The Treatment of Iron Deficiency in Heart Failure: Options, Guideline Recommendations, and Recent Developments

THE SCOPE OF THE PROBLEM

For patients with heart failure (HF), iron deficiency (ID) is an independent predictor of outcomes and a major contributor to decreased exercise intolerance and quality of life regardless of the presence or absence of anemia.[1] ID is common in patients with HF, with an estimated prevalence up to 50% in chronic heart failure patients, and an even higher prevalence (up to 80%) in patients with acute heart failure.[2] Yet the condition remains not only underdiagnosed, but also undertreated in this setting.[3]

There is considerable interest in iron deficiency as an emerging therapeutic target after positive results from several clinical trials investigating intravenous iron treatment in HF patients. These trials, including the latest results from the AFFIRM-AHF trial, have shown statistically significant beneficial effects of intravenous ferric carboxymaltose versus placebo or standard of care, on symptoms, functional capacity, oxygen consumption, quality of life, and HF hospitalizations.[4-9] Because of this evidence, HF treatment guidelines have recognized the importance of addressing ID, and have made specific recommendations to do so.[10,11] Furthermore, ongoing studies are evaluating the effects of ferric carboxymaltose on morbidity and mortality outcomes across the HF spectrum.[12]

However, despite the evidence, awareness about iron deficiency in HF remains low, even among cardiologists. During a symposium on this topic at the 2020 American Heart Association (AHA) scientific sessions, 58% of participants indicated that they treat ID in HF patients, but 35% of them do so with oral iron, which has been shown to not be effective in HF patients and not currently recommended in the guidelines.[4,13]

THE EARLY EVIDENCE FOR INTRAVENOUS IRON REPLETION IN HEART FAILURE

Several formulations of supplemental intravenous iron are approved for therapeutic use, albeit for patients with chronic kidney disease, including ferric carboxymaltose, iron sucrose, iron isomaltoside (not available in the US), sodium ferric gluconate, ferumoxytol, and iron dextran.[1,4,12] Of these, only ferric carboxymaltose (FCM) and iron sucrose have been evaluated in patients with HF, with FCM being the most studied agent.[4,12]

The FAIR-HF, CONFIRM-HF and EFFECT-HF trials showed statistically significantly beneficial effects of intravenous ferric carboxymaltose versus placebo or standard of care, on symptoms, functional capacity and oxygen consumption, respectively.[5,6,8] Intravenous ferric carboxymaltose has been shown to improve self-reported patient global assessment, quality of life and NYHA class (over 6 months) in the FAIR-HF trial both in anemic and non-anemic patients with HF, and in the CONFIRM-HF trial, exercise capacity improved over 24 weeks.[5,6] In the analysis of secondary endpoints in the CONFIRM-HF trial, intravenous iron reduced the risk of HF hospitalizations in iron-deficient patients with HFrEF (Ponikowski 2014).[6]

The EFFECT-HF study evaluated 172 patients with HF and ID and also reported an improvement in peak VO_2 with ferric carboxymaltose compared to placebo irrespective of the presence of baseline anemia.[8] In addition, ferric carboxymaltose improved NYHA class global assessment at 12- and 24-weeks post-treatment.[8]

THE INADEQUACY OF ORAL IRON IN HEART FAILURE

The same efficacy, however, has not been observed in trials with oral iron supplements. Of the trials that have been completed in patients with heart failure the results have been mixed. A retrospective study showed that oral iron supplementation over 180 days resulted in an increase in ferritin, TSAT, serum iron, and hemoglobin concentration in iron deficient HFrEF patients; however, after 5 months of therapy, the level of ferritin was still far below the threshold for an absolute ID in HF.[14] In another trial, the use of oral iron did not demonstrate improvements in several outcomes, including NYHA status, measured by exercise endurance, oxygen use during exercise, renal function and plasma B-type natriuretic peptide levels, and the need for hospitalization.[15] Finally, the IRON-OUT trial studied oral iron replacement in anemic patients with HFrEF and results demonstrated no improvement in peak VO_2, 6-min walking distance, oxygen kinetics, ventilatory efficiency, and health-related quality of life (HRQoL) score, and very little effect in replacing iron stores.[16] Reasons for the lack of response to oral iron in HF patients are not entirely clear, and oral iron only led to modest iron repletion despite very large doses administered compared to intravenous iron trials.[17] Additionally, oral iron is not absorbed well, particularly in HF patients and is associated with GI side effects, which limit patient adherence.[17]

NEWER EVIDENCE WITH INTRAVENOUS IRON IN HEART FAILURE AND GUIDELINE RECOMMENDATIONS

The recently-concluded AFFIRM-AHF trial, which evaluated the efficacy and safety of i.v. FCM on outcomes in patients with acute heart failure and iron deficiency, showed that treatment with i.v. FCM was safe and reduced the risk of HF hospitalizations, with no apparent effect on the risk of cardiovascular (CV) death in this patient population.[7] Despite the neutral effects on CV death, the trial was the first to show that treating ID can have benefits on major HF outcomes, given the significant impacts of HF hospitalizations on patients, clinicians, and health systems.[7] Additionally, recently-published subanalyses of this study have shown that FCM treatment significantly improved quality of life and is cost-effective.[2,9]

Summarizing the evidence to date, a recent meta-analysis of i.v. iron repletion trials in HF showed that i.v. iron reduces the risk of heart failure hospitalization (HHF) or cardiovascular mortality, with these outcomes being primarily driven from a reduction in HHF.[18]

Based on the earlier trials with i.v. iron repletion, current guidelines recommend considering i.v. iron in symptomatic HF patients with ID to improve HF symptoms, as well as exercise capacity and quality of life (Table 1).[10,11] However, given the recent evidence, it is possible that a stronger recommendation might be given for i.v. iron in HF patients with ID when HF guidelines are updated in the near future.

Professional Society	Recommendations for Iron Repletion in HF
ESC Heart Failure Guidelines[10]	Stage C HF With Reduced Ejection Fraction (HFrEF): Class IIb recommendation (Level of Evidence: B-R) for intravenous iron replacement in patients with New York Heart Association (NYHA) class II and III HF and iron deficiency (ferritin <100 ng/ml or 100-300 ng/ml if transferrin saturation <20%), to improve functional status and QoL
ACC/AHA/HFSA Heart Failure Guidelines[11]	Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms and improve exercise capacity and quality of life.

Table 1. Current guideline recommendations for iron repletion therapy in ID patients with HF.[10,11]

ONGOING STUDIES

Given that AFFIRM-AHF demonstrated for the first time that thinking of ID as a therapeutic target in HF can lead to improved outcomes, there is a need for additional evidence from large-scale trials that add to this evidence. Several such trials are ongoing (Table 2), and will look at the efficacy and safety of FCM in ID patients across the HF spectrum, including those with heart failure with preserved ejection fraction (HFpEF).

Study	Inclusion Criteria	Iron	Outcome
Intravenous Iron in Patients With Systolic Heart Failure and Iron Deficiency to Improve Morbidity & Mortality. FAIR-HF2, NCT03036462 (n=1200)[19]	HF, confirmed iron deficiency, Hb 9.5-14.0 g/dL	FCM (1,000 mg, then 500- 1,000 mg within 4 weeks [max 2,000 mg total], then 500 mg every 4 months	HF hospitalizations and CV death (composite endpoint)
A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Injectafer® (Ferric Carboxymaltose) as Treatment for Heart Failure With Iron Deficiency. HEART-FID, NCT03037931 (n=3014)[20]	NYHA II-IV, LVEF ≤35% or LVEF ≤25% in prior 2 years, Hb >9.0 g/dL and <13.5 g/dL (F) or <15.0 g/dL (M), ferritin <100 µg/L or 100 - 299 µg/L with TSAT <20%, either HFH within 12 months or elevated NP	FCM (2 doses of 15 mg/kg to a max. individual dose of 750 mg 7 days apart and a maxi combined dose of 1,500 mg, repeated every 6 months) vs placebo	Death and HFH at 1 year, and change in 6MWD at 6 months
Effectiveness of Intravenous Iron Treatment vs Standard Care in Patients With Heart Failure and Iron Deficiency: a Randomized, Open-label Multicenter Trial. IRONMAN, NCT02642562 (n=1299)[21]	NYHA II-IV, LVEF <45%, Hb ≥9.0 g/dL and ≤13.0 g/dL (F) or ≤14.0 g/dL (M), ferritin <100 µg/L and/or TSAT <20% (with ferritin ≤400 µg/L), either HFH in 6 months or elevated NP	Iron isomaltoside (doses based on weight and Hb) vs "usual care"	CV mortality or HFH
Effect of IV Iron (Ferric Carboxymaltose) on Exercise Tolerance, Symptoms and Quality of Life in Patients With HFpEF and Iron Deficiency With and Without Anemia. FAIR-HFpEF, NCT03074591 (n=200)[22]	HF with preserved LVEF (HFpEF) and diastolic dysfunction, LVEF ≥45%, NYHA II-III, either HFH within 1 year or elevated NP, Hb >9.0 g/dL and ≤14.0 g/dL, ferritin <100 µg/L or ferritin 100-299 with TSAT <20%, 6MWD <450 m	FCM vs placebo	Exercise capacity: change in 6MWD from baseline to 12 months

Table 2. Ongoing iron repletion trials in HF patients with ID FCM: ferric carboxymaltose; HFH: heart failure hospitalization; 6MWD: 6-minute walking distance

The results of the other ongoing trials will provide information on the efficacy of iron repletion therapy in improving hard outcomes in HF, such as cardiovascular mortality or HF hospitalizations, as well as further inform about the safety of long-term iron repletion therapy in this setting .[4] Results are expected within the next 1-3 years.[19-22]

CONCLUSION

Iron deficiency with or without anemia is a common and important comorbidity in patients with HF, and it can have significant impacts on morbidity and mortality. Despite this burden, the diagnosis and assessment of ID is not widely sought by clinicians that see patients with HF, leading to underdiagnosis, misdiagnosis, and delayed treatment. These gaps become more apparent considering that we now have real means to improve HF symptoms, quality of life, and prevent HF hospitalizations in ID patients with HF by considering i.v. iron repletion and ID as a treatment target. Additionally, ongoing trials that are evaluating the role of this approach on hard outcomes across the HF spectrum may add to this evidence, which can help address the current clinical inertia.

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