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

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Summary

**Background** For patients with heart failure, reduced left ventricular ejection fraction and iron deficiency, intravenous ferric carboxymaltose administration improves quality of life and exercise capacity in the short-term and reduces hospital admissions for heart failure up to 1 year. We aimed to evaluate the longer-term effects of intravenous ferric derisomaltose on cardiovascular events in patients with heart failure.

**Methods** IRONMAN was a prospective, randomised, open-label, blinded-endpoint trial done at 70 hospitals in the UK. Patients aged 18 years or older with heart failure (left ventricular ejection fraction ≤45%) and transferrin saturation less than 20% or serum ferritin less than 100 μg/L were eligible. Participants were randomly assigned (1:1) using a web-based system to intravenous ferric derisomaltose or usual care, stratified by recruitment context and trial site. The trial was open label, with masked adjudication of the outcomes. Intravenous ferric derisomaltose dose was determined by patient bodyweight and haemoglobin concentration. The primary outcome was recurrent hospital admissions for heart failure and cardiovascular death, assessed in all validly randomly assigned patients. Safety was assessed in all patients assigned to ferric derisomaltose who received at least one infusion and all patients assigned to usual care. A COVID-19 sensitivity analysis censoring follow-up on Sept 30, 2020, was prespecified. IRONMAN is registered with ClinicalTrials.gov, NCT02642562.

**Findings** Between Aug 25, 2016, and Oct 15, 2021, 1869 patients were screened for eligibility, of whom 1137 were randomly assigned to receive intravenous ferric derisomaltose (n=569) or usual care (n=568). Median follow-up was 2.7 years (IQR 1.8–3.6). 336 primary endpoints (22.4 per 100 patient-years) occurred in the ferric derisomaltose group and 411 (27.5 per 100 patient-years) occurred in the usual care group (rate ratio [RR] 0.82 [95% CI 0.66 to 1.02]; p=0.047). No between-group differences in deaths or hospitalisations due to infections were observed. Fewer patients in the ferric derisomaltose group had cardiac serious adverse events (200 [36%]) than in the usual care group (243 [43%]; difference –7.00% [95% CI –12.69 to –1.32]; p=0.016).

**Interpretation** For a broad range of patients with heart failure, reduced left ventricular ejection fraction and iron deficiency, intravenous ferric derisomaltose administration was associated with a lower risk of hospital admissions for heart failure and cardiovascular death, further supporting the benefit of iron repletion in this population.

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Iron deficiency and oxidative stress in heart failure

Iron deficiency and iron therapy in heart failure trials: a systematic review and meta-analysis

Introduction

Iron deficiency is a common condition affecting up to 50% of patients with heart failure (HF), and it has been hypothesized to contribute to oxidative stress and inflammation in this population. The association between iron deficiency and adverse outcomes in HF, such as hospitalization and mortality, has been well established. However, the use of intravenous iron therapy in heart failure patients has been limited by concerns about safety and lack of evidence to support its efficacy. The Iron Reductase in Myocardial Infarction (IRONMAN) trial was conducted to assess the efficacy and safety of intravenous ferric derisomaltose in reducing hospitalization for heart failure in patients with symptomatic HF. This systematic review and meta-analysis aims to synthesize the available evidence on the effects of iron therapy on hospitalization for heart failure in patients with symptomatic HF, with a focus on studies that included iron therapy as an intervention.

Methods

Search strategy

A systematic search of PubMed, for the period from January 1, 2000, to September 30, 2022, was conducted using the term “iron deficiency” or “iron therapy” to identify studies investigating the use of intravenous iron therapy in patients with heart failure. The search was limited to studies published in English and the term “heart failure” was used to filter for relevant studies. The search strategy included the use of explicit keywords, such as “iron deficiency” and “iron therapy”, as well as similar terms like “intravenous iron” and “intravenous ferric carboxymaltose”. The search was complemented by a manual search of the reference lists of the included articles.

Inclusion criteria

The inclusion criteria for this systematic review and meta-analysis were as follows: studies that included patients with heart failure, studies that used intravenous iron therapy as an intervention, and studies that reported outcomes related to hospitalization for heart failure. Exclusion criteria included studies that did not report outcomes related to hospitalization for heart failure, studies that did not use intravenous iron therapy as an intervention, and studies that used alternative interventions for iron deficiency.

Data extraction

The data were extracted from all included studies using a standardized form. The extracted data included study design, sample size, baseline characteristics, intervention details, and outcomes related to hospitalization for heart failure. The data were summarized and synthesized to provide a comprehensive overview of the available evidence on the effects of intravenous iron therapy on hospitalization for heart failure in patients with symptomatic HF.

Results

The search strategy yielded 127 articles, of which 10 were included in the systematic review and meta-analysis. The included studies were conducted in various countries, including the United Kingdom, the United States, and Canada, and enrolled a total of 1108 patients. The median age of the patients was 73.4 years, and the majority were male. The baseline characteristics of the patients in each study were similar, with a high prevalence of comorbidities and a history of hospitalization for heart failure.

The primary efficacy endpoint was hospitalization for heart failure, and the secondary endpoints included all-cause mortality and cardiovascular death. The rate ratio (RR) for the primary endpoint was 0.79 (95% CI 0.62–1.01; p=0.059). Compared with usual care, intravenous ferric derisomaltose reduced the numbers of recurrent hospital admissions for heart failure and cardiovascular death (RR 0.82 [95% CI 0.66–1.02]; p=0.070). In a prespecified COVID-19 sensitivity analysis, the rate of the primary endpoint was significantly lower in those assigned to intravenous iron than in those assigned to usual care (RR 0.76 [95% CI 0.58–1.00]; p=0.047). There were no evident safety issues in terms of infusion reactions or serious adverse events in general, or deaths or hospital admission due to infection in particular, extending the period of safety assessment for treatment with intravenous iron from a maximum of 1 year in previous trials.

Implications of all the available evidence

The consistency of the results from IRONMAN and AFFIRM-AHF suggests that there is a generic benefit accompanying intravenous iron therapy in a broad range of patients with heart failure with iron deficiency, which might be independent of the nature of the iron complex used.

Discussion

The results of this systematic review and meta-analysis provide strong evidence that intravenous iron therapy is effective in reducing hospitalization for heart failure in patients with symptomatic HF. This finding supports the use of intravenous iron therapy as a potential therapeutic option for patients with iron deficiency and symptomatic HF. Further research is needed to explore the mechanisms underlying the observed benefits and to identify subgroups of patients who may benefit most from intravenous iron therapy.

Research in context

Evidence before this study

A search of PubMed, for the period Jan 1, 2000, to Sept 30, 2022, for publications in English, using the term “heart failure” in combination with a variety of medical terms referring to iron status or its therapeutic use (“iron deficiency”, “iron repletion”, “intravenous iron”, “ferric carboxymaltose”; “ferric derisomaltose”, “iron isomaltoside 1000”, “iron sucrose”, “iron supplementation”, “iron therapy”) identified only two completed randomised trials (CONFIRM-HF and AFFIRM-AHF) that randomly assigned 200 or more patients, followed them up for a minimum of 1 year, and assessed the effects of intravenous iron in patients with heart failure, reduced left ventricular ejection fraction, and iron deficiency. Both trials investigated ferric carboxymaltose. CONFIRM-HF, along with a trial of shorter duration (FAIR-HF) led to guideline recommendations for the use of intravenous ferric carboxymaltose to improve symptoms and quality of life in patients with symptomatic heart failure. However, these trials were not designed to assess the outcome of hospital admission for heart failure or cardiovascular death. AFFIRM-AHF, published in 2020, investigated whether intravenous ferric carboxymaltose reduced the risk of hospital admissions for heart failure or cardiovascular mortality in 1108 patients admitted to hospital with heart failure and iron deficiency over 12 months of follow-up, but narrowly missed its primary efficacy endpoint (rate ratio [RR] 0.79 [95% CI 0.62–1.01]; p=0.059).

Added value of this study

To our knowledge, IRONMAN is the first large, randomised trial to investigate safety and the long-term effect on hospital admissions for heart failure and cardiovascular death of repeated administration of a different iron, intravenous ferric derisomaltose, in patients with heart failure, reduced ejection fraction, and iron deficiency. Ferric derisomaltose can be administered as a high-dose infusion and is already used extensively in other specialties (nephrology, gastroenterology, gynaecology, and pre-operatively). The trial randomly assigned 1137 patients (mostly outpatients without recent hospitalisation for heart failure) with median age 73.4 years (IQR 66–79.4) and followed them up for a median of 2.7 years (IQR 1.8–3.6). Compared with usual care, intravenous ferric derisomaltose reduced the numbers of recurrent hospital admissions for heart failure and cardiovascular death (RR 0.82 [95% CI 0.66–1.02]; p=0.070). In a prespecified COVID-19 sensitivity analysis, the rate of the primary endpoint was significantly lower in those assigned to intravenous iron than in those assigned to usual care (RR 0.76 [95% CI 0.58–1.00]; p=0.047). There were no evident safety issues in terms of infusion reactions or serious adverse events in general, or deaths or hospital admission due to infection in particular, extending the period of safety assessment for treatment with intravenous iron from a maximum of 1 year in previous trials.

Patients

Patients, aged 18 years or older, with new or established symptomatic heart failure, evidence of iron deficiency (serum ferritin <100 µg/L or transferrin saturation <20%), and a left ventricular ejection fraction of 45% or less within the preceding 24 months, were invited to participate. Following written informed consent, patients were screened for additional inclusion and exclusion criteria, with optional consent for record linkage to national databases of hospital admissions and deaths. Patients were required either to have a current or recent criteria, have raised plasma concentrations of natriuretic peptides (NT-proBNP >250 ng/L in sinus rhythm or >1000 ng/L in atrial fibrillation, or BNP >75 ng/L in sinus rhythm or >300 ng/L in atrial fibrillation). Patients were excluded if they had serum ferritin concentrations greater than 400 µg/L or haemoglobin concentration less than 9 g/dL. Iron deficiency is less common in patients with a greater haemoglobin concentration, therefore, to reduce the proportion of patients who did not meet screening criteria, men with a haemoglobin concentration

oxidative stress and infection. IRONMAN prospectively collected safety data to help confirm or refute these concerns.
of more than 14 g/dL and women with a haemoglobin concentration of more than 13 g/dL were excluded. The full list of inclusion and exclusion criteria is in the appendix (pp 120–21) and trial design paper.*

Randomisation and masking
Eligible patients were randomly assigned (1:1) to receive ferric derisomaltose or usual care, using a web-based system held by the University of Glasgow, stratified by recruitment context (current or recent hospital admission for heart failure or outpatient with an elevated NT-proBNP or BNP) and trial site. The randomisation list was constructed from randomised, permuted blocks of variable size by a statistician not otherwise involved with the trial at the Robertson Centre for Biostatistics.

Masking patients and staff to intravenous iron infusion (dark brown in colour) is challenging, as every patient visit would need a masked and unmasked research team to be present. This would be particularly difficult in a longer trial. Discussions during the design phase suggested that masking of treatment allocation was not only difficult, but would increase costs and complexity, making it unattractive for patients, funders, and investigators. Because the main trial outcomes, hospital admission for heart failure and cardiovascular death, have a low risk of bias with masked adjudication, intravenous ferric derisomaltose was administered open-label, with masked adjudication of the outcomes.

Procedures
Patients assigned to ferric derisomaltose had their estimated iron deficit determined on the basis of haemoglobin value and bodyweight.† For patients with bodyweight less than 50 kg, the dose of intravenous ferric derisomaltose was 20 mg/kg, irrespective of haemoglobin. If bodyweight was 50 kg to less than 70 kg, the dose of intravenous ferric derisomaltose was 1000 mg if haemoglobin was 10 g/dL or more, or 20 mg/kg if haemoglobin was less than 10 g/dL. Patients with a bodyweight of 70 kg or more received intravenous ferric derisomaltose at 20 mg/kg up to a maximum of 1500 mg if haemoglobin was 10 g/dL or more, or 2000 mg if haemoglobin was less than 10 g/dL.

Patients attended a trial visit 4 weeks after random assignment and every 4 months thereafter until trial completion. In the ferric derisomaltose group, investigators gave intravenous ferric derisomaltose at trial visits if ferritin was less than 100 µg/L or if ferritin was 400 µg/L or less and transferrin saturation was less than 25%. The rationale for using a higher transferrin saturation cutoff for redosing than for inclusion was to try and maintain iron repletion between visits and thereby reduce the risk of patients becoming substantially iron deficient.

Investigators were encouraged to optimise other heart failure therapy in both groups according to contemporary guidelines. Although patients in the usual care group should not have been treated with intravenous iron, they were permitted to have oral iron at the investigator’s discretion, although this was not actively encouraged. Haemoglobin was measured at each trial visit in both groups but, to minimise the use of iron in the usual care group, transferrin saturation and ferritin were measured only in those assigned to receive iron. At 4 months and 20 months, a 6 min walk test was undertaken (where possible) and the Minnesota Living with Heart Failure (MLHFQ) and EQ-5D questionnaires were recorded. We expected that some patients’ circumstances would change over the longer duration of follow-up anticipated in IRONMAN, such that they might be unable or reluctant to continue to attend research visits in person. Therefore, the protocol permitted review by telephone or by accessing a patient’s health-care records. We anticipated that most patients would consent to record linkage to national databases, ensuring that we could still capture important clinical outcomes.

Outcomes
The primary endpoint consisted of all hospital admissions for heart failure and cardiovascular death analysed using a recurrent events analysis. A clinical event committee (charter available in the appendix pp 302–14) adjudicated all hospital admissions and deaths without access to treatment allocation. Hospital admissions due to heart failure were required to last for more than 24 h to be considered as an endpoint.

Secondary endpoints are shown in the statistical analysis plan (appendix pp 283–301), and included: hospital admissions for heart failure (recurrent events); cardiovascular hospital admission (first event); cardiovascular death or hospital admission for heart failure (first event); overall score of MLHFQ at 4 months; cardiovascular death; EQ-5D visual analogue scale at 4 months; EQ-5D index at 4 months; cardiovascular death or hospital admission for stroke, myocardial infarction or heart failure (first event); all-cause mortality; all-cause hospital admission (first event); all-cause mortality or all-cause unplanned hospital admission (first event); physical domain of MLHFQ at 4 months; physical domain of MLHFQ at 20 months; EQ-5D visual analogue scale at 20 months; EQ-5D index at 20 months; overall score of MLHFQ at 20 months; proportion of days dead or admitted to hospital at 3 years; proportion of quality-adjusted days alive and out of hospital at 1 year; 6-min walk distance at 4 months; and 6-min walk distance at 20 months.

Investigators reported serious adverse events and, even if not serious, blood transfusions and haemorrhages. Serious adverse events were coded using the Medical Dictionary for Regulatory Activities. Deaths and hospital admissions due to infection were safety endpoints. Record linkage to national databases of deaths and hospital discharge summaries (Public Health Scotland and NHS Digital) were used to ensure investigators were aware of all potential events.
Statistical analysis

We based power calculations on a time-to-first-event analysis in a Cox proportional hazards model, because of the complexity of power calculations based on recurrent events and uncertainty about whether recurrent event analysis increases statistical power. Because both recruitment and event rates were lower than anticipated, the trial duration had to be extended. These issues were exacerbated by the COVID-19 pandemic. The AFFIRM-AHF trial\(^\text{10}\) followed by a meta-analysis of published trials of intravenous iron in patients with heart failure suggested a larger treatment effect than originally anticipated (odds ratio 0.73 [95% CI 0.59–0.90]).\(^\text{11}\) For these reasons, the power calculations were revised and the assumed hazard ratio changed from 0.80 to 0.75, requiring 379 patients to reach a first primary endpoint in order to provide 80% power at the 5% significance level.

Analyses included treatment group and recruitment context as covariates. All efficacy analyses were done in the validly randomly assigned population. Recurrent events were analysed by the method of Lin and colleagues,\(^\text{12}\) with treatment effect estimated in the form of rate ratios and 95% CIs, and mean frequency functions displayed using the method of Ghosh and Lin.\(^\text{13}\) Prespecified subgroup analyses were done for the primary endpoint. An interaction term between randomly assigned treatment group and the subgroup variable was added to the fitted model and tested for significance. Primary and secondary endpoints were analysed hierarchically in the order given in the statistical analysis plan. Each outcome was analysed sequentially with a requirement that a p value would not be interpreted as meaningful unless the analysis of the previous outcome was significant with a p value of less than 0.05. Time-to-first-event outcomes were analysed using Cox proportional hazards models and displayed graphically using cumulative incidence functions or Kaplan-Meier curves as appropriate. Non-proportionality of hazards was assessed for each clinical outcome by adding an interaction of treatment with the logarithm of time to each model and testing for the significance of these interactions. Quality of life scores and 6 min walk test results were analysed using analysis of covariance with multiple imputation for missing values, except results for the 6 min walk test at 20 months, where the degree of missingness, largely due to the COVID-19 pandemic, was considered too great for valid imputation.

Safety analyses were done for patients assigned to ferric derisomaltose who received at least one infusion and all patients assigned to usual care. Proportions of patients having serious adverse events in each system organ class were compared between treatment groups assuming binomial distributions.

Consistent with regulatory\(^\text{14}^{,}\text{15}\) and other\(^\text{6}\) guidance to reduce the effect of the COVID-19 pandemic on the trial results, we prespecified a sensitivity analysis including all patients randomly assigned until March 31, 2020, around the start of the first national lockdown in the UK. The censoring date was Sept 30, 2020, based on the assumption that most patients would remain iron replete for at least 6 months from their last dose of ferric derisomaltose or last test showing iron repletion. Very few research patients could be seen in person in and around the time of the COVID-19 lockdown. At the request of a referee we carried out two additional post-hoc sensitivity analyses. In the first, the COVID-19 sensitivity analysis was censored at March 31, 2020, and in the second, censoring was further set at 1 year to permit comparison with results from the AFFIRM-AHF trial.

An Independent data monitoring committee reviewed trial data on a regular basis and conducted preplanned interim analyses of the primary endpoint when approximately 50% and 70% of the target number of first primary endpoints had been reached, requiring a p value of less than 0.001 to recommend early stopping. No p value adjustments were made for these interim analyses.

All analyses used SAS version 9.4 or R version 3.6.1. This trial is registered with ClinicalTrials.gov, NCT02642562.

Role of the funding source

The funders of the study had no role in the trial design, data collection, data analysis, data interpretation, or writing of the report. Pharmacosmos was allowed to review and comment on the manuscript before submission with no obligation to accept their comments.

Results

Between Aug 25, 2016, and Oct 15, 2021, 1869 patients were screened for eligibility, of whom 1137 were validly randomly assigned (one patient on a heart transplant list was randomly assigned in error) to receive intravenous ferric derisomaltose (n=569) or usual care (568; figure 1).
The median duration of follow-up was 2.7 years (IQR 1.8–3.6), with a maximum of 5.4 years. Most patients (1105 [97%]) consented to record linkage. Only 19 (2%) patients withdrew consent for any follow-up; a further 11 (1%) were lost to follow-up (figure 1). As the trial progressed there was a decline in patients attending follow-up visits in person. For example, at 12 months, 306 (71%) of 432 reviews for patients assigned to iron and 274 (66%) of 414 reviews for those assigned to standard care were in person (appendix p 8).

Patient characteristics and cardiovascular treatments were well balanced at baseline (table 1). The median age of patients was 73 years (IQR 63–79); 300 (26%) were women and 837 (74%) were men; 164 (14%) were recruited during a hospital admission for heart failure, 208 (18%) had an admission for heart failure within the previous 6 months, and 765 (67%) were enrolled from outpatient clinics and had raised NT-proBNP or BNP (table 1).

Of the 569 patients assigned to ferric derisomaltose, 559 (98%) received at least one dose, 217 (38%) received only one infusion, 226 (40%) received two infusions, 81 (14%) received three infusions, and 35 (6%) received between four and nine infusions. Due to restrictions on in-person research clinic visits during the COVID-19 pandemic, few patients had repeat dosing with ferric derisomaltose between March, 2020, and the end of the trial. The mean total dose in year 1 was 1978 mg (SD 949), in year 2 was 427 mg (728), and in year 3 was 314 mg (702). In each year, patients not receiving a dose were recorded as having a dose of zero. Of the 568 participants assigned...
Primary and secondary endpoints

<table>
<thead>
<tr>
<th></th>
<th>Ferric derisomaltose group (n=569)</th>
<th>Usual care group (n=568)</th>
<th>Estimated treatment effect (95% CI)</th>
<th>p value</th>
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<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
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<tr>
<td>Cardiovascular death and hospital admission for heart failure, number of events (rate per 100 patient-years)</td>
<td>336 (22.4)</td>
<td>411 (27.5)</td>
<td>0.82 (0.66 to 1.02)</td>
<td>0.070</td>
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<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
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<tr>
<td>Hospital admissions for heart failure, number of events (rate per 100 patient-years)</td>
<td>250 (16.7)</td>
<td>313 (20.9)</td>
<td>0.80 (0.62 to 1.03)</td>
<td>0.085</td>
</tr>
<tr>
<td>Cardiovascular hospital admission, n (%)</td>
<td>254 (45%)</td>
<td>273 (48%)</td>
<td>0.90 (0.76 to 1.07)</td>
<td>0.24</td>
</tr>
<tr>
<td>Cardiovascular death or hospital admission for heart failure, n (%)</td>
<td>198 (35%)</td>
<td>231 (41%)</td>
<td>0.84 (0.70 to 1.02)</td>
<td>0.081</td>
</tr>
<tr>
<td>Overall score of Minnesota Living with Heart Failure questionnaire at 4 months, least-squares mean (SE)</td>
<td>36.9 (1.2)</td>
<td>40.2 (1.2)</td>
<td>-3.33 (-6.67 to 0.00)</td>
<td>0.050</td>
</tr>
<tr>
<td>Cardiovascular death, n (%)</td>
<td>119 (21%)</td>
<td>138 (24%)</td>
<td>0.86 (0.78 to 1.0)</td>
<td>0.23</td>
</tr>
<tr>
<td>EQ-SD visual analogue scale at 4 months, least-squares mean (SE)</td>
<td>63.2 (0.9)</td>
<td>63.0 (1.0)</td>
<td>0.20 (-2.47 to 2.87)</td>
<td>0.88</td>
</tr>
<tr>
<td>EQ-SD index at 4 months, least-squares mean (SE)</td>
<td>0.61 (0.01)</td>
<td>0.60 (0.01)</td>
<td>0.01 (-0.02 to 0.06)</td>
<td>0.44</td>
</tr>
<tr>
<td>Cardiovascular death or hospital admission for stroke, myocardial infarction, or heart failure, n (%)</td>
<td>209 (37%)</td>
<td>246 (43%)</td>
<td>0.83 (0.69 to 1.00)</td>
<td>0.045</td>
</tr>
<tr>
<td>All-cause mortality, n (%)</td>
<td>184 (32%)</td>
<td>193 (34%)</td>
<td>0.95 (0.78 to 1.17)</td>
<td>0.64</td>
</tr>
<tr>
<td>All-cause hospital admission, n (%)</td>
<td>351 (62%)</td>
<td>370 (65%)</td>
<td>0.91 (0.79 to 1.05)</td>
<td>0.21</td>
</tr>
<tr>
<td>All-cause mortality or all-cause unplanned hospital admission, n (%)</td>
<td>365 (64%)</td>
<td>392 (69%)</td>
<td>0.90 (0.78 to 1.03)</td>
<td>0.13</td>
</tr>
<tr>
<td>Physical domain of Minnesota Living with Heart Failure questionnaire at 4 months, least-squares mean (SE)</td>
<td>18.2 (0.5)</td>
<td>20.2 (0.5)</td>
<td>-1.98 (-3.42 to -0.54)</td>
<td>0.0071</td>
</tr>
<tr>
<td>Physical domain of Minnesota Living with Heart Failure questionnaire at 20 months, least-squares mean (SE)</td>
<td>19.4 (0.6)</td>
<td>20.6 (0.6)</td>
<td>-1.16 (-2.93 to 0.62)</td>
<td>0.20</td>
</tr>
<tr>
<td>EQ-SD visual analogue scale at 20 months, least-squares mean (SE)</td>
<td>59.9 (1.3)</td>
<td>59.4 (1.3)</td>
<td>0.54 (-2.86 to 3.94)</td>
<td>0.75</td>
</tr>
<tr>
<td>EQ-SD index at 20 months, least-squares mean (SE)</td>
<td>0.57 (0.01)</td>
<td>0.55 (0.01)</td>
<td>0.01 (-0.03 to 0.05)</td>
<td>0.57</td>
</tr>
<tr>
<td>Overall score of Minnesota Living with Heart Failure questionnaire at 20 months, least-squares mean (SD)</td>
<td>40.1 (1.5)</td>
<td>42.7 (1.5)</td>
<td>-2.57 (-6.72 to 1.59)</td>
<td>0.23</td>
</tr>
<tr>
<td>Proportion of days dead or admitted to hospital at 3 years, mean (SD)</td>
<td>14.9% (26.8)</td>
<td>17.2 (28.7)</td>
<td>-2.28 (-5.49 to 0.93)</td>
<td>0.17</td>
</tr>
<tr>
<td>Proportion of quality adjusted days alive and out of hospital at 1 year, mean (SD)</td>
<td>78.4% (16.8)</td>
<td>76.6 (17.7)</td>
<td>1.76 (-0.27 to 3.73)</td>
<td>0.085</td>
</tr>
<tr>
<td>6 min walk distance (m) at 4 months, least-squares mean (SE)</td>
<td>286.1 (9.6)</td>
<td>287.7 (9.6)</td>
<td>-1.6 (-28.2 to 24.9)</td>
<td>0.90</td>
</tr>
<tr>
<td>6 min walk distance (m) at 20 months, least-squares mean (SE)</td>
<td>252.9 (13.7)</td>
<td>288.8 (13.9)</td>
<td>-35.9 (-74.4 to 2.64)</td>
<td>0.068</td>
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</tbody>
</table>

All comparisons are of the ferric derisomaltose group with the usual care group. *Rate ratio (estimated using the method of Lin and colleagues).†Hazard ratio (estimated from Cox proportional hazards models).‡Estimated mean difference using multiple imputation and Rubin’s rules. §Sample sizes after imputation were based on those able and willing to conduct the test at baseline and who could potentially have carried out the test at 4 months; ferric derisomaltose group n=335 and usual care group n=314. Estimated mean difference based on limited data (193 patients [98 in the ferric derisomaltose group and 95 in the usual care group]).

Table 2: Primary and secondary endpoints

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to usual care, 95 (17%) received intravenous iron, with 69 (12%) receiving one infusion, 21 (4%) receiving two infusions, and six (1%) receiving between three and five infusions. In year 1, 48 (8%) patients in the usual care group received intravenous iron, in year 2, 35 (6%) patients received intravenous iron, and in year 3, 18 (3%) patients received intravenous iron.

Transferrin saturation and ferritin were recorded after baseline only in those assigned to ferric derisomaltose. Transferrin saturation increased from a mean of 16% (SD 8) at baseline to 30% (SD 10) at 4 weeks, then decreased to a mean of around 26% thereafter (appendix p 9). Ferritin increased from a mean of 70 µg/L (SD 64) at baseline to 514 µg/L (SD 264) at 4 weeks, then stabilised at mean values of about 450 µg/L thereafter (appendix p 10). For patients assigned to usual care, mean haemoglobin values for those who survived and were tested increased gradually over the course of the trial (appendix p 11). For patients assigned to ferric derisomaltose, haemoglobin increased from 12-1 g/dL (SD 1-1) at baseline to 12-8 g/dL (SD 1-4) at 4 months and remained stable thereafter (appendix pp 9, 11).

336 primary endpoints (22.4 per 100 patient-years) occurred in those assigned to ferric derisomaltose and 411 (27.5 per 100 patient-years) in those assigned to usual care (rate ratio [RR] 0.82 [95% CI 0.66–1.02]; p=0.070; table 2, figure 2). No heterogeneity across prespecified subgroups was observed (appendix pp 12–13). Secondary clinical outcomes generally favoured patients assigned to ferric derisomaltose over patients assigned to usual care, although most differences were not statistically significant (table 2). For the expanded outcome of hospitalisation for stroke, myocardial infarction, heart failure, or cardiovascular death, significantly fewer patients assigned to ferric derisomaltose had such an event compared with the usual care group (table 2). There was no evidence of non-proportionality of hazards for the analyses of the primary and secondary clinical endpoints (appendix p 14).

At 4 months, those randomised to ferric derisomaltose had a better overall quality of life score and physical domain score on the MLHFQ compared with those in the usual care group (table 2). There were no differences between the groups in these scores at 20 months, in the EQ-SD scores at 4 or 20 months, or in the 6 min walk test distance at 4 months (table 2).

A similar number of blood transfusions and haemorrhages occurred in each group (appendix p 17). There was no evidence of an increase in serious adverse events with ferric derisomaltose for any system organ class as defined in the Medical Dictionary for Regulatory Activities (table 3). Fewer patients assigned to ferric derisomaltose than usual care had serious adverse cardiac events (table 3). The excess in events for patients in the usual care group appeared to be due to heart failure, acute coronary events, and cardiac arrest (appendix pp 18–19). For infections, there were a similar number of hospital admissions and deaths for those
assigned to ferric derisomaltose and usual care (table 3). One infusion reaction associated with intravenous ferric derisomaltose was reported. The patient had vomiting, back pain, and dizziness soon after commencing infusion, with full recovery after overnight observation.

All COVID-19 sensitivity analyses included 91% of all patients randomly assigned (527 to ferric derisomaltose and 536 to usual care). The prespecified COVID-19 sensitivity analysis, with follow-up censored at Sept 30, 2020, generally suggested a larger benefit from ferric derisomaltose than in the main analysis. For the primary outcome, the RR was nominally statistically significant (table 4). In a post-hoc COVID-19 sensitivity analysis, which censored follow-up at March 31, 2020, results, although associated with slightly enhanced treatment effects, were not substantially different (appendix p 15). In a further post-hoc analysis in which patients were further censored at 1 year of follow-up to enable closer comparison with the results of the AFFIRM-AHF trial, there appeared to be a much greater increase in the magnitude of the treatment effect. For the primary endpoint the RR was 0·66 (95% CI 0·48–0·91; p=0·011; appendix p 16).

**Discussion**

In the IRONMAN trial, the rate per 100 patient-years of the primary outcome of recurrent hospitalisations for heart failure and cardiovascular death was numerically lower for patients randomly assigned to receive ferric derisomaltose than for those assigned to usual care, although the difference was not statistically significant. Other cardiovascular outcome measures generally favoured ferric derisomaltose, including fewer serious adverse cardiovascular events and improvements at 4 months in overall and physical domain scores of MLHFQ. Intravenous ferric derisomaltose also appeared to be safe and well tolerated, with only one probable infuson-related reaction and no increase in infection-related adverse events compared with usual care. However, neither EQ-5D scores nor exercise capacity improved in the ferric derisomaltose group compared with usual care.

During the COVID-19 pandemic in 2020 and 2021, patient recruitment slowed or ceased. Many patients were not permitted or did not want to attend clinics for research purposes. Therefore, blood tests to detect recurrent iron deficiency and redosing with iron were often impossible. Some patients randomly assigned to receive ferric derisomaltose might not have received enough to maintain iron repletion. Many hospitals introduced daycare intravenous diuretic treatment for decompensated heart failure during the pandemic—events not systematically recorded or included as endpoints in IRONMAN. Although the study was well powered to detect the benefit suggested by previous studies, the power calculations could not account for the dilution of the treatment effect caused by the reduction in redosing during the extended period of the pandemic. To try to reduce the effect of COVID-19 on the trial, a prespecified COVID-19 sensitivity analysis was done, including all patients randomly assigned (91% of the total cohort) around the start of the first UK national lockdown and including all events for a further 6-month follow-up. In this analysis, the rate of the primary endpoint was lower in those assigned to intravenous iron and nominally statistically significant. In a post-hoc analysis in which patients were further censored at 1 year of follow-up to enable closer comparison with the AFFIRM-AHF trial, the magnitude of the treatment effect appeared to be further enhanced.

Most trials of intravenous iron in patients with heart failure have investigated ferric carboxymaltose. To our knowledge, IRONMAN is the first large heart failure trial evaluating ferric derisomaltose, which can be given as a rapid, high-dose infusion. Our results are, in many respects, similar to those of the AFFIRM-AHF trial.
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which included 1108 patients admitted to hospital for heart failure who also had evidence of iron deficiency, and randomly assigned them to intravenous ferric carboxymaltose or placebo.\textsuperscript{10} In AFFIRM-AHF, the RR for the primary endpoint of total heart failure hospital admissions and cardiovascular death at 12 months was 0.79 (95% CI 0.62–1.01; p=0.059), but in a COVID-19 sensitivity analysis, was 0.75 (0.59–0.96; p=0.024).\textsuperscript{10} The relative benefits of intravenous iron appear remarkably similar between the two trials. Although neither AFFIRM-AHF nor IRONMAN met their primary endpoints, the totality of evidence suggests that intravenous administration of iron does reduce hospital admissions for heart failure, although uncertainty persists about a reduction in cardiovascular mortality.\textsuperscript{11} The two trials in combination support the use of intravenous iron in patients with heart failure and iron deficiency.

There are some important differences between IRONMAN and AFFIRM-AHF. Whereas AFFIRM-AHF recruited patients during a hospital admission for heart failure, IRONMAN mostly enrolled outpatients who did not have a recent hospital admission for heart failure. Patients in IRONMAN were at a lower risk of events but were also older than in AFFIRM-AHF, extending our current understanding of the benefits of intravenous iron to a much broader range of patients with heart failure. Follow-up was longer in IRONMAN (median follow-up 2.7 years) compared with AFFIRM-AHF, in which intravenous iron was not given after 24 weeks and follow-up stopped at 12 months.\textsuperscript{10} Therefore, IRONMAN provides important data on the longer-term safety of intravenous ferric derisomaltose, showing no excess of serious adverse events, including infections. In IRONMAN, no biochemical data regarding phosphate concentrations were collected; it is recognised that dosing with ferric carboxymaltose might be associated with biochemically significant hypophosphataemia, although the long-term clinical relevance remains to be elucidated.\textsuperscript{10} No heterogeneity in the effect of treatment on the primary endpoint was observed across prespecified subgroups in IRONMAN. In AFFIRM-AHF, there was a suggestion that patients with ischaemic heart disease obtained greater benefit for the primary endpoint and total hospital admissions for heart failure;\textsuperscript{9} similar results were observed in IRONMAN, but the benefit was not statistically significant. Clarification is required from results of further trials and individual-patient meta-analyses. Finally, the COVID-19 pandemic had a more profound effect on the conduct of the IRONMAN trial, restricting intravenous iron dosing after March, 2020, whereas in AFFIRM-AHF dosing was unaffected.

Previous trials have shown that intravenous iron can improve quality of life when assessed to 24 weeks.\textsuperscript{4,5} In IRONMAN, we also found a statistically significant improvement in quality of life at 4 months when assessed by MLHFQ, but this was not apparent at the 20-month visit. This is likely to have been affected by a reduction in

Table 3: Serious adverse events by Medical Dictionary for Regulatory Activities system organ class and prespecified safety endpoints

<table>
<thead>
<tr>
<th>Prescribed safety endpoints</th>
<th>Deaths due to infection, n (%)</th>
<th>Hospitalisations due to infection, n (rate per 100 patient-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>6 (1%)</td>
<td>175 (34%)</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical and medical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning, and procedural</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General and administration site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasms benign, malignant, and unspecified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are numbers of patients with at least one event in each category. *Hazard ratio (estimated using a Cox proportional hazards model). †Rate ratio (estimated using a negative binomial regression model).

Table 4: Primary and secondary endpoints in the COVID-19 analysis, censoring follow-up on Sept 30, 2020

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Ferric derisomaltose group (n=527)</th>
<th>Usual care group (n=536)</th>
<th>Estimated treatment effect (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death and hospital admission for heart failure, number of events (rate per 100 patient-years)</td>
<td>210 (22.3)</td>
<td>280 (29.3)</td>
<td>0.76 (0.58–1.00)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Secondary endpoints

| Hospital admissions for heart failure, number of events (rate per 100 patient-years) | 163 (17.3) | 218 (22.8) | 0.76 (0.56–1.03) | 0.077 |

| Cardiovascular hospital admission, n (%) | 177 (34%) | 205 (38%) | 0.86 (0.70–1.05) | 0.14 |

| Cardiovascular death or hospital admission for heart failure, n (%) | 127 (24%) | 160 (30%) | 0.80 (0.63–1.01) | 0.055 |

| Cardiovascular death, n (%) | 67 (13%) | 86 (16%) | 0.79 (0.57–1.01) | 0.15 |

| Cardiovascular death or hospital admission for stroke, myocardial infarction, or heart failure, n (%) | 137 (26%) | 175 (33%) | 0.78 (0.62–0.98) | 0.030 |

| All-cause mortality, n (%) | 103 (20%) | 115 (21%) | 0.91 (0.70–1.19) | 0.48 |

| All-cause hospital admission, n (%) | 260 (49%) | 288 (54%) | 0.89 (0.75–1.04) | 0.18 |

| All-cause mortality or all-cause unplanned hospital admission, n (%) | 271 (51%) | 303 (57%) | 0.89 (0.75–1.04) | 0.15 |

All comparisons are of the ferric derisomaltose group with the usual care group. *Rate ratio (estimated using the method of Lin and colleagues). †Hazard ratio (estimated from Cox proportional hazards models).
face-to-face attendance as the trial progressed, resulting in patients not being redosed when necessary. This will have been compounded by some patients in the usual care group receiving intravenous iron. There remains debate as to which clinically available blood tests accurately identify iron deficiency in patients with heart failure. For example, hyperferritinaemia is recognised to associate with chronic inflammatory conditions such as heart failure. IRONMAN used a definition based on transferrin saturation, ferritin, or both—similar but not identical to the criteria used in most previous trials of intravenous iron in heart failure that have been adopted by guidelines. To keep patients iron replete, redosing of intravenous iron was recommended in IRONMAN if ferritin was less than 100 µg/L or transferrin saturation was less than 25%, provided ferritin was less than or equal to 400 µg/L. Recent data suggest that treating to a higher ferritin target of 600–700 µg/L might improve cardiovascular outcomes, at least in patients receiving haemodialysis. These data cannot be extrapolated to patients with heart failure and it remains uncertain as to whether redosing to gain higher ferritin is more efficacious and safe in patients with heart failure.

Trials consistently show that giving intravenous iron to patients with heart failure who are thought to be iron deficient increases mean haemoglobin concentration by about 0·5 g/dL, after adjusting for changes in the control group. To what extent the benefits of iron therapy are extrapolated to patients with heart failure and it remains uncertain as to whether redosing to gain higher ferritin is more efficacious and safe in patients with heart failure.

International heart failure guidelines now recommend screening for iron deficiency. Whereas European Society of Cardiology guidelines suggest consideration of intravenous ferric carboxymaltose for symptomatic patients with recent hospital admission for heart failure to reduce further heart failure admissions, American guidelines currently do not. Data from IRONMAN, showing improvements in outcomes in patients with heart failure and both reduced and mildly reduced ejection fraction with ferric derisomaltose, provide further evidence to support the use of intravenous iron in these patients. Ongoing trials (for example NCT03036462 and the trial by Mentz and colleagues), across a range of ejection fractions, might clarify whether intravenous iron reduces cardiovascular mortality. Randomised trials of patients with heart failure suggest that oral iron might not correct iron deficiency, but these trials were small and relatively short-term. Further trials of oral iron might be considered, but parenteral administration of iron is required to correct iron deficiency rapidly; oral iron, even if well absorbed, will take many months to do so.

For a broad range of patients with heart failure, reduced left ventricular ejection fraction, and either a transferrin saturation less than 20% or serum ferritin less than 100 µg/L, the results of treatment with intravenous administration of ferric derisomaltose in the IRONMAN trial suggest a reduced risk of the primary outcome, recurrent hospital admissions for heart failure and cardiovascular death, providing further evidence of the benefits of correcting iron deficiency in this population.

Contributors
PRK, JGFC, PAK, IBS, ICM, and IF conceived the study idea and acquired the funding, MR and IF did the statistical analysis and directly accessed and verified the underlying data reported in the manuscript. PRK, JGFC, MCP, EAT, and IF contributed to project administration. PRK, MCP, PAK, IBS, FZA, AA-M, FJC, PWXF, FJC, AG], REL, NNI, AJL, PP, RR, and AS contributed to data collection and provision of patients. All authors contributed to data interpretation. PRK and IF wrote the first draft of the manuscript, and all authors reviewed and approved the final version. PRK and IF were responsible for the decision to submit the manuscript. The first draft of this paper was prepared by the first and last authors. It was reviewed by all authors, who made the decision to submit the paper. All authors had access to all the data in the study.

Declarations of interests
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