IRONMAN – Intravenous Ferric Derisomaltose in Patients with Heart Failure and Iron Deficiency in the UK

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BACKGROUND	
Citation	Kalra PR, Cleland JGF, Petrie MC, et al. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. *Lancet*. 2022;400(10369):2199-2209. doi:10.1016/S0140-6736(22)02083-9
Background	● In patients with iron deficiency, LVEF <50%, and stabilized after an ADHF event, treatment with ferric carboxymaltose is safe and reduces the risk of heart failure hospitalizations (AFFIRM-AHF). ● Iron repletion with ferric carboxymaltose in patients with chronic heart failure and iron deficiency with or without anemia improves NYHA classification, 6-minute walk test, and quality of life (FAIR-HF). ➡ Ferric carboxymaltose improves QOL and exercise capacity in the short-term and reduces hospital admissions for HF for up to 1 year.
Objectives	● This trial aimed to evaluate the longer-term efficacy and safety of ferric derisomaltose on CV events in patients with heart failure and iron deficiency.
Funding	British Heart Foundation and Pharmacosmos Funders had no role in trial design, data collection, analysis, interpretation, or writing of the report.
Trial Design	Investigator-initiated, prospective, randomized, open-label, blinded-endpoint, event driven (PROBE) trial Interventions: ferric derisomaltose infusion dosed according to Hgb and weight in addition usual care or usual care alone **Table 1** Intravenous ferric derisomaltose infusion dose regimen **Haemoglobin** / **Body weight <50 kg*** / **Body weight 50– <70 kg** / **Body weight ≥70 kg** ≥10 g/dL / 20 mg/kg / 1000 mg / 20 mg/kg up to a maximum of 1500 mg <10 g/dL / 20 mg/kg / 20 mg/kg / 20 mg/kg up to a maximum of 2000 mg ● Visits at 4 weeks after randomization and every 4 months until conclusion of the trial ● Patients received treatment if ferritin <100 µg/L or ≤400 µg/L and TSAT <25%; goal to maintain repletion
Inclusion Criteria	● Age ≥18 years ● LVEF ≤45% within last 2 years ● NYHA class II-IV ● Iron deficient – defined as TSAT <20% and/or ferritin <100 µg/L ● Current or recent (within 6 months) hospitalization for HF OR ● Outpatient NT-proBNP >250 ng/L in sinus rhythm or >1000 ng/L in afib (or BNP >75 pg/mL or >300 pg/mL, respectively)
Exclusion Criteria	● Hgb <9 g/dL or >13 g/dL in women and >14 g/dL in men ● Ferritin >400 µg/L ● eGFR <15 mL/min/1.73m^2 ● likely to need or already receiving an erythropoiesis stimulating agent ● blood transfusion in the previous 3 months or active clinically relevant bleeding

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	● Planned cardiac surgery or revascularization ● Any major vascular event in previous 3 months, including type 1 MI, CVA, major CV surgery or PCI ● Awaiting or treated by cardiac transplantation or LVAD ● Active infection ● Anemia due to other causes other than iron deficiency
Efficacy Assessment	Primary Endpoint ● Composite: CV death and hospital admission for HF Secondary Endpoints ● Hospital admissions for worsening HF (recurrent events) ● CV hospital admission (first event) ● CV death or hospitalization for HF (time to first event) ● Overall MLHFQ score at 4 months ● CV death ● All cause mortality
Safety Assessment	● Death due to infection ● Hospitalization primarily for infection
Statistical Analysis	● Intention-to-treat ● Power calculations based on time-to-first-event using a Cox proportional hazards model and displayed in Kaplain-Meier curves, as appropriate ● Assuming a HR of 0.75, 379 first primary endpoints would provide 80% power with an alpha of 0.05. ● Rate ratios used with 95% confidence intervals ● Primary and secondary endpoints analyzed hierarchically ● COVID-19 sensitivity analyses performed ● Preplanned interim analysis when 50% and 70% of target first primary endpoints reached, with a p value <0.001 to recommend early stopping

Baseline Characteristics	● 1137 patients randomized 1:1
	● Baseline characteristics were similar
	  ● ~75% male and ~90% white
	  ● 67% outpatients w/ raised natriuretic peptides
	  ● Mostly NYHA class II and III
	  ● Hgb: 12.1 g/dL; TSAT: 15%; Ferritin: ~50 µg/L
	  ● Good use of GDMT except for SGLT2i

Results	Primary Endpoint ● 22.4 events/100 patient-years in the ferric derisomaltose group and 27.5 events/100 patient-years in the usual care group which gives an rate ratio of 0.82 (CI: 0.66-1.02; p value: 0.07) Secondary Endpoints ● None showed a statistically significant difference between groups but did generally favor the ferric derisomaltose group COVID-19 Analysis ● No statistically significant differences between the groups
Adverse Events	Prespecified Safety Endpoints

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	● Deaths due to infection: 6% in iron group compared to 5% in usual care group with a hazard ratio of 1.22 (0.74 to 2.02; 0.43) ● Hospitalizations due to infection: 11.7 events/100 patient-years in the iron group compared to 14.2 in the usual care group with a rate ratio of 0.82 (0.62-1.08; 0.16) ● Serious adverse events: There was no evidence of an increase in SAEs with ferric derisomaltose. Fewer patients in the ferric derisomaltose group had serious adverse cardiac events.
DISCUSSION AND CONCLUSION	
Study Strengths	● 1,137 patients randomized and included in analysis ● Wide variety of HF patients – increased generalizability ● Median follow-up was 2.7 years ● The endpoints committee that adjudicated events were blinded to treatment group ● Protocol permitted follow-up by phone and/or medical records if patient was unable to attend in person
Study Limitations	● Excluded patients with Hgb <9 g/dL and >13/14 in women/men ● Excluded patients with low eGFR who might really benefit from iron ● Excluded patients with planned cardiac surgery, major vascular event in past 3 months, and those awaiting transplant or with an LVAD, which excludes a lot of high risk HF patients ● 17% of patients assigned to the usual care group received IV iron ● Open-label design ● Predominantly white population ● Did not include HFpEF patients ● COVID pandemic hindered recruitment and follow-up
Applicability and Impact	● Although the results of this trial were not statistically significant, the results were favorable for IV iron supplementation with ferric derisomaltose, which can be infused quickly and at a high dose. ● This study in addition to the other literature published for iron supplementation in HF patients provides a sound reason for using IV iron supplementation in HF patients to reduce hospitalizations due to HF and to improve patients' exercise capacity and QOL. This will reduce the economic burden of continuous readmissions in this population and most importantly improve patient's lives.
Conclusions and Recommendations	● HF patients should be screened for iron deficiency upon diagnosis. ● Ferric derisomaltose is a reasonable option for HFrEF patients with iron deficiency to reduce hospitalizations for HF and improve exercise capacity and quality of life.

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