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The impact of ferric derisomaltose on cardiovascular and non-cardiovascular events in patients with anemia, iron deficiency and heart failure with reduced ejection fraction

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Essential Title Page Information**Title**

The impact of ferric derisomaltose on cardiovascular and non-cardiovascular events in patients with anemia, iron deficiency and heart failure with reduced ejection fraction

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Proposed tweet

Intravenous ferric derisomaltose (FDI) administered in patients with heart failure with a reduced ejection fraction and iron deficiency anemia, has favorable medium-term effects on quality of life and may reduce morbidity and mortality with no evidence of harm

Abstract

Background

In some countries, intravenous (IV) ferric derisomaltose (FDI) is only licensed for treating iron deficiency with anemia. Accordingly, we investigated the effects of intravenous FDI in a subgroup of patients with anemia in the IRONMAN trial.

Method and Results

IRONMAN enrolled patients with heart failure, left ventricular ejection fraction (LVEF) $\leq 45\%$ and iron deficiency (ferritin $< 100 \mu\text{g/L}$ or TSAT $< 20\%$), 771 (68%) of whom had anemia (hemoglobin $< 12 \text{ g/dL}$ for women; $< 13 \text{ g/dL}$ for men). Patients were randomized, open-label, to FDI (n=397) or usual care (n=374) and followed for a median of 2.6 years. The primary endpoint, recurrent hospitalization for heart failure and cardiovascular death, occurred less frequently for those assigned to FDI (rate ratio 0.78 [95% CI 0.61 – 1.01]; $p=0.063$). First-event analysis for cardiovascular death or hospitalization for heart failure, less affected by the COVID pandemic, gave similar results (hazard ratio 0.77 [95% CI 0.62 – 0.96]; $p=0.022$). Patients randomized to FDI reported a better Minnesota Living with Heart Failure quality-of-life, for overall ($p = 0.013$) and physical-domain ($p = 0.00093$) scores at four months.

Conclusion

In patients with iron deficiency anemia and heart failure with reduced LVEF, IV FDI improves quality of life and may reduce cardiovascular events.

Introduction

Iron deficiency is common in patients with heart failure and a reduced left ventricular ejection fraction (LVEF) and when present it is associated with greater impairment of quality

of life and a higher risk of hospitalization for heart failure and cardiovascular death (1-4).

Iron deficiency is more common in patients with co-existent anemia (5).

The IRONMAN (effectiveness of intravenous (IV) iron treatment versus standard care in patients with heart failure and iron deficiency) trial evaluated the impact of repeated doses of IV ferric derisomaltose (FDI) on the composite endpoint of recurrent heart failure hospitalizations and cardiovascular death in a broad range of patients with heart failure, reduced LVEF ($\leq 45\%$) and iron deficiency (6). Patients were excluded if they had hemoglobin below 9.0 g/dL. Men with a hemoglobin up to 14 g/dL and women with hemoglobin up to 13 g/dL could be enrolled, therefore many patients did not have anemia (7).

Overall, FDI reduced the primary endpoint, although this was not statistically significant (rate ratio for the primary analysis 0.82, 95% CI 0.66 – 1.02, $p=0.07$) (8). Given that a sizeable proportion of the trial was conducted during the COVID-19 pandemic, with concerns that recurrent iron deficiency may not have been detected or corrected and noting the pandemic's impact on heart failure hospitalization, a pre-specified COVID-19 sensitivity analysis was performed. This included all patients randomized until 31 March 2020 with follow up censored on 30 September 2020 (see methods), and showed a larger and significant reduction in the primary endpoint with a rate ratio of 0.76 (95% CI 0.58 – 1.00, $p=0.047$) (8).

In some countries, IV FDI is licensed only for the treatment of iron deficiency when accompanied by anemia. Accordingly, we now report the effects of IV FDI in the population of patients with heart failure and iron deficiency anemia in the IRONMAN trial.

Methods

The study design of IRONMAN, a prospective randomized open-label blinded-endpoint (PROBE) event-driven trial, has been described in detail (6,8). Briefly, patients aged 18 years or older, with LVEF $\leq 45\%$ and iron deficiency (ferritin $< 100 \mu\text{g/L}$ and/or TSAT $< 20\%$, provided ferritin $\leq 400 \mu\text{g/L}$) were invited to participate if they had a current or recent (within 6 months) hospitalization for heart failure or elevated natriuretic peptide plasma concentration. The full inclusion and exclusion criteria have been published (6). Patients were randomized to usual care alone (which permitted oral iron at investigators' discretion but not IV iron) or IV FDI, the dose of which was calculated according to patients' weight and hemoglobin to a maximum of 2000 mg per infusion (6). Randomization was stratified by recruitment context and trial site. Follow-up occurred at 4 weeks, 4 months, and then every four months and for patients randomized to IV FDI, further infusion was given if either ferritin was $< 100 \mu\text{g/L}$ or TSAT was $< 25\%$ (provided ferritin $\leq 400 \mu\text{g/L}$). At each study visit, investigators were encouraged to optimize other treatments directed towards heart failure in all patients according to contemporary guidelines. At 4 months and 20 months, the Minnesota Living with Heart Failure (MLHFQ) questionnaire was recorded.

Patients were invited to consent to record linkage to national databases of deaths and hospital discharge summaries (NHS Digital and Public Health Scotland). These were then used to highlight potential events to local investigators so that they could be reviewed and submitted per protocol, thereby maximizing completeness of event recording. All hospitalizations and deaths were adjudicated blindly.

The analyses presented in this manuscript included only those patients who met the World Health Organization (WHO) criteria for anemia at randomization: women with hemoglobin $< 12 \text{ g/dL}$ and men with hemoglobin $< 13 \text{ g/dL}$. The outcomes, assessed on an intention to treat basis, included the primary endpoint (recurrent hospitalization for heart failure and cardiovascular death) and other key secondary endpoints undertaken in the main trial analysis

and ordered as per the original statistical analysis plan (8): hospitalization for heart failure (recurrent events); cardiovascular hospitalization (first event); cardiovascular death or hospitalization for heart failure (first event); cardiovascular death; cardiovascular death or hospitalization for stroke, myocardial infarction or heart failure (first event); all-cause mortality; all-cause mortality or all-cause unplanned hospitalization (first event). Quality of life scores were also evaluated using the overall score and physical domain of MLHFQ at 4 and 20 months, as these were the areas of most interest in the original analysis (8).

Given that a large portion of the trial occurred during the COVID-19 pandemic, in keeping with regulatory guidance (9-11), a pre-specified COVID-19 sensitivity analysis was performed. Here, we present the subgroup results of IRONMAN for the main outcomes for only those patients who were anemic at randomization.

Statistical analysis

All formal analyses included treatment group and recruitment context as covariates. Efficacy analyses were done in the intention to treat population excluding one patient who was inappropriately randomized. The analyses in this subpopulation were not pre-specified and any p values quoted should be considered as exploratory. Recurrent events were analyzed by the method of Lin and colleagues (12) with treatment effects estimated in the form of rate ratios and 95% CIs. Mean frequency functions are displayed using the method of Ghosh and Lin (13). Time-to-first-event outcomes were analyzed using Cox proportional hazards models and hazard ratios, 95% CIs and p-values calculated. Data are displayed graphically using cumulative incidence functions or Kaplan-Meier curves as appropriate. MLHFQ scores at 4 and 20 months were analyzed using analysis of covariance, adjusting for the randomization stratification variable. Patients who died were assigned the worst possible score after death. Multiple imputation methods were used to account for other missing scores.

within each treatment group separately using SAS PROC MI using the regression approach adjusting for the stratification variable. Fifty datasets were generated and results analyzed by ANCOVA within each dataset and results combined using Rubin's rules using the SAS PROC MIANALYZE procedure.

Safety analyses were done for patients assigned to FDI 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.

We conducted a prespecified COVID-19 sensitivity analysis including only patients randomized 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 FDI or last test showing iron repletion.

All analyses used SAS version 9.4 or R version 3.6.1.

Results

Of 1,137 patients randomized, 771 patients (68%) were anemic at baseline and were randomly assigned to receive either IV FDI (n=397) or usual care (n=374). The median duration of follow-up was 2.6 years (interquartile range [IQR] 1.4 – 3.5). Baseline patient characteristics and cardiovascular medications were similar for randomized groups (Table 1). The median age of the patients was 74 (IQR 68 – 80) years and 602 (78%) were men. Most patients were recruited from outpatient clinics (n = 502; 65%) with a raised plasma NT-proBNP or BNP. A further 130 (17%) were enrolled during a hospital admission for heart failure and 139 (18%) had a prior heart failure admission within 6 months. Baseline median

(IQR) hemoglobin was 11.5 (10.8 – 12.2) g/dL, serum ferritin was 48 (28 – 86) μ g/L and TSAT was 14 (9 – 18) %.

Iron treatment

Of the 397 patients randomized to IV FDI, 391 (98%) received at least one dose: 149 patients (38%) received only one infusion, 155 (40%) received two infusions, 59 (15%) received three infusions, and 28 (7%) received between four and nine infusions. Among the 374 participants assigned to usual care, 79 (21%) received IV iron off-protocol, with 55 (15%) receiving one infusion, 19 (5%) receiving two infusions, and five (6%) receiving between three and five infusions.

Primary and secondary endpoints

A total of 253 primary endpoints (25.0 per 100 patient-years) occurred in patients randomized to FDI, compared to 304 endpoints (32.4 per 100 patient-years) in those randomized to usual care, resulting in a rate ratio (RR) of 0.78 (95% confidence interval [CI] 0.61 – 1.01; $p=0.063$; Table 2, Figure 1). In general, secondary clinical outcomes favored patients assigned to FDI (Table 2, Figure 1). When considering the individual components of the primary end point, while there were numerically fewer heart failure hospitalizations and cardiovascular deaths with FDI, neither analysis reached statistical significance.

Cardiovascular hospitalization as a first event was lower and statistically significant in the group receiving FDI compared to usual care (hazard ratio 0.76 [95% CI 0.62 to 0.93]; $p=0.0084$), as was the time to first event of hospitalization for heart failure or cardiovascular death (hazard ratio 0.77 [95% CI 0.62 – 0.96]; $p=0.022$), and the time to first event for

cardiovascular death or hospitalization for myocardial infarction, stroke or heart failure (hazard ratio 0.75 [95% CI 0.61 to 0.93]; $p=0.0091$).

While no statistically significant between treatment difference was seen for all-cause mortality, FDI was associated with a statistically significant reduction in the outcomes of all-cause hospitalization and all-cause mortality or all-cause unplanned hospitalization (Table 2).

Quality of life

At 4 months, patients randomized to receive FDI had better overall quality of life scores (estimated mean difference -5.17 [95% CI -9.25 to -1.09]; $p = 0.013$) and physical domain (-2.94 [95% CI -4.68 to -1.20]; $p = 0.00093$) scores on the MLHFQ compared to those in the usual care group (Table 2). The absolute differences in scores at 20 months was similar to those at 4 months but these did not reach statistical significance.

Hemoglobin and hematological parameters

At follow up visits, TSAT and ferritin measurements were assessed only for patients randomized to FDI. For patients that received at least one dose of FDI, TSAT increased from a median (IQR) of 14 (10 – 18) % at baseline to 27 (21 – 34) % at 4 weeks and 27 (21 – 32) % at 4 months. Serum ferritin increased from a median (IQR) of 49 (28 – 88) $\mu\text{g/L}$ at baseline to 466 (331– 639) $\mu\text{g/L}$ at 4 weeks, and then 301 (207 – 424) $\mu\text{g/L}$ at 4 months. For patients assigned to IV FDI who received at least one dose ($n=391$), hemoglobin levels increased from median (IQR) 11.6 (10.8 – 12.3) g/dL at baseline to 12.3 (11.6 – 13.0) g/dL at 4 weeks and to 12.5 (11.7 – 13.5) g/dL at 4 months. For patients assigned to usual care ($n=374$) the

median (IQR) values were 11.4 g/dL (10.8 – 12.1) at randomization, 11.6 g/dL (10.9 – 12.4) at 4 weeks and 11.9 g/dL (10.9 – 12.7) at 4 months.

Serious adverse events

Patients assigned to FDI experienced significantly fewer serious adverse events (Table 3), primarily driven by fewer heart failure, arrhythmias and acute coronary events, and had no increase in serious adverse events in any system organ class as defined in the Medical Dictionary for Regulatory Activities (Table 3). Of note, FDI did not increase the number of hospital admissions and deaths due to infection. For patients assigned to usual care, there were 82 blood transfusion events (8.7 per 100 patient years) compared to 46 blood transfusion events (4.6 per 100 patient years) in those assigned to ferric derisomaltose (p=0.07).

COVID-19 sensitivity analysis

The predefined COVID-19 sensitivity analyses included 92% of all randomly assigned patients (363 receiving FDI and 350 receiving usual care). The rate ratio for the primary outcome was 0.73 [95% CI 0.53 – 1.01] and not statistically significant (p= 0.054, Table S1), and secondary clinical outcomes again favored patients assigned to FDI.

Discussion

This analysis, evaluating the impact of repeated dosing with IV FDI on patients with anemia, iron deficiency and heart failure with a reduced LVEF, found a reduction in the primary endpoint of recurrent heart failure hospitalization and cardiovascular death. While this did not reach statistical significance it was of similar magnitude to that observed in the main IRONMAN trial (8) and subsequent meta-analyses (4,14) and pre-specified COVID sensitivity analyses. Of note, when the primary composite endpoint was analyzed as a time to first event analysis a stronger effect was identified, possibly because many of these events occurred prior to the COVID pandemic, when patients assigned to FDI were more likely to be iron replete. In addition, there were statistically significant reductions in the risk of cardiovascular hospitalization (24% lower) and the combined endpoint of cardiovascular hospitalization or cardiovascular death (25% lower) with FDI. There were numerically fewer cardiovascular deaths in the FDI arm.

For patients with anemia, the IRONMAN results suggest that IV FDI not only reduces cardiovascular endpoints but also reduces a broader range of outcomes including a 21% reduction in all cause hospitalization and a 19% reduction in the composite endpoint of all-cause hospitalization or all-cause mortality. It is likely that, in patients with heart failure and iron deficiency, those with anemia may be more symptomatic and at higher risk of adverse outcomes. Anemia may also help to identify patients with true iron deficiency. Iron is not just needed for hemoglobin and oxygen carriage and delivery but has many other essential biological roles. These include generation of cellular energy and mitochondrial function, and immunological pathways (15-18). It is plausible that correction of iron deficiency improves the immune function of patients with heart failure and/or makes them more resilient to the

adverse impact of other co-morbidities or illnesses. We also found that a greater increase in haemoglobin was seen in patients receiving FDI and this was apparent as early as 4 weeks. Evidence of specific impact of IV iron on non-cardiovascular endpoints merits further evaluation in future meta-analysis.

In AFFIRM-AHF, which investigated the effects of IV ferric carboxymaltose on recurrent heart failure hospitalization and cardiovascular death in patients randomized pre-discharge after heart failure decompensation, 54.6% were anemic at baseline (according to the WHO definition) (2). In the analysis that included anemic patients the annualized event rate for the primary outcome with ferric carboxymaltose was 68.9 per 100 patient-years as compared to 81.3 in those patients receiving placebo (RR, 0.85, 95% CI, 0.61–1.18) (19). This analysis of the AFFIRM-AHF trial did not report the impact on of ferric carboxymaltose on all cause hospitalization and death (19).

There were fewer cardiovascular deaths in this analysis with FDI as compared with usual care alone, although this did not reach statistical significance. The HEART-FID trial, with over 3,000 patients with heart failure and reduced ejection fraction recently showed a modest impact of ferric carboxymaltose on the hierarchical endpoint of all-cause mortality, heart failure hospitalization and change in 6-minute walk test (20). Of note, the mean baseline TSAT was much higher than seen in either IRONMAN or AFFIRM-AHF (2,8). A non-significant reduction in CV death (14%) was seen with IV iron in HEART-FID (20). A subsequent individual patient meta-analysis of heart failure trials with ferric carboxymaltose, including HEART-FID, showed a significant reduction in the co-primary end point of cardiovascular hospitalization and cardiovascular death (21). Subgroup analysis for this

outcome showed a significant interaction with baseline TSAT level and a trend towards interaction with hemoglobin suggesting that the benefit of IV ferric carboxymaltose was primarily seen in patients with low TSAT or hemoglobin (20). Given these findings it is timely to review the diagnostic criteria used to identify patients with heart failure who might gain most benefit from IV iron. This is likely to focus on patients with reduced TSAT (<20%) and those with lower hemoglobin. Further individual patient meta-analysis, including IRONMAN, will help in this respect and also explore the important question as to whether correction of iron deficiency in patients with heart failure impacts cardiovascular death and whether this is influenced by the presence of anemia.

In this analysis, there was a statistically significant benefit on quality of life assessed by the MLHFQ at 4 months in patients assigned to IV FDI both when considering the total score and specifically the physical domain. The magnitude of improvement in QoL at 20-months was similar to that observed at 4 months although the confidence intervals were wider and statistical significance was lost. This was likely due to the fact that many patients did not report their QoL at 20 months, partly due to disruption in patient-visits during the COVID pandemic. In addition, underdosing with IV iron in the FDI arm, and use of IV iron and more blood transfusions in the usual care arm may have played a role. It is plausible that the open label nature of the IRONMAN trial may have influenced quality of life assessments in favor of the FDI arm, or against the FDI iron arm because more symptomatic patients may have been more likely to have attended study visits and had have their quality of life assessed. In the masked AFFIRM-AHF trial, improvements in quality of life (KCCQ-12 OSS) were seen with IV ferric carboxymaltose at 6, 12 and 24 weeks in the cohort of patients with anemia (2). No statistically significant differences were found beyond 24 weeks, a finding that might reflect trial design; no further iron was given beyond this time point.

Over a median follow-up of 2.6 years, it is reassuring that IV FDI was associated with statistically fewer serious adverse events as compared with usual care alone. There was no excess risk of hospitalization or death due to infection with FDI. Around one fifth of patients assigned to usual care received IV iron outside the protocol and as such this may have reduced the magnitude of benefit of IV FDI in our analyses, which were all performed on an intention to treat basis. Given that in some countries FDI's labelled indications are restricted to patients with iron deficiency anemia (which will include those with heart failure), these findings will help inform clinicians and patients during the shared decision-making process around treatment options.

The results of IRONMAN were inevitably impacted by the COVID-19 pandemic. There were substantial periods of time during the pandemic when research patients were not able to be seen in person (or did not want to attend secondary care institutions) and as such it was impossible to do blood tests to assess iron deficiency or deliver IV iron (8). This will have led to undertreatment within the group assigned to IV FDI and together with use of IV iron in the usual care arm outside the protocol will have almost certainly diluted the magnitude of benefit. Although the COVID-19 sensitivity analyses typically suggested greater reductions in the risk of key cardiovascular endpoints with IV FDI, the reduced number of events in this subpopulation resulted in less statistical power.

There are potential limitations when considering secondary analyses on subpopulations. However, this is still a large cohort (about two thirds of the main trial population) and with a median age of around 74 years and with frequent co-morbidities that are representative of the

demographic of patients seen in routine clinical practice in higher-income countries. A minority of patients were women and the vast majority Caucasian. Randomization in IRONMAN was not stratified by WHO criteria for anemia so we cannot assume the randomized groups within this subgroup analysis are completely balanced, although it is reassuring that there are no apparent major differences in measured characteristics. Whilst the PROBE design could have impacted behavior for patients (particularly with respect to quality of life assessments) and clinicians, the fact that all hospitalizations and deaths were adjudicated blindly is a strength of the trial. Furthermore, it is unlikely when considering the open label design of the trial that the behavior of patients (or clinicians) with respect to the various endpoints will have been influenced by the fact that the patients were anemic, including how patients completed quality of life questionnaires. The consistent suggestions of benefit with IV FDI across a number of 'hard' secondary endpoints (cardiovascular and non-cardiovascular) and on quality of life (assessed at 4-months) are reassuring. IRONMAN only included patients with heart failure and reduced or mildly reduced LVEF and as such data should not be extrapolated to those with values $>45\%$. Few patients in this dataset were receiving an SGLT2 inhibitor at baseline. Given their potential impact on hemoglobin and iron handling (22,23) more data on the interaction between IV iron and this drug class is needed in patients with heart failure. While we do not compare patients with and without anemia in this analysis, we have previously shown that when considering the full IRONMAN trial population, there was not a statistically significant interaction for the primary endpoint between patients without anemia and those with mild or moderate anemia (8).

Conclusion

In a broad range of patients with heart failure with a reduced LVEF and iron deficiency anemia, administration of IV FDI increased hemoglobin, had favorable medium-term effects on quality of life, may have reduced morbidity and mortality and had no evidence of harm

with fewer serious adverse events. As the use of FDI is restricted to iron deficiency anemia in some countries, this analysis may help inform clinicians and patients on the value of administration of IV iron to a group of patients with, on average, poorer quality of life and worse outcomes.

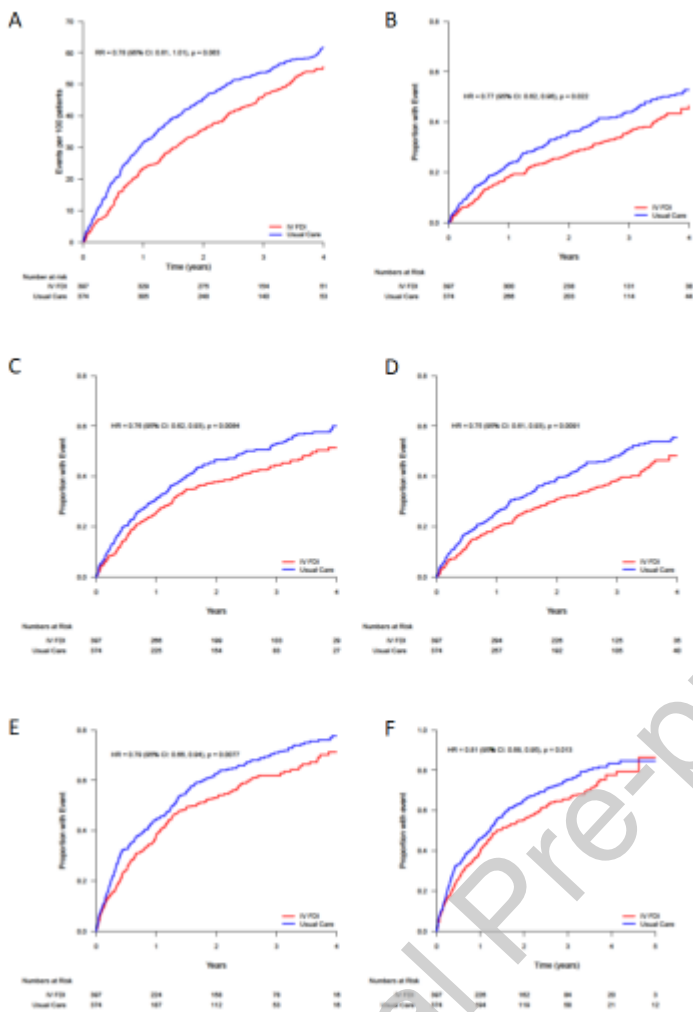
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Figure 1 Estimated mean frequency functions and cumulative incidence curves for key cardiovascular outcomes

- (A) Cumulative events for the primary efficacy end point (cardiovascular death and hospitalizations for heart failure). Recurrent events plotted in the form of mean frequency functions.
- (B) Cardiovascular death or hospitalization for heart failure (first event).
- (C) Cardiovascular hospitalization (first event)
- (D) Cardiovascular death or hospitalization for stroke, myocardial infarction, or heart failure
- (E) All-cause hospitalization (first event).
- (F) All-cause mortality or all-cause unplanned hospitalization (first event).

B, C, D, E and F show cumulative incidence functions, correcting for the competing risk of non-cardiovascular death. The hazard ratios (HR) and rate ratios (RR) are with 95% CIs and were adjusted for the baseline stratification variable of recruitment context (in hospital for heart failure, recent hospital admission for heart failure (within 6 months), or with elevated natriuretic peptide level).



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Table 1: Baseline characteristics of patients with anemia at randomization

Characteristic	Ferric derisomaltose (N=397)	Usual care (N=374)
Age (median (IQR)) — years	74 (68 to 81)	74 (68 to 80)
Male sex — no. (%)	319 (80)	283 (76)
Body-mass index (median (IQR)) – kg/m ²	29 (25 to 33)	28.3 (25 to 33)
Race — no. (%)		
White	356 (90)	343 (92)
Black	10 (3)	5 (1)
Asian	28 (7)	22 (6)
Other	3 (1)	4 (1)
Recruitment context — no. (%)		
Heart failure predischarge	66 (17)	64 (17)
Recent (within 6 months) heart failure in-patient	69 (17)	70 (19)
Outpatient with raised natriuretic peptide level	262 (66)	240 (64)
NYHA functional classification — no. (%)		
II	213 (54)	194 (52)
III	175 (44)	174 (47)
IV	9 (2)	6 (2)
Heart rate (median (IQR)) — beats/min	70 (60 to 80)	69 (61 to 80)
Systolic blood pressure (median (IQR)) — mm Hg	118 (105 to 132)	118 (105 to 132)
Left ventricular ejection fraction (median (IQR)) — %	31 (25 to 37)	35 (26 to 37)
Principal cause of heart failure — no. (%)		
Ischemic	233 (59)	215 (57.5)
Nonischemic	121 (31)	122 (33)
Unknown	43 (11)	37 (10)
Prior Medical history — no. (%)		
Hospitalization for heart failure	238 (60)	222 (59)
De novo hospitalization for heart failure	35 (9)	39 (10)
Atrial fibrillation	201 (51)	170 (46)
Acute coronary syndrome	206 (52)	197 (53)
Hypertension	214 (54)	212 (57)
Diabetes mellitus§	191 (48)	197 (53)
Device therapy — no. (%)		
Implantable cardioverter–defibrillator¶	54 (14)	49 (13)
Cardiac resynchronization therapy	95 (24)	77 (21)
Hemoglobin (median (IQR)) – g/dL	11.6 (10.8 to 12.3)	11.4 (10.8 to 12.1)
Transferrin Saturation (median (IQR)) - %	14 (10 to 18)	14 (9 to 19)
Ferritin (median (IQR)) - µg/L	49 (28 to 88)	47.0 (28 to 82)
TSAT <20%	307 (77)	296 (79)
Estimated glomerular filtration rate (calculated by CKD EPI) (median (IQR)) — ml/min/1.73m ²	50 (37 to 67)	49 (36 to 67)

Table 1. (Continued.)		
Characteristic		
Heart failure medication — no. (%)		
Loop diuretic	328 (83)	317 (85)
Angiotensin-converting enzyme inhibitor (ACEi)	195 (49)	185 (50)
Angiotensin receptor blocker (ARB)	58 (15)	72 (19)
Sacubitril-valsartan	83 (21)	69 (18)
ACEi, ARB or sacubitril-valsartan	331 (83)	322 (86)
Beta-blocker	349 (88)	332 (89)
Mineralocorticoid receptor antagonist	227 (57)	205 (55)
Digoxin	48 (12)	46 (12)
Sodium-glucose cotransporter-2 inhibitor	13 (3)	8 (2)

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Table 2: Primary and secondary endpoints for patients with anemia at randomization

End Point	Ferric derisomaltose (N= 397)	Usual care (N= 374)	Estimated Treatment Effect (95% CI)	P-value
Primary endpoint				
Cardiovascular death and hospitalization for heart failure — no. of events (rate per 100 patient-yr)	253 (25)	304 (32)	0.78 (0.61 to 1.01)*	0.063
Hospitalizations for heart failure — no. of events (rate per 100 patient-yr)	189 (19)	227 (24)	0.78 (0.58 to 1.07)*	0.12
Cardiovascular hospitalization (first event) — no. (%)	177 (45)	202 (54)	0.76 (0.62 to 0.93) †	0.0084
Cardiovascular death or hospitalization for heart failure (first event) — no. (%)	146 (37)	172 (46)	0.77 (0.62 to 0.96) †	0.022
Cardiovascular death — no. (%)	90 (23)	109 (29)	0.77 (0.58 to 1.02) †	0.068
Cardiovascular death or hospitalization for stroke, myocardial infarction, or heart failure (first event) — no. (%)	155 (39)	184 (49)	0.75 (0.61 to 0.93) †	0.0091
All-cause mortality — no. (%)	134 (34)	150 (40)	0.83 (0.66 to 1.05) †	0.13
All-cause hospitalization (first event) — no. (%)	246 (62)	264 (71)	0.79 (0.66 to 0.94) †	0.0077
All-cause mortality or all-cause unplanned hospitalization (first event) — no. (%)	262 (66)	280 (75)	0.81 (0.68 to 0.95) †	0.013
Physical domain of Minnesota Living with heart failure questionnaire at 4 months - least squares mean (SE)	18 (1)	21 (1)	-2.94 (-4.68 to -1.20) ‡	0.00093
Physical domain of Minnesota Living with heart failure questionnaire at 20 months - least squares mean (SE)	20 (1)	22 (1)	-1.90 (-4.07 to 0.26)	0.084
Overall score of Minnesota Living with heart failure questionnaire at 4 months - least squares mean (SE)	37 (1)	42 (2)	-5.17 (-9.25 to -1.09) ‡	0.013
Overall score of Minnesota Living with heart failure questionnaire at 20 months - least squares mean (SE)	42 (2)	46 (2)	-4.22 (-9.31 to 0.86)	0.10

Footnote: SE= standard error, * Rate ratio, † Hazard ratio, ‡ estimated mean difference using multiple imputation and Rubin's rules

Table 3: Serious adverse events tabulated by MedDRA system organ class and preferred term with 95% confidence intervals for differences in percentages. Counts are number of patients with at least one event in each category. Prespecified infection related safety endpoints are also shown.

	Ferric derisomaltose (N=391)	Usual Care (N=374)		
Serious adverse events by system organ class	n (%)	n (%)	Difference (95% CI)	P-value
ALL	291 (74)	305 (82)	-7.13 (-12.97, -1.28)	0.017
Cardiac	143 (37)	173 (46)	-9.68 (-16.64, -2.73)	0.0063
Infections and infestations	101 (26)	107 (29)	-2.78 (-9.09, 3.53)	0.39
Surgical and medical	59 (15)	52 (14)	1.19 (-3.80, 6.17)	0.64
Gastrointestinal	43 (11)	50 (13)	-2.37 (-7.01, 2.27)	0.32
Injury, poisoning and procedural	44 (11)	44 (2)	-0.51 (-5.04, 4.01)	0.82
Respiratory, thoracic and mediastinal	36 (9)	46 (12)	-3.09 (-7.49, 1.30)	0.17
Renal and urinary	43 (11)	49 (13)	-2.10 (-6.72, 2.51)	0.37
General and administration site	43 (11)	36 (10)	1.37 (-2.94, 5.68)	0.53
Nervous system	36 (9)	32 (9)	0.65 (-3.38, 4.68)	0.75
Metabolism and nutrition	27 (7)	36 (10)	-2.72 (-6.63, 1.19)	0.17
Vascular disorders	26 (7)	27 (7)	-0.57 (-4.17, 3.03)	0.76
Neoplasms benign, malignant and unspecified	14 (4)	16 (4)	-0.70 (-3.45, 2.06)	0.62
Musculoskeletal and connective tissue	12 (3)	22 (6)	-2.81 (-5.75, 0.12)	0.06
Prespecified safety endpoints				
Death due to infection	24 (6)	21 (6)	1.09 (0.61, 1.95)*	0.78

	Ferric derisomaltose (N=391)	Usual Care (N=374)		
Serious adverse events by system organ class	n (%)	n (%)	Difference (95% CI)	P-value
Hospitalizations due to infection (first event) — no. (%)	79 (20)	93 (25)	0.77 (0.57, 1.04) *	0.091

*Hazard ratio (estimated using a Cox proportional hazards model). †Rate ratio (estimated using a negative binomial regression model).