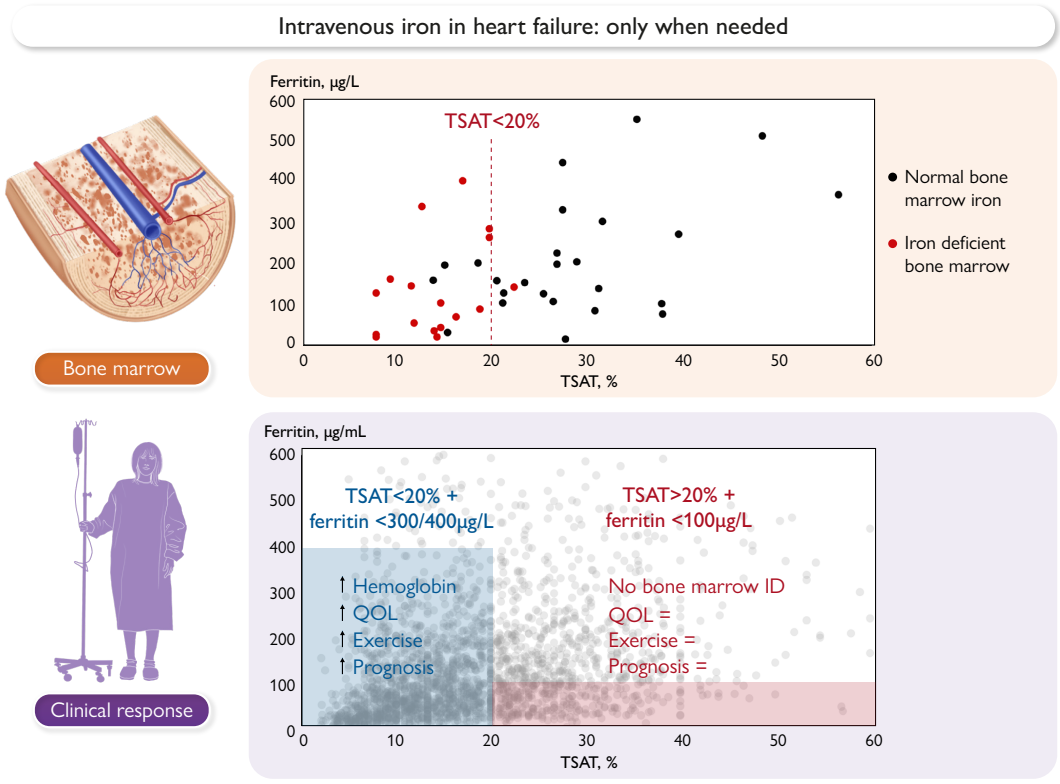
This editorial refers to 'Intravenous iron for heart failure, iron deficiency definitions, and clinical response: the IRONMAN trial', by J.G.F. Cleland *et al.*, https://doi.org/10.1093/eurheartj/ehae086.

Graphical Abstract



Iron deficiency can be defined using circulating plasma or serum parameters, bone marrow iron staining, and clinical response to intravenous iron. When we compare the two most often used circulating parameters, transferrin saturation (TSAT) and ferritin, with bone marrow iron staining and clinical response to intravenous iron, two important observations can be made. (i) Top panel: a deficiency of iron in the bone marrow is observed in patients with a transferrin saturation (TSAT) <20%, independent of ferritin; an isolated low ferritin level does not predict bone marrow iron shortage. (ii) Lower panel: patients with a TSAT <20% (and a ferritin <300/400 µg/L, depending on the specific randomized controlled trial) improve in terms of biomarkers, quality of life (QOL), exercise capacity, and prognosis when treated with intravenous iron. Those with an isolated low ferritin, however, do not shown clinical improvements.

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The landscape of heart failure management has witnessed a surge of interest in the role of intravenous iron supplementation, with the hope of alleviating symptoms, improving quality of life, and potentially altering the prognosis for a subset of patients. However, recent large randomized controlled trials (RCTs) have left clinicians in a state of puzzlement, as the outcomes fail to deliver a decisive verdict on the efficacy of intravenous iron in patients with heart failure.

All these RCTs are hampered by the same issue: the absence of solid inclusion criteria for the definition of iron deficiency rooted in robust evidence. Together with the challenges of the COVID-19 pandemic for the conduct and interpretation of the most recent, and largest, clinical trials, and the stringent cut-off value of $P < .01$ in the HEART-FID trial, this complicates the translation of these results to practical clinical guidelines.

A combination of the transferrin saturation (TSAT), ferritin, and haemoglobin has been applied, with various cut-offs, to identify patients with iron deficiency. Cleland *et al*., in their study published in this issue of the *European Heart Journal*, sought to answer the question of which of these markers best predicted a favourable response to the administration of intravenous iron.[1] For this purpose, the IRONMAN trial was used.[2] The IRONMAN trial was the second largest RCT on the topic of intravenous iron administration in patients with heart failure. Also it was the first large RCT with ferric derisomaltose, as previous RCTs utilized mostly ferric carboxymaltose.[2]

In IRONMAN, patients were included when they had a TSAT <20% or a serum ferritin <100 μg/L. Ferritin levels >400 μg/L were an exclusion criterion, as was a haemoglobin below 9 g/dL or above 14 (men) or 13 (women) g/dL. This is a slightly different definition from that of the other trials.[3–6] The AFFIRM-AHF, CONFIRM-HF, EFFECT-HF, and HEART-FID defined iron deficiency as a ferritin <100 μg/L or a combination of ferritin 100–300 μg/L with a TSAT <20%.[3–6] Essentially, IRONMAN targeted the same patient population with the addition of those with a TSAT <20% and a ferritin 300–400 μg/L.

The primary endpoint, a reduction in recurrent hospital admissions for heart failure and cardiovascular death, was narrowly missed in IRONMAN: rate ratio 0.82 [95% confidence interval (CI) 0.66–1.02], $P = .070$. However, a pre-specified COVID-19 analyses did show a significant risk reduction: rate ratio 0.76 (95% CI 0.58–1.00), $P = .047$. To define a clinical response to intravenous iron, Cleland *et al*. investigated changes in haemoglobin, Minnesota Living with Heart Failure score, and 6-min walk distance between baseline and 4 months, and clinical events including heart failure hospitalizations and cardiovascular death.

Cleland *et al*. reported a significantly larger increase in haemoglobin in those patients who at baseline had a lower haemoglobin, a lower ferritin, or a lower transferrin saturation. However, none of the pre-defined categories could predict the response in any of the other, more clinically relevant, endpoints. Previously we have shown a TSAT <20%, independent of ferritin, to be the optimal definition of iron deficiency, when compared with the gold standard (i.e. iron content of the bone marrow).[7] When the authors focused on those 841 patients, compared with the 269 patients with a TSAT ≥20% (and thus per inclusion criterion a ferritin <100 μg/L), differences were observed. In the usual care group, patients with a TSAT ≥20% had a lower rate of the primary endpoint compared with those with a TSAT <20%. In those treated with intravenous iron, patients with a TSAT ≥20% showed no prognostic benefit, while patients with a TSAT <20% showed a trend towards improved prognosis: rate ratio 0.80 (95% CI 0.63–1.03); $P = .084$ with a significant result in the COVID-19 sensitivity analysis [rate ratio 0.67 (95% CI 0.48–0.93); $P = .016$].

Although not entirely convincing on its own, this study adds to the growing body of data showing that a substantial proportion of patients included in RCTs are unlikely to have iron deficiency. Ferritin is not a reliable marker of iron status in patients with heart failure, and should not be used as such. In IRONMAN, those patients with the lowest ferritin levels (<30 μg/L) were those with the most favourable clinical profile: outpatients with a low New York Heart Association class, low N-terminal pro-brain natriuretic petide (NT-proBNP), relatively high estimated glomerular filtration rate (eGFR), and more often without the need for diuretics. This is in line with previous work of Masini *et al*. showing that in 4422 patients with heart failure (including a large proportion of patients with a preserved ejection fraction), a low ferritin (<100 or <30 μg/L) identified those patients with the best prognosis.[8] One of the first showing this phenomenon in a large group of heart failure patients were Moliner *et al*. in 2017.[9] In that study, a group of patients with 'isolated impaired iron storage' was identified. These patients, with solely a ferritin <100 μg/L, had a similar prognosis compared with patients without iron deficiency and a significantly better prognosis than those with a TSAT <20%.[9]

An explanation was provided by work of our group. We correlated bone marrow iron, the gold standard to diagnose iron deficiency, with circulating markers of iron status. By doing so, we found that ferritin did not associate with bone marrow iron status (area under the curve: 0.666).[7] Ferritin had both a low sensitivity and specificity for the detection of iron deficiency. TSAT performed significantly better (area under the curve: 0.932). The addition of ferritin to TSAT only decreased the diagnostic capacity of TSAT (area under the curve: 0.772). Furthermore, a low TSAT identified those patients with worse prognosis, while again patients with an isolated low ferritin (and by definition a normal TSAT) had the best prognosis, even comparable with those without iron deficiency.[7] Finally, in an individual patient data meta-analysis of 839 patients treated with ferric carboxymaltose vs. placebo, patients with a TSAT <20% showed a favourable response to intravenous iron in terms of cardiovascular hospitalization and mortality [rate ratio 0.45 (95% CI 0.29–0.71)], while those with a TSAT ≥20% showed no response [rate ratio 1.55 (95% CI 0.69–3.47)], P for interaction = .009.[7]

Unfortunately, this was unknown when the largest trial to date, the HEART-FID, or any of the other mentioned trials, was designed. HEART-FID included 3065 patients with heart failure and iron deficiency. Patients were primarily included in the trial based on a low ferritin, which resulted in a mean TSAT of 23.9% in the ferric carboxymaltose-treated group. Although numerical differences were observed, a non-significant difference in the win ratio of death, heart failure hospitalization, and 6-min walk distance was observed ($P = .02$, with a pre-defined cut-off of $P = .01$). Subgroup analyses showed a trend towards significant improvements for those with a TSAT <20% and a ferritin 100–300 μg/L, but the whole group of patients with a TSAT <20% (thus including those with a ferritin <100), was not analyzed.

The subgroup analyses of patients with a TSAT <20% was performed in the recent meta-analysis based on individual patient data including 4475 patients of the largest RCTs with ferric carboxymaltose (primarily HEART-FID, but also including the aforementioned AFFIRM-AHF and CONFIRM-HF).[10] In the entire population treated, the meta-analysis showed improvements in the combined endpoint of cardiovascular hospitalizations and cardiovascular death, and in hospitalizations alone (for either heart failure or cardiovascular reasons) with the use of ferric carboxymaltose. Most strikingly, subgroup analyses revealed a loss of effect of intravenous iron when looking at patients with a TSAT >20%. Similar findings, a larger benefit for those with a TSAT <20% [odds ratio 0.67 (95% CI 0.49–0.92], interaction P-value .07] were observed in a meta-analysis by Graham *et al*., excluding HEART-FID, but including many of the smaller trials.[11] Both are completely in line with the findings of Cleland *et al*. reported here.[1,11]

To summarize and simplify these data from epidemiological, observational, and interventional studies, patients historically included in the RCTs with intravenous iron can be stratified into two groups (*Graphical Abstract*). (i) Those who are unlikely to have iron deficiency (TSAT >20% and ferritin <100). Their prognosis is not worse compared with patients without iron deficiency, they do not have bone marrow iron deficiency, and they do not respond to treatment in IRONMAN or the trials using ferric carboxymaltose.[2,4–6] (ii) Those with heart failure and iron deficiency [TSAT <20% and ferritin <300 µg/L (400 µg/L for IRONMAN)]; intravenous iron therapy improved haemoglobin, quality of life, and exercise capacity,[1] and improved prognosis (in meta-analyses of 2018 and 2023[7,10,11]).

The current paper studied three baseline laboratory measurements: haemoglobin, ferritin, and TSAT, and stratified patients into a large number of groups. This strategy has its drawbacks. The intertwining nature of these variables, where anaemic patients are more likely to exhibit a TSAT <20% for instance, necessitates a meticulous examination of this interplay. Ideally, we suggest future analyses to define 'treatment response', to subsequently explore associations with a wide range of baseline variables in multivariable analyses.

In summary, while the field of iron deficiency holds promise, it has not fully met its anticipated potential. It still appears poised to significantly impact the prognosis of a substantial number of patients, yet the data are not as convincing as expected, and questions remain to be answered. The current study provides one step forward in solving the puzzle. Hopefully an individual patient data meta-analyses of all conducted trials can answer the question of whether we should treat patients with intravenous iron. And in our eyes even more importantly: which patients?

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Declarations

Disclosure of Interest

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