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 (QoL) regardless of the presence or absence of anemia.[1] ID is common in patients with HF, with an estimated prevalence of more than 50% in chronic HF patients, and an even higher prevalence (up to 80%) in patients with acute HF.[2] Yet the condition remains not only underdiagnosed, but also undertreated in this setting.[3] There is considerable interest in ID as an emerging therapeutic target after positive results from several clinical trials investigating intravenous (IV) iron treatment in HF patients. These trials, including the latest results from the AFFIRM-AHF trial, have shown statistically significant beneficial effects of IV ferric carboxymaltose (FCM) versus placebo or standard of care, on symptoms, functional capacity, oxygen consumption, QoL 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 FCM on morbidity and mortality outcomes across the HF spectrum.[12] However, despite the evidence, awareness about ID 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 be ineffective in HF patients and not recommended in current guidelines.[4,13]

THE EARLY EVIDENCE FOR INTRAVENOUS IRON REPLETION IN HEART FAILURE

Several formulations of supplemental IV iron are approved for therapeutic use, albeit for patients with chronic kidney disease, including FCM, iron sucrose, iron isomaltoside, sodium ferric gluconate, ferumoxytol, and iron dextran.[1,4,12] Of these, only FCM, iron sucrose, and iron isomaltoside 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 IV FCM versus placebo or standard of care, on symptoms, functional capacity and oxygen consumption, respectively.[5,6,8] IV FCM has been shown to improve self-reported patient global assessment, QoL 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, IV iron reduced the risk of HF hospitalizations in iron-deficient patients with HFrEF.[6] The EFFECT-HF study evaluated 172 patients with HF and ID and also reported an improvement in peak VO2 with FCM compared to placebo irrespective of the presence of baseline anemia.[8] In addition, FCM was associated with 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 HF 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 VO2, 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 IV 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 AFFIRM-AHF randomized controlled trial, which evaluated the efficacy and safety of IV FCM on outcomes in patients with acute HF and ID, showed that treatment with IV 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] A recent AFFIRM-AHF subgroup analysis examined the relationship between hemoglobin levels and FCM treatment effects, and found that the effects of FCM on patient outcomes in AFFIRM-AHF were independent of hemoglobin level.[18] Additional sub-analyses of this study have shown that FCM treatment significantly improved QoL and is cost-effective.[2,9] A meta-analysis of IV iron repletion trials in HF conducted prior to 2020, including AFFIRM-AHF, FAIR-HF, CONFIRM-HF and EFFECT-HF, showed that IV iron reduces the risk of hospitalization for heart failure (HHF) or CV mortality, with these outcomes being primarily driven from a reduction in HHF.[19]

The latest published clinical trials of IV iron in HF patients are IRONMAN, and the HEART-FID study.[20,21] The UK-based IRONMAN trial randomly assigned iron-deficient HF patients to receive ferric derisomaltose (also known as iron isomaltoside) or usual care. Unlike AFFIRM-AHF, patients were primarily ambulatory without recent HF admissions. Similar to AFFIRM, the primary endpoint in IRONMAN, total HHF and CV death, was not met. However, after a COVID-19 sensitivity analysis censoring follow-up after the first UK lockdown, the rate of the primary endpoint was found to be lower in the IV iron group and statistically significant.[20] In the latest published trial evaluating IV iron replacement in HF, HEART-FID, 3065 patients were randomly assigned to receive FCM or placebo. This large trial enrolled 3 times the number of patients of IRONMAN, and similarly did not meet its primary outcome of 12-month all-cause mortality, 12-month HHF, and change in 6-minute walk distance (6MWD).[21] A more stringent 99% confidence interval was used, hence the P value of 0.02 did not meet statistical significance but may suggest a treatment effect that was not confirmed in this study. Of note, the HEART-FID patient population was low-risk in comparison to that of AFFIRM-AHF and IRONMAN, with a much lower rate of deaths and hospitalizations for HF. Also, some patients in HEART-FID may have lacked true ID, as the mean baseline TSAT was 23.9%, in comparison to approximately 15.2% in AFFIRM-AHF.[7,20-21] While the results of HEART-FID alone do not show a clear outcomes benefit, when combined with those of CONFIRM and AFFIRM-AHF in a recent meta-analysis, a clearer picture has begun to emerge. The meta-analysis pooling participant data from these trials included a total of 4,501 patients with HFrEF or HFmrEF who were followed for at least 52 weeks. Therapy with FCM significantly reduced the co-primary composite endpoint of total CV hospitalizations or CV death. A trend toward reduction of the other primary outcome, total HHF or CV death, was noted, but statistical significance was not reached with this outcome. Patients in the lowest TSAT tertile (<15%) were found to benefit most from FCM with regards to total CV hospitalizations or CV death. Treatment effects were found to be likely a result of lower hospitalizations, rather than improved survival. Study authors commented that HF patients would benefit from continued research on specific populations likely to benefit most from IV iron, as well as improved criteria for initial and repeat dosing.[22]

Based on clinical trial results, multiple guidelines recommend considering IV iron in symptomatic HF patients with ID regardless of anemia status (Table 1).[10,11] The European Society of Cardiology (ESC) recently issued an update to its 2021 recommendation in a 2023 focused guideline update, in which IV iron now has a stronger, class I (previously class IIa) recommendation for use in HFrEF and HFmrEF patients for the purposes of symptom alleviation and improved QoL. Additionally, the level of evidence for the use of IV iron for hospitalization reduction was changed from level B to A to reflect the greater quality of evidence now available.[10] Some differences between current guidelines exist, as shown in Table 1. Following these guideline updates, the FDA recently granted the first HF indication for IV iron to FCM in order to improve exercise capacity.[23] FCM is the most extensively studied form of IV iron.

Table 1. Current guideline recommendations for iron repletion therapy in ID patients with HF

Professional Society	Treatment Recommendations for Iron Repletion in HF
2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[10]	• Intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to alleviate HF symptoms and improve quality of life (Class I, Level A evidence) • Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to reduce the risk of HF hospitalization (Class IIa, Level A evidence)
2022 ACC/ AHA/HFSA Heart Failure Guidelines[11]	• In patients with HFrEF and iron deficiency with or without anemia, IV iron replacement is reasonable to improve functional status and QOL (Class 2a, level B-R evidence) • In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality (Class 3: harm, level B-R evidence)

In a recently released Scientific Statement from the Heart Failure Society of America (HFSA) on ID in HF, statement authors highlighted recent guideline updates and emphasized the importance of effective, coordinated strategies within health systems for ID screening and management, including dosing and administration of IV iron.[24]

Strategic care coordination in HF management may result in not only improved outcomes, but an improved patient experience and QoL. In line with the growing focus on patient experience and patient-centered care, an increasing research focus is being placed on QoL and patient-reported outcomes in HF. In a recently published analysis of the AFFIRM-AHF population, the impact of IV FCM on HRQoL was evaluated using the 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12). The questionnaire was administered prior to randomization and at multiple intervals throughout the 52-week study duration. Patients who had received treatment with IV FCM were found to have improved HRQoL in comparison to the placebo group. Benefits were seen as early as 4 weeks post-FCM treatment, and lasted up to week 24.[25] In a prospective, observational study of 152 adults receiving IV FCM during the course of routine clinical care, PROMIS (Patient-Reported Outcomes Measurement Information System) was used to evaluate patients prior to FCM treatment and after 3 and 6 months. Patients reported substantial improvements in fatigue, physical function, and global health at 3 and 6 months after FCM treatment.[26]

ONGOING STUDIES

Several clinical trials are ongoing (Table 2) and will continue to look at the efficacy and safety of IV iron in ID patients across the HF spectrum, including those with HF with preserved ejection fraction (HFpEF). Results are expected within the next 1-2 years.[27-31]

Study	Inclusion	Iron	Outcome
Intravenous Iron in Patients With Systolic Heart Failure and Iron Deficiency to Improve Morbidity & Mortality. FAIR-HF2, NCT03036462 (n=1200)[27]	HF, confirmed iron deficiency, Hgb 9.5-14.0 g/dL	FCM (1000 mg, then 500-1000 mg within 4 weeks [max 2000 mg total], then 500 mg every 4 months	HHF and CV death (composite endpoint)
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)[28]	HFpEF, LVEF ≥45%, NYHA II-III, HHF within 1 year or elevated NP, Hgb >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
Impact of Intravenous Iron Repletion on Mechanisms of Exercise Intolerance in HFpEF. IRONMET-HFpEF, NCT04945707 (n=66)[29]	NYHAII-IV; EF 50%; NT-proBNP >125 ng/L or PCWP>15 mmHg(rest) or PCWP/CO2 (exercise) or HF hospitalization within 12 months; Hgb 9-15 g/dL (males); Hgb 9.0-13.5 g/dL (females); pVO2 75% predicted	Ferric derisomaltose 1000 mg vs placebo	Change in peak oxygen uptake pVO2 from baseline to week 12 in HFpEF subjects with functional iron deficiency
The Prevalence of Iron Deficiency and the Effectiveness of Ferinject® in Patients With HFpEF. ID-HFpEF NCT05793996, (n=100)[30]	NYHA II-IV; EF 50%; ID (ferritin <100 µg/L, or <300 µg/L when TSAT <20%; Hgb at the time of switching on (90-150 g/L)	FCM vs. diet therapy without drug therapy vs. no intervention	Change of 5 or more points on the KCCQ (0-100 points) + change in 6MWD - 150 meters or more) by 35 m or more
The Effects of Ferric Derisomaltose in Patients With Acute Heart Failure and Iron Deficiency on Exercise Capacity and Quality of Life. COREVIVE-HFrEF NCT05971732, (n=146)[31]	Patients with HFrEF (EF 50%); currently hospitalized for an episode of acute HF, NYHA II-IV; with ID (ferritin <100 ng/mL or ferritin 100-299 ng/mL and TSAT <20%)	FCM vs. placebo	Difference of 6-minute walking distance in meters from baseline to day 3 after IV iron injection
Effect of INtravenous FERRic Carboxymaltose Onmortality and Cardiovascular Morbidity, and Quality of Life in Iron Deficient Patients With Recent Myocardial infarction. INFERRCT NCT05759078, (n=2000)[32]	Patients with HFrEF (EF 50%); diagnosis of acute MI (STEMI or NSTEMI) up to 4 weeks before randomization; and with iron deficiency (TSAT<20% and/or serum ferritin <100 ng/mL)	FCM vs. placebo	Time to CV death; number of HF events; time to first HF event; change in quality of life
Investigator-initiated, Randomized, Double-blind, Controlled, Multi-center Trial of Intravenous Iron in Patients With Cardiovascular Disease and Concomitant Iron Deficiency. iCHF2, NCT03991000 (n=480)[33]	Cohort A: Acute MI within 10 days, without prior HF, Cohort B: Paroxysmal or persistent atrial fibrillation, Cohort C: HF, LVEF ≤ 45 %, all NYHA; ferritin < 100 ng/mL or ferritin 100-299 ng/mL with TSAT < 20 %, Hgb ≤ 15.5 g/dL	FCM vs. placebo	Functional status
Iron Intravenous Therapy in Reducing the Burden of Severe Arrhythmias in Heart Failure With Reduced Ejection Fraction. RESAFE, NCT04974021 (n=106)[34]	HFrEF (LVEF≤40%), implanted cardiac electronic device with 3 months of recorded arrhythmic history, scheduled to receive IV FCM to treat diagnosed ID	FCM	Arrhythmic burden, HHF

ABBREVIATIONS: *6MWD, 6-minute walking distance; CV, cardiovascular; FCM, ferric carboxymaltose; Hgb, hemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; ID, iron deficiency; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; (N)STEMI, (non) ST elevation myocardial infarction; NYHA, New York Heart Association; NT-proBNP, pro B-type natriuretic peptide; PCWP, pulmonary capillary wedge pressure; pVO2, maximal oxygen consumption; TSAT, transferrin saturation.*

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CONCLUSION

Iron deficiency with or without anemia is a common and important comorbidity in patients with HF and 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 when considering that by treating ID, we now have substantial means to improve HF symptoms and QoL, as well as prevent HF hospitalizations in ID patients with HF. Furthermore, ongoing trials evaluating the role of this approach on additional outcomes across the HF spectrum may add to this evidence, which can help address the current clinical inertia.

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