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EDITORIAL

Defining iron replete status in patients with heart failure treated with intravenous iron

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Background

Iron deficiency is an important therapeutic target in patients with heart failure and reduced ejection fraction (HFrEF). Over the past two decades, several trials of intravenous (IV) iron supplementation in HFrEF have shown favorable effects on symptoms, functional status, and heart failure (HF) hospitalizations.[1-4] The HEART FID (ferric carboxymaltose in heart failure with iron deficiency) trial was the largest and had the longest follow-up of IV iron trials in HFrEF.[5] Given the consistency of findings from previous trials and meta-analyses,[6-8] many thought that the results of HEART FID would be a forgone conclusion. However, the trial results were neutral, the reasons for which are not clear yet. Herein, we discuss possible explanations for the results of the HEART FID trial.

The HEART FID trial

The HEART FID trial was a large outcomes trial to confirm findings of efficacy of IV iron in patients with HFrEF.[5] The trial enrolled 3065 ambulatory patients with symptomatic HFrEF, and the primary outcome was a hierarchical composite of 12-months all-cause mortality and HF hospitalizations, and the change in 6-minute walk test (6MWT) from baseline to 6 months assessed using an unmatched win ratio approach with a pre-specified p-value of <0.0099 to be considered significantly different. The second primary endpoint (also referred to by the authors as the main secondary outcome) was the composite of cardiovascular mortality and HF hospitalizations evaluated as a time-to-event outcome assessed during the complete follow-up of the trial of about 1.9 years (interquartile range, 1.3 to 3.0 years) and considered significant with a pre-specified p<0.0399. This approach was as per agreement with the US Food and Drug Administration to obtain an indication based on one trial.

In contrast to prior evidence, the trial did not achieve a statistically significant difference in the primary endpoint between ferric carboxymaltose (FCM) and placebo, with an unmatched win ratio of 1.10 (95%CI 0.99-1.23, p=0.019). For the second primary endpoint, the outcome was neutral with a hazard ratio of 0.93 (95%CI: 0.81-1.06, p>0.2). The trial also found a very modest change in 6MWT with FCM compared to previous studies. There are several reasons that could have contributed to the results of HEART FID that are contradictory to prior studies.

Defining iron deficiency

Across most IV iron trials in HFrEF including HEART FID, iron deficiency (ID) is typically defined as serum ferritin <100 µg/L or serum ferritin 100-300 µg/L (or 100-299 µg/L) and low transferrin saturation (TSAT) levels <20% (Table 1). However, this definition has not been validated with gold standard bone marrow iron staining. Of course, how exactly such a validation can produce *valid* results in the setting of functional iron deficiency is not exactly clear. The ongoing use of the above ID criteria in trials is based on historical use in earlier IV iron in HF studies, and since these trials essentially all have shown positive results, the natural conclusion was that the ID definition criteria employed must have been reasonable.[9-16]

Use of serum ferritin in defining ID has also been debated as it can be elevated in inflammatory states like HFrEF, which could lead to underestimation of true prevalence of ID and lack of reliability in assessing response to iron repletion. TSAT <20% and serum iron <13 µmol/L have been found to correlate more consistently with ID diagnosed on the basis of bone marrow iron staining and also reliably predict mortality risk.[17] In the HEART FID trial, the mean TSAT at inclusion of the patients recruited was 24%. A contemporary analysis showed that the prognosis and prevalence of HF patients varies significantly with ID diagnosed using different criteria and noted that 1 in 4 patients with serum ferritin ≥300 µg/L had a TSAT <20% and would not be characterized as ID based on conventional criteria.[18] Other biomarkers including soluble transferrin receptors

Table 1. Study characteristics, definition of iron deficiency, iron repletion protocol, and iron withholding parameters across major intravenous iron trials.

	FAIR-HF	CONFIRM-HF	AFFIRM-AHF	IRONMAN	HEART-FID	FAIR-HF2
Study design	FCM in chronic HFrEF with ID irrespective of anemia, N=459, 2:1	FCM in chronic HFrEF with ID irrespective of anemia, N=304, 1:1	FCM in recent worsening HFrEF with ID irrespective of anemia, N=1132, 1:1	FDM in chronic stable HFrEF with ID, N=1137, 1:1	FCM in patients with chronic HFrEF with ID irrespective of anemia, N=3068, 1:1	FCM in patients with chronic HFrEF for at least 12 months, aim: N=1200, 1:1
Follow-up	24 weeks	52 weeks	52 weeks	2.7 years (IQR 1.8-3.6 years)	1.9 years (IQR 1.3-3.0 years)	Expected to be 2-3 years
Main findings	Improvement in functional capacity, symptoms, and quality of life	Improvement in 6MWT and hospitalization for HF	Reduction in composite of HF hospitalization and CV death	Reduction in composite of HF hospitalization and CV death	No significant difference in the composite outcome of all-cause mortality, HF hospitalizations, and changes in 6MWT	-
Definition of iron deficiency	Ferritin <100 µg/L or ferritin 100-299 µg/L, if TSAT<20% (and Hb 9.5-13.5 g/dL)	Ferritin <100 µg/L or ferritin 100-300 µg/L if TSAT<20% (and Hb <15 g/dL)	Ferritin <100 µg/L or ferritin 100-299 µg/L, if TSAT<20% (Hb >8 g/dL and <15 g/dL)	Ferritin <100 µg/L or TSAT<20% (and Hb men ≤14 g/dL and women ≤13 g/dL)	Ferritin <100 µg/L or ferritin 100-299 µg/L, if TSAT<20% (Hb >9 and <13.5 g/dL women, 15 g/dL men)	Ferritin <100 µg/L, or 100-299 µg/L, if TSAT<20% (and Hb 9.5-14.0 g/dL)
Iron repletion protocol	Ganzoni formula, dose given weekly until iron repletion complete, then every 4 weeks starting at 8 or 12 weeks	500-1000 mg FCM at baseline and 6 weeks as therapy doses, maintenance dose of 500 mg at weeks 12, 24, and 36 if ID still present	FCM dose at discharge and 6 weeks after, considered repletion doses. Then maintenance doses at 12 and 24 weeks to those still with ID	Iron dosed as per body weight and baseline Hb, 1st dose at randomization, follow-up at 4 weeks and then every 4 months with iron checks	1500 mg over a 7-day period initially, and repeated every 6 months if iron deficient	1000 mg initially followed by optional 500-1000 mg within the first 4 weeks (depending on weight and Hb), followed by 500 mg FCM at every 4 months
Thresholds for withholding iron	Repeated iron doses not given if serum ferritin >800 µg/L, if serum ferritin 500-800 µg/L with TSAT >50%, or if Hb >16 g/dL	Repeated iron doses not given after 6 weeks if serum ferritin >300 µg/L	Repeated iron doses not given, if Hb >15 g/dL	Repeated iron doses not given, if serum ferritin >400 µg/L or TSAT ≥25%	Repeated iron doses not given, if serum ferritin >300 µg/L or TSAT ≥20%	Repeated iron doses not given, if Hb >16 g/dL or serum ferritin >800 µg/L
Mean total dose during trial	1850 mg (SD 433) over 6 months (median 2000 mg, range 200-2400)	1500 mg in 12 months (range 500-3500), over 75% received more than 2 doses	1352 mg in 12 months (SD 568) over study period	Year 1: 1978 mg (SD 949) Year 2: 427 mg (SD 728) Year 3: 314 mg (SD 702)	Total: 2317 mg (SD 1366) Year 1: 1809 mg (SD 680) Year 2: 481 mg (SD 819) Year 3: 420 mg (SD 722)	-

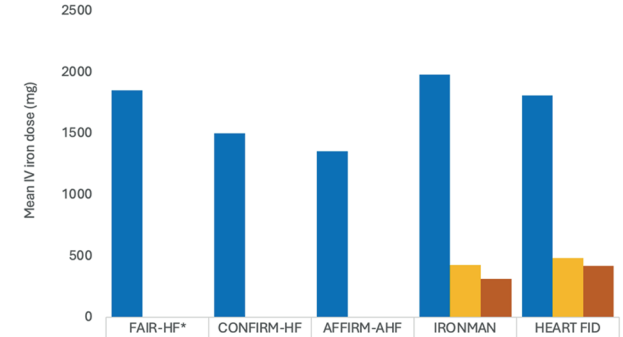
have also been identified as accurately reflecting depleted iron stores.[19] Moreover, use of sodium-glucose cotransporter-2 inhibitors in HFrEF causes a reduction in serum ferritin which reflects alleviation of a pro-inflammatory state rather than worsening ID, making serum ferritin a less reliable marker of ID to govern iron supplementation.[20-22] These issues are critical in determining the appropriate target patient population with ID that would benefit from IV iron therapy.

An updated individual participant data meta-analysis evaluating efficacy of FCM in HFrEF including the AFFIRM-AHF, CONFIRM-HF, and HEART FID trials showed that treatment with FCM to a moderate degree significantly decreased the risk of cardiovascular death and hospitalizations (relative risk 0.86; 95%CI 0.75, 0.98).[23] At one year follow-up, there was a significant interaction between baseline TSAT levels and risk of cardiovascular hospitalization and death, and cardiovascular death. There was also a significant treatment effect in the low TSAT group (<15%), whereas patients with TSAT of 24% or higher derived no benefit of IV iron therapy.

Loading and maintenance dosing

There has been marked variation in iron repletion and even more so in the IV iron therapy maintenance protocols across trials leading to large differences in inter-study cumulative and mean iron doses. The monthly therapeutic dose of FCM was highest in FAIR-HF, with a mean of 348 mg/month in the 6 months of therapy that was 50-100% higher than other subsequent trials. In the CONFIRM-HF trial, the mean dose of FCM throughout the trial (12 months) was 1500 mg, with a significant proportion of the doses administered within the first 6 months (233 mg/month over the first 6 months), followed by a mean dose of 18.5 mg/month in the following 7-12 months. In the AFFIRM-AHF, those treated with FCM received a mean dose of 1352 mg over the course of this 12-month trial, the majority of which was administered during the first 6 months (222 mg/month over the first 6 months) compared to a mean dose of only 22 mg/month from 7-2 months.[1] In the IRONMAN study, the mean monthly FDM dose was 165 mg in year 1 and only approximately 26-36 mg in years 2 and 3,[16] whereas in the HEART FID trial, the mean monthly FCM dose was approximately 150 mg in year 1 and 35-40 mg in years 2 and 3 (Table 1 and Figure 1).[5] In HEART FID dosing was performed every 6 months, but only in those patients who fulfilled the same ID criteria as were set for baseline inclusion. Consequently, at the 6-monthly visits for redosing between month 6 and 36, only 13-19% of patients were dosed at the respective time point (Table 1).

When most patients during an average follow-up period of ~2 years receive one IV iron dose and only approximately 35-40% of patients receive one additional IV iron dose during the follow-up period, the convergence of event curves towards a null difference is expected, as observed in the HEART-FID study. It may not explain the results pertaining to change in 6MWT observed in the first 6 months, which could be attributed to recruitment of a population with high TSAT levels at baseline (Figure 2). There may also be a component of IV iron exerting on-treatment effects only in patients actively receiving higher doses of IV iron, which dissipate after cessation of IV iron following perceived normalization of iron stores. These improvements in laboratory parameters may mask underlying functional ID which may lead to a worsening disease state despite receiving appropriate therapy early in the trial. The ongoing FAIR-HF2 (Ferric carboxymaltose Assessment of morbidity and mortality in patients with IRon deficiency and chronic Heart Failure) trial is a cardiovascular outcomes trial evaluating the effect of FCM in patients with HFrEF in reducing HF hospitalizations and cardiovascular death.[24] The trial has employed a novel approach to iron repletion, in comparison to a much more stringent protocol employed in the HEART-FID trial, comprising of a fixed dose of 500-2000 mg at enrolment



*In FAIR-HF, intravenous iron was dosed over 6 months, and hence 0-12 months actually denotes the cumulative dose over 0-6 months.

Figure 1. Mean intravenous iron doses across different time intervals in major trials in heart failure.

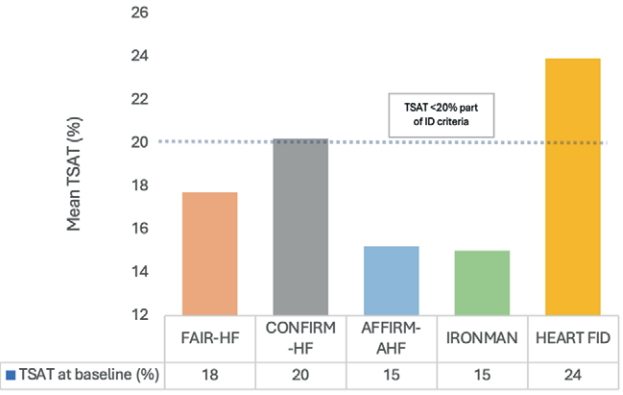


Figure 2. Mean transferrin saturation (TSAT) in the treatment arm of intravenous iron trials in heart failure. The dotted line indicates the upper limit of TSAT used as part of criteria to diagnose iron deficiency.

(as per FCM label, expected median 1500 mg) followed by administration of 500 mg every 4 months throughout the trial with iron store repletion not being a criterion for treatment cessation; instead, the only criterion for discontinuation of IV iron is a concern for iron overload (hemoglobin >16g/dL or ferritin >800 µg/L) as a safety precaution.[25] This protocol should equate to a mean monthly dose of 165-200 mg for year 1, and 100-120 mg for year 2, representing a higher cumulative dose compared to prior trials. This strategy has been employed in iron repletion trials to assess for efficacy in patients undergoing hemodialysis,[26] but such an approach is yet to be tested in trials in HF.

Future directions

The HEART FID study has raised questions regarding the utility of iron replacement therapy in HFrEF and failed to show comparable results vis a vis prior trial. The neutral results and the lack of long-term iron replacement raises significant concerns about how IV iron should be best utilized in the long run. HEART FID has mainly concluded that the same criteria cannot be used for both diagnosing ID and assessing iron repletion as it leads to too few patients receiving IV iron. It will be most interesting to the field now to follow the results of the ongoing FAIR-HF2 trial with regards to event-related outcomes, as it employs a more inclusive liberal approach towards iron replacement. Until then, it is important to recognize the highest form of wisdom applies to the field of IV iron therapy *i.e.,* we acknowledge that the treatment benefits of short-term therapy (up to 1-year duration) seem clear and endorsed by the recent European Society of Cardiology guidelines. Beyond 1 year, however, further clarity is needed.

Conflict of interest

KMT has nothing to disclose.

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