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Lessons from trials

# Benefits of intravenous iron supplementation in heart failure

Susy Kotit

## ABSTRACT

**Introduction:** Iron deficiency (ID) is one of the most frequent comorbidities in patients with heart failure (HF) and is estimated to be present in up to 80% of acute patients regardless of their ejection fraction. Randomized controlled trials have shown that supplementary intravenous iron results in improved clinical outcomes; however, the current understanding of the effects of intravenous iron on morbidity and mortality remains limited.

**Study and results:** The meta-analysis pooled individual participant data from three randomized placebo-controlled trials of ferric carboxymaltose (FCM) in adult patients ( $n = 4,501$ ) with heart failure and iron deficiency (CONFIRM-HF, AFFIRM-AHF, and HEART-FID). FCM therapy significantly reduced the co-primary composite endpoint of total cardiovascular hospitalizations and cardiovascular death, with a rate ratio (RR 0.86; 95% CI 0.75 to 0.98;  $p = 0.029$ ). FCM therapy was associated with a 17% relative rate reduction in total cardiovascular hospitalizations (RR 0.83; 95% CI 0.73 to 0.96;  $p = 0.009$ ) and a 16% relative rate reduction in total heart failure hospitalizations (RR 0.84; 95% CI 0.71 to 0.98;  $p = 0.025$ ).

**Lessons learned:** The meta-analysis shows that in iron-deficient patients with heart failure and reduced or mildly reduced left ventricular ejection fraction, intravenous ferric carboxymaltose (FCM) is associated with a reduced risk of total cardiovascular hospitalization and cardiovascular mortality. These findings indicate that intravenous FCM should be considered in iron-deficient patients with heart failure and reduced or mildly reduced ejection fractions.

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## INTRODUCTION

Iron deficiency (ID) is one of the most frequent comorbidities in patients with heart failure (HF)<sup>1-6</sup> and is estimated to be present in up to 80% of patients<sup>2,4,7-21</sup>, regardless of their ejection fraction<sup>6,11</sup>, and is a strong independent predictor of HF outcomes<sup>2,4,22-25</sup>.

In patients with HF, ID is associated with reduced quality of life<sup>1-6,22</sup>, exercise capacity<sup>1-6</sup>, peak  $\text{VO}_2$ <sup>24</sup>, and survival<sup>6</sup>, and an increased risk of hospitalization<sup>6</sup>, independent of demographics and clinical variables, including anaemia<sup>2,4,23-26</sup>.

Iron is the most important essential trace element in the body, as it maintains the oxygen-carrying capacity of the blood through erythropoiesis and is independently crucial for oxygen uptake, transport, storage, and metabolism, as well as cellular immune responses<sup>27,28</sup>. In addition, iron serves as a fundamental component of hemoglobin, myoglobin, and diverse enzymes involved in cellular respiration, nitric oxide generation, oxidative phosphorylation, the citric acid cycle, oxygen radical production, and other vital cellular and body functions<sup>29</sup>.

Metabolic active cells with high energy demands, such as skeletal muscle cells and myocytes, depend on iron for their structural integrity and function<sup>10,27,30-32</sup>. At the cellular level, ID decreases enzymatic activity of both the Krebs cycle and the respiratory chain in the mitochondria, leading to disturbance in the energetic metabolism of cells<sup>33</sup>. ID can therefore decrease oxygen storage in myoglobin and reduce tissue oxidative capacity, causing structural and functional change in the myocardium, leading to mitochondrial and myocardial dysfunction<sup>34,35</sup>, and adverse remodelling.

Furthermore, reduced oxygen delivery to metabolizing tissues triggers proinflammatory cytokine activation<sup>36-38</sup>, as well as hemodynamic, neurohormonal, and renal alterations<sup>38</sup>, leading to increased myocardial workload, adverse myocardial remodelling, left ventricle hypertrophy<sup>39,40</sup>, progressive fibrosis<sup>35,41-47</sup>, reduced exercise capacity<sup>35,48-50</sup> and decline in prognosis (Figure 1).

Moreover, patients with HF and ID frequently have several comorbidities, including chronic kidney disease, cardiac cachexia-associated poor nutritional status, and low albumin levels<sup>51-53</sup>, all of which have a significant impact on outcomes.

The 2021 European Society of Cardiology (ESC) guidelines on HF acknowledge the importance of iron deficiency and provide specific recommendations for the diagnosis and treatment of ID<sup>54</sup>. However, iron deficiency remains under-recognized and undertreated in clinical practice<sup>18,55-58</sup>, partially owing to a lack of practical guidance for clinicians.

Importantly, oral iron administration, initially the first route used for iron repletion, has not demonstrated any benefit in patients with HF and reduced ejection fraction, as it did not affect peak  $\text{VO}_2$  (the primary endpoint of the study) or increase serum ferritin levels<sup>59</sup>.

In contrast, randomized controlled trials have shown that in patients with heart failure and reduced ejection fraction, supplementary intravenous iron results in improvements in symptoms, functional capacity, peak oxygen consumption<sup>60</sup>, quality of life<sup>60-66</sup>, and decreased risk of first hospitalization for worsening HF<sup>66,67</sup>. Consequently, correction of iron deficiency in patients with HF and reduced ejection fraction (EF) with intravenous ferric carboxymaltose is now recommended to improve clinical outcomes<sup>54</sup>. Although the clinical and prognostic significance of ID in HF is now widely acknowledged<sup>12,68,69</sup>, our current understanding of the effects of intravenous iron on morbidity and mortality remains limited<sup>70</sup>.

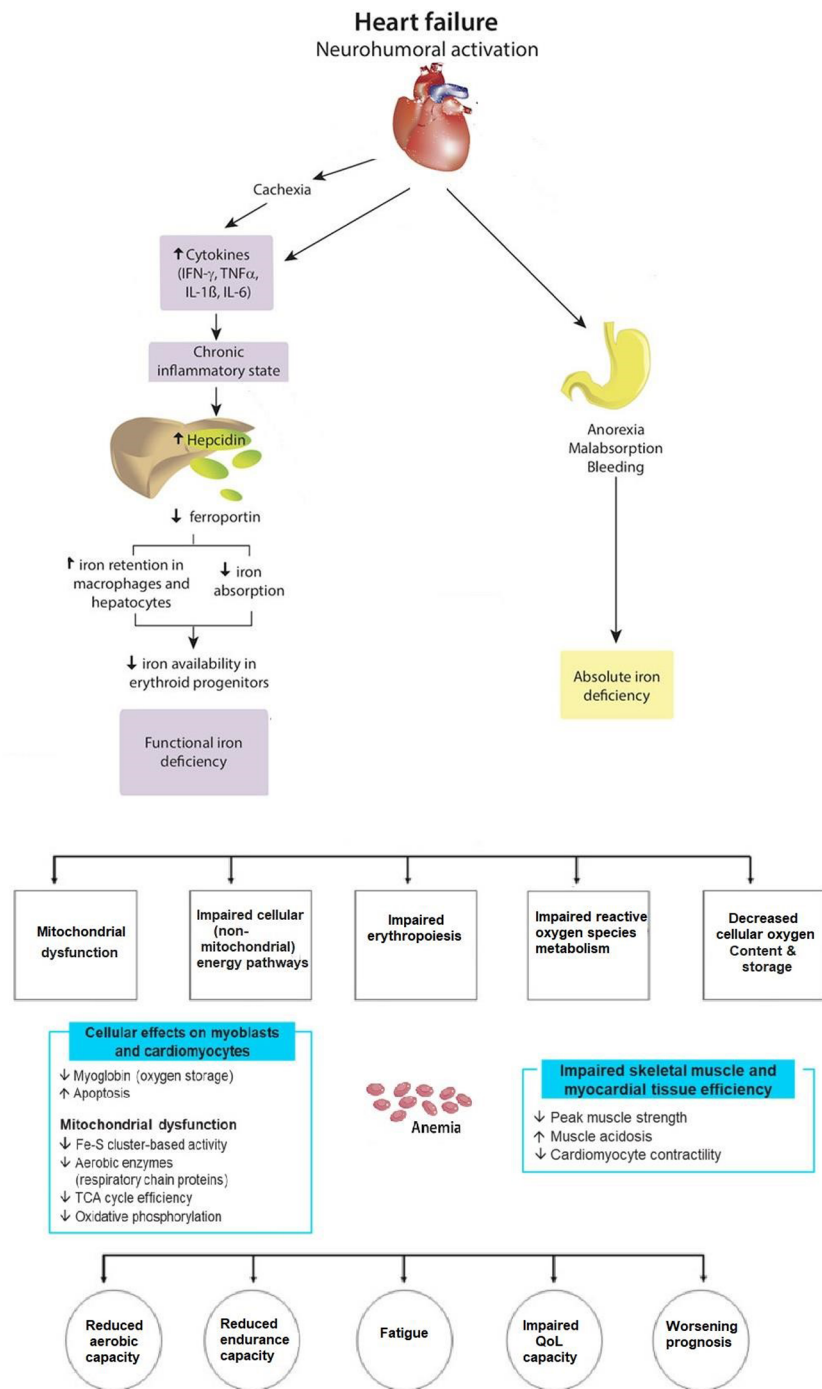


Figure 1. Iron deficiency in heart failure<sup>32,71-76</sup>.

### THE META-ANALYSIS

This meta-analysis pooled individual participant data from three randomized, placebo-controlled trials of intravenous ferric carboxymaltose (FCM) in adult patients with heart failure and iron deficiency with at least 52 weeks of follow-up (CONFIRM-HF<sup>61</sup>, AFFIRM-AHF<sup>66</sup>, and HEART-FID<sup>77</sup>) to evaluate the effects of FCM therapy on hospitalization and mortality in iron-deficient patients with heart failure and reduced or mildly reduced left ventricular ejection fraction (LVEF).

The analysis had two primary efficacy endpoints that were examined through 52 weeks of follow-up: (1) composite of total cardiovascular hospitalizations and cardiovascular death and (2) composite of total heart failure hospitalizations and cardiovascular death. The prospectively recorded clinical outcomes included first and recurrent HF and CV hospitalizations, CV death, and all-cause mortality.

The CONFIRM-HF trial included ambulatory HF patients in New York Heart Association (NYHA) class II–III, with left ventricular ejection fraction (LVEF)  $\leq 45\%$  and elevated natriuretic peptide levels<sup>61</sup>. The AFFIRM-AHF trial recruited patients hospitalized for acute HF with LVEF  $< 50\%$ <sup>66</sup> and the HEART-FID trial enrolled patients with HF and LVEF  $\leq 40\%$  who had recent (within 12 months) hospitalization for HF and/or elevated natriuretic peptide levels<sup>77</sup>.

Iron deficiency was reported using the same definition across all three trials: ferritin  $< 100$  ng/mL or ferritin 100–300 ng/mL with a transfer  $< 20\%$ ).

## RESULTS

Over the three trials, a total of 4,501 patients with heart failure, reduced left ventricular ejection fraction, and iron deficiency were randomly assigned to FCM ( $n = 2,251$ ) or placebo ( $n = 2,250$ ) (Figure 2). The mean age of the total population was 69.2 years, 63% were men, and the mean left ventricular ejection fraction was 31.6%.

The meta-analysis showed that compared with placebo, FCM therapy significantly reduced the co-primary composite endpoint of total cardiovascular hospitalization and cardiovascular death, with a rate ratio (RR) of 0.86 (95% confidence interval [CI] 0.75 to 0.98;  $p = 0.029$ ). Although statistically non-significant, there was a trend towards

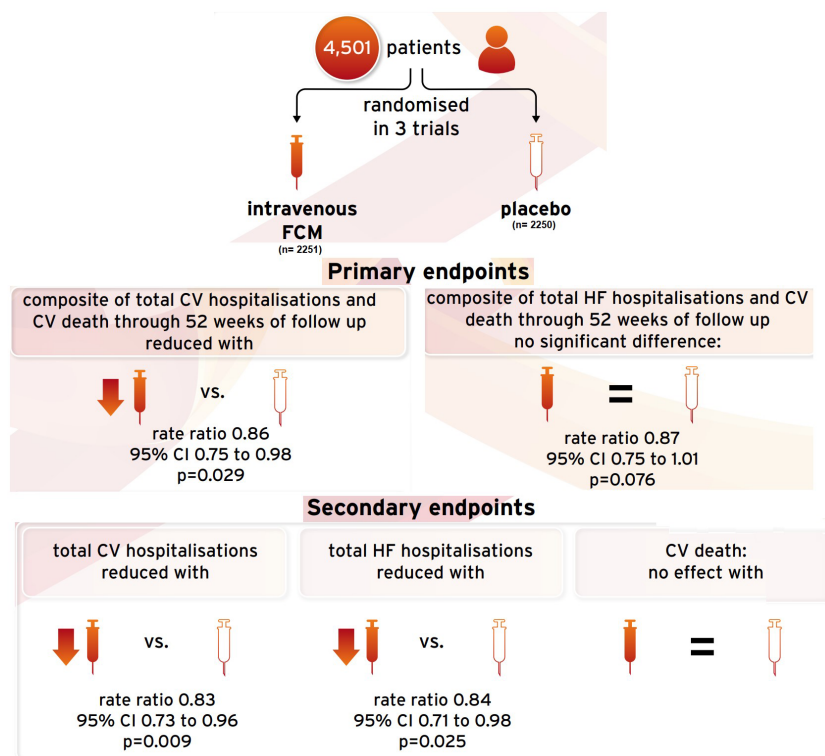


Figure 2. Meta-analysis design and results<sup>78</sup>.

reduction of the co-primary composite endpoint of total heart failure hospitalizations and cardiovascular death (RR, 0.87; 95% CI 0.75 to 1.01;  $p = 0.076$ ).

FCM therapy was associated with a 17% relative rate reduction in total cardiovascular hospitalizations (RR 0.83; 95% CI 0.73 to 0.96;  $p = 0.009$ ) and a 16% relative rate reduction in total heart failure hospitalizations (RR 0.84; 95% CI 0.71 to 0.98;  $p = 0.025$ ).

FCM therapy reduced the time to first CV death or HF hospitalization by 12% (HR, 0.88; 95% CI [0.78–0.99];  $P = 0.039$ ) and the time to first CV death or CV hospitalization by 11% (HR 0.89; 95% CI [0.80–0.99];  $P = 0.033$ ).

Subgroup analyses showed that patients in the lowest transferrin saturation (TSAT) tertile (<15%) derived greater benefits from FCM for CV death (interaction  $p = 0.035$ ) and the composite endpoint of total cardiovascular hospitalization or cardiovascular death (interaction  $p = 0.019$ ) than those with higher baseline TSAT.

Importantly, FCM treatment appeared to be safe and well-tolerated.

## DISCUSSION

This study represents the largest pooled meta-analysis using individual participant data to examine the effects of FCM therapy on hospitalization and mortality in iron-deficient patients with HF and reduced or mildly reduced LVEF.

The analysis showed that in iron-deficient patients with heart failure and reduced or mildly reduced LVEF, intravenous ferric carboxymaltose (FCM) was associated with a reduced risk of the composite outcome of total cardiovascular hospitalization and cardiovascular death through 52 weeks compared with placebo, with a statistically non-significant trend towards reduction of the rate of composite of CV death and total HF hospitalizations. Overall, the treatment appeared to be safe and well tolerated.

There was no evidence for the heterogeneity of treatment effects by sex, age, and baseline serum ferritin, concluding that FCM exerts favorable effects on clinical outcomes across subgroups<sup>23,79,80</sup>.

Importantly, patients with ischemic HF etiology tended to demonstrate greater benefits of FCM therapy regarding the reduction in HF hospitalization and CV death, indicating potential heterogeneity by HF etiology. However, this finding requires further investigation in prospectively designed studies with a robust definition of the underlying HF etiology.

Additionally, there was a difference in the effect of FCM on CV mortality among subgroups based on baseline TSAT, with statistically significant reductions in all-cause and CV mortality in patients with HF and the lowest TSAT values (<15%) and less favorable effects in patients with TSAT of 24% or greater.

According to the current understanding of ID in HF, intravenous iron therapy is often prescribed based on serum ferritin and TSAT levels. However, recent evidence suggests that these markers may not accurately reflect the depletion of iron in bone marrow or the iron status of peripheral target tissues, such as the myocardium or skeletal muscles<sup>49,81–83</sup>. Therefore, it is proposed that the current definition of ID in HF should be re-evaluated as the main indication for intravenous iron therapy.

Furthermore, a higher 6-month cumulative dose of ferric carboxymaltose as a result of re-dosing may be associated with a slightly greater treatment effect; however, additional research to identify eligibility criteria for an optimal re-dosing strategy is warranted.

In conclusion, this large meta-analysis provides further evidence that treatment with intravenous FCM significantly reduces recurrent HF and CV hospitalizations, with no new safety concerns. Importantly, the current study supports continued research to identify

patients who are most likely to benefit from FCM treatment and the development of eligibility criteria for an optimal administration strategy.

## LESSONS LEARNED

The meta-analysis shows that in iron-deficient patients with heart failure and reduced or mildly reduced left ventricular ejection fraction, intravenous ferric carboxymaltose (FCM) is associated with a reduced risk of the composite outcome of total cardiovascular hospitalization and cardiovascular mortality over 52 weeks compared with placebo.

These findings indicate that intravenous FCM should be considered in iron-deficient patients with heart failure and reduced or mildly reduced ejection fraction to reduce the risk of hospitalization and adverse cardiovascular events.

Importantly, challenging the current definition of ID based on serum ferritin and TSAT levels as the main indication for intravenous iron therapy in patients with HF is warranted.

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