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Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial

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Summary

Background Intravenous ferric carboxymaltose has been shown to improve symptoms and quality of life in patients with chronic heart failure and iron deficiency. We aimed to evaluate the effect of ferric carboxymaltose, compared with placebo, on outcomes in patients who were stabilised after an episode of acute heart failure.

Methods AFFIRM-AHF was a multicentre, double-blind, randomised trial done at 121 sites in Europe, South America, and Singapore. Eligible patients were aged 18 years or older, were hospitalised for acute heart failure with concomitant iron deficiency (defined as ferritin <100 µg/L, or 100–299 µg/L with transferrin saturation <20%), and had a left ventricular ejection fraction of less than 50%. Before hospital discharge, participants were randomly assigned (1:1) to receive intravenous ferric carboxymaltose or placebo for up to 24 weeks, dosed according to the extent of iron deficiency. To maintain masking of patients and study personnel, treatments were administered in black syringes by personnel not involved in any study assessments. The primary outcome was a composite of total hospitalisations for heart failure and cardiovascular death up to 52 weeks after randomisation, analysed in all patients who received at least one dose of study treatment and had at least one post-randomisation data point. Secondary outcomes were the composite of total cardiovascular hospitalisations and cardiovascular death; cardiovascular death; total heart failure hospitalisations; time to first heart failure hospitalisation or cardiovascular death; and days lost due to heart failure hospitalisations or cardiovascular death, all evaluated up to 52 weeks after randomisation. Safety was assessed in all patients for whom study treatment was started. A pre-COVID-19 sensitivity analysis on the primary and secondary outcomes was prespecified. This study is registered with ClinicalTrials.gov, NCT02937454, and has now been completed.

Findings Between March 21, 2017, and July 30, 2019, 1525 patients were screened, of whom 1132 patients were randomly assigned to study groups. Study treatment was started in 1110 patients, and 1108 (558 in the carboxymaltose group and 550 in the placebo group) had at least one post-randomisation value. 293 primary events (57·2 per 100 patient-years) occurred in the ferric carboxymaltose group and 372 (72·5 per 100 patient-years) occurred in the placebo group (rate ratio [RR] 0·79, 95% CI 0·62–1·01, p=0·059). 370 total cardiovascular hospitalisations and cardiovascular deaths occurred in the ferric carboxymaltose group and 451 occurred in the placebo group (RR 0·80, 95% CI 0·64–1·00, p=0·050). There was no difference in cardiovascular death between the two groups (77 [14%] of 558 in the ferric carboxymaltose group *vs* 78 [14%] in the placebo group; hazard ratio [HR] 0·96, 95% CI 0·70–1·32, p=0·81). 217 total heart failure hospitalisations occurred in the ferric carboxymaltose group and 294 occurred in the placebo group (RR 0·74; 95% CI 0·58–0·94, p=0·013). The composite of first heart failure hospitalisation or cardiovascular death occurred in 181 (32%) patients in the ferric carboxymaltose group and 209 (38%) in the placebo group (HR 0·80, 95% CI 0·66–0·98, p=0·030). Fewer days were lost due to heart failure hospitalisations and cardiovascular death for patients assigned to ferric carboxymaltose compared with placebo (369 days per 100 patient-years *vs* 548 days per 100 patient-years; RR 0·67, 95% CI 0·47–0·97, p=0·035). Serious adverse events occurred in 250 (45%) of 559 patients in the ferric carboxymaltose group and 282 (51%) of 551 patients in the placebo group.

Interpretation In patients with iron deficiency, a left ventricular ejection fraction of less than 50%, and who were stabilised after an episode of acute heart failure, treatment with ferric carboxymaltose was safe and reduced the risk of heart failure hospitalisations, with no apparent effect on the risk of cardiovascular death.

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Research in context

Evidence before this study

We searched PubMed for articles published in English or with English language abstracts, as well as completed trials recorded in ClinicalTrials.gov, up to Oct 5, 2020, with the medical subject heading terms ("heart failure" AND "iron deficiency" AND "intravenous iron") and either the supplementary term ("mortality") or ("heart failure hospitalisation"). We included only randomised clinical trials with at least 200 participants. The search identified two relevant trials, FAIR-HF and CONFIRM-HF. These two studies neither aimed nor were powered to investigate prospectively the effect of intravenous iron therapy on the risk of heart failure hospitalisations or cardiovascular death in patients with heart failure with reduced left ventricular ejection fraction. An individual patient data meta-analysis that included these two trials showed that treatment with ferric carboxymaltose was associated with a lower rate of recurrent heart failure hospitalisations or cardiovascular mortality in these patients. However, to our knowledge, it has never been prospectively investigated whether this therapy would favourably affect hard outcomes in patients with iron deficiency after admission for acute heart failure. In addition, no data are available concerning the potential impact that the COVID-19 pandemic could have on study outcomes and follow-up in ongoing clinical trials.

Added value of this study

Iron deficiency is highly prevalent (approximately 80%) in acute heart failure and is associated with poor prognosis, irrespective of anaemia status. To our knowledge, AFFIRM-AHF is the first randomised clinical trial to evaluate the effect of intravenous ferric carboxymaltose on morbidity and mortality in patients with iron deficiency after an episode of acute heart failure. It is also one of the first large randomised trials that is reporting outcomes occurring during the COVID-19 pandemic. In 1108 patients hospitalised for acute heart failure and with iron deficiency from 15 countries worldwide, intravenous ferric carboxymaltose was safe and reduced the risk of recurrent heart failure hospitalisations, with no apparent effect on cardiovascular mortality during the 12-month follow-up.

Implications of all the available evidence

The results of the AFFIRM-AHF trial support the recommendation to administer intravenous ferric carboxymaltose in patients hospitalised for acute heart failure with concomitant iron deficiency and with a left ventricular ejection fraction of less than 50%. In ongoing clinical trials, planning a pre-COVID-19 sensitivity analysis would be sensible.

Introduction

Iron deficiency is common in patients with heart failure[1–3] and is associated with exercise intolerance, poor quality of life,[4,5] and increased risk for hospitalisation and mortality,[2,3] regardless of the presence or absence of anaemia. Randomised clinical trials have shown that intravenous ferric carboxymaltose improves symptoms, exercise capacity, and quality of life in ambulatory patients with chronic heart failure and left ventricular ejection fraction of 45% or less who have iron deficiency.[6,7] An individual patient data meta-analysis reported that treatment with ferric carboxymaltose was associated with a lower rate of total heart failure hospitalisations or cardiovascular mortality in these patients.[8] However, it has never been prospectively investigated whether this therapy could favourably affect outcomes in iron-deficient patients after admission for acute heart failure, when risk of rehospitalisation and mortality is high.

Hospitalisations due to acute heart failure represent a growing health-care problem associated with a high risk of adverse clinical outcomes and a large economic burden.[9] Iron deficiency is common in patients with acute heart failure and is associated with poor prognosis.[10,11] Patients with an episode of acute heart failure and concomitant iron deficiency constitute a high-risk target population, in whom treatment of iron deficiency with intravenous iron could translate into a positive effect on outcomes.

AFFIRM-AHF (A Randomised, Double-blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and Mortality in Iron Deficient Subjects Admitted for Acute Heart Failure) was designed to evaluate the effect of intravenous ferric carboxymaltose or placebo initiated shortly before hospital discharge in patients with acute heart failure and iron deficiency on total heart failure hospitalisations and cardiovascular death up to 52 weeks after randomisation.

Methods

Study design

AFFIRM-AHF was a multicentre, randomised, double-blind, placebo-controlled trial done at 121 sites in Europe, South America, and Singapore (appendix pp 3–8). The study design has been published previously.[12] The trial protocol and subsequent amendments and the statistical analysis plan are provided in the appendix (pp 181–607). The protocol and amendments were approved by the institutional review boards at each participating centre. The trial was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and local and national regulations.

Patients

Eligible patients were aged 18 years or older, were hospitalised for acute heart failure (signs or symptoms of acute heart failure and elevated natriuretic peptide levels), treated with at least 40 mg furosemide intravenously (or equivalent), and had a left ventricular

ejection fraction of less than 50%. In addition, eligible patients were iron-deficient, defined as serum ferritin of less than 100 ng/mL, or 100–299 ng/mL with transferrin saturation of less than 20%. The complete list of inclusion and exclusion criteria is provided in the appendix (pp 12–14). Written informed consent was obtained from all patients before any study-related procedures were done.

Randomisation and masking

Eligible patients were randomly assigned (1:1) using a secure, central, interactive, web-based response system, to receive either ferric carboxymaltose or placebo. Randomisation was done using a minimisation algorithm that included a random variable and was stratified by sex, age, heart failure aetiology, duration of heart failure, country, and centre. Because the ferric carboxymaltose solution is a dark brown colloidal solution of nanoparticles and therefore easily distinguishable, unmasked study personnel not involved in any study assessments were responsible for study drug preparation and administration. To maintain patient masking and masking of other site personnel, black syringes and a curtain or similar partition were used. The local laboratory iron and haemoglobin results were viewed only by unmasked study personnel.

Procedures

The first dose of study treatment was administered intravenously shortly before discharge (index hospitalisation) and the second dose was administered at week 6 (visit three). These two doses were considered to be the repletion doses. The baseline and week 6 doses were based on the screening haemoglobin and bodyweight values. The subsequent doses of study treatment (maintenance doses) were given at weeks 12 (visit four) and 24 (visit five), only for patients in whom iron deficiency persisted and for whom haemoglobin was 8–15 g/dL. Further details of the dosing regimen are provided in the appendix (p 15). In addition to the dosing visits, patients were also assessed for efficacy and safety outcomes at weeks 4, 12, 36, and 52, at the outpatient clinic or by telephone if patients were unable to come to the clinic (appendix p 16).

Outcomes

The primary endpoint was a composite of total heart failure hospitalisations and cardiovascular death up to 52 weeks of follow-up. Secondary outcomes were the composite of total cardiovascular hospitalisations and cardiovascular death; cardiovascular death; total heart failure hospitalisations; time to first heart failure hospitalisation or cardiovascular death; and days lost due to heart failure hospitalisations or cardiovascular death, all evaluated up to 52 weeks after randomisation. All hospitalisations, urgent heart failure visits, and deaths were adjudicated blindly by an independent clinical endpoint committee using prespecified criteria. Safety assessments included the occurrence of adverse events (according to the Medical Dictionary for Regulatory Activities), evaluation of blood test results, vital signs, and heart failure signs or symptoms at each visit. Periodic safety monitoring was done by an independent data monitoring committee.

Statistical analysis

Based on previous acute heart failure trial[13] and registry[14] data, a rate of recurrent heart failure hospitalisations or cardiovascular death of 0·7 events per year in the placebo group was anticipated. The dispersion factor used in a negative binomial regression was assumed to be 1. The sample size required to compare two negative binomial rates was calculated using the method of Zhu and Lakkis[15] and PASS-14 software (NCSS, Kaysville, UT, USA). A total of 1000 patients (500 per treatment group) was required to detect a rate ratio of 0·75 for the primary composite endpoint of total heart failure hospitalisations and cardiovascular deaths, with a power of 80% and two-sided α of 0·05. To allow for a 9% loss to follow-up, 1100 patients were planned. Further details are provided in the statistical analysis plan.

The efficacy analysis used the modified intention-to-treat principle and included all randomised patients who received at least one dose of study treatment and for whom at least one data point was known after randomisation until the end of 52 weeks (plus or minus 10 days) of

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See **Online** for appendix

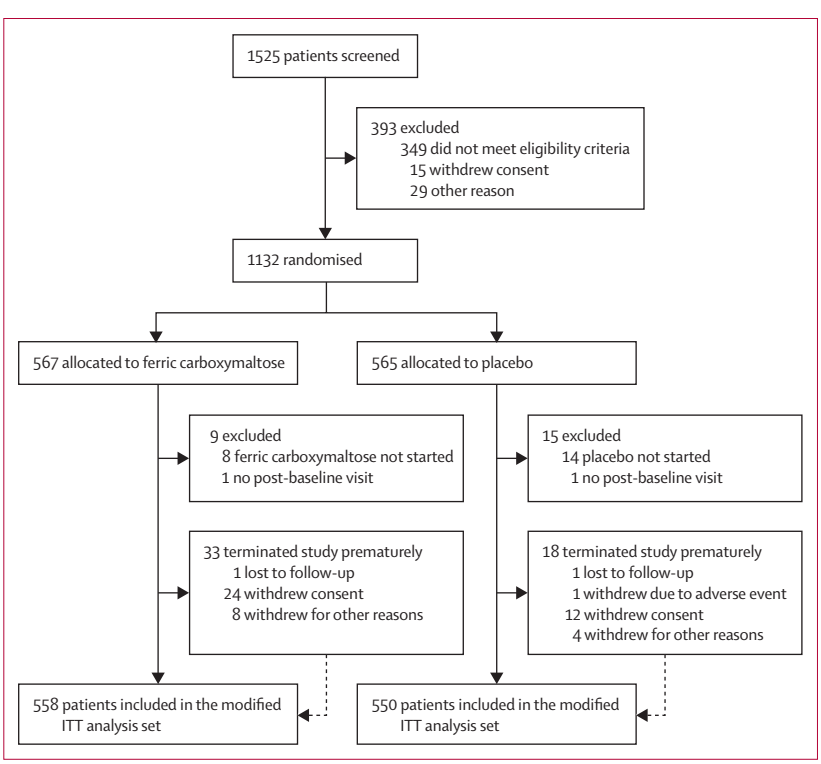

Figure 1: **Trial profile**
ITT=intention-to-treat.

follow-up. The primary outcome (ie, recurrent heart failure hospitalisations and cardiovascular death) was reported as the rate per 100 patient-years by treatment group. The rate ratio (RR; with 95% CI and p value) was analysed using a negative binomial model,[16,17] adjusted for the following covariates: age (<70 years or ≥70 years), cause of heart failure (ischaemic, non-ischaemic, or unknown), heart failure duration (newly diagnosed at index hospitalisation or known documented heart failure before index hospitalisation), and country. For the secondary outcomes of total cardiovascular hospitalisations and cardiovascular death and total heart failure hospitalisations, the same method was used. A sensitivity analysis was done using the joint frailty model to account for the competing risk of death. Cumulative incidence plots were used for both first and recurrent events; the hazard ratio (HR; with 95% CI and p value) was analysed for time to first events, whereas the RR (with 95% CI and p value) was analysed for recurrent events. For the primary outcome, the consistency of the treatment effect among 16 prespecified subgroups was assessed. The safety analysis included all patients for whom study treatment was started.

	Ferric carboxymaltose (n=558)	Placebo (n=550)
Age, years	71·2 (10·8)	70·9 (11·1)
Sex		
Male	314 (56%)	300 (55%)
Female	244 (44%)	250 (45%)
Race		
White	528 (95%)	523 (95%)
Asian	26 (5%)	22 (4%)
Other	4 (1%)	5 (1%)
Comorbidities		
Previous myocardial infarction	229 (41%)	213 (39%)
Previous stroke	53 (9%)	66 (12%)
Previous coronary revascularisation	195 (35%)	206 (37%)
Hypertension	468 (84%)	471 (86%)
Atrial fibrillation or flutter	314 (56%)	305 (55%)
Diabetes	227 (41%)	243 (44%)
Dyslipidaemia	300 (54%)	292 (53%)
Chronic kidney disease	222 (40%)	227 (41%)
Smoking	217 (39%)	202 (37%)
Systolic blood pressure, mm Hg	119·8 (15·2)	119·7 (15·6)
Diastolic blood pressure, mm Hg	72·6 (10·3)	71·9 (9·9)
Heart rate, beats per min	74·5 (13·2)	74·2 (12·8)
Body-mass index, kg/m²	28·1 (5·6)	28·0 (5·7)
NYHA functional class*		
Class I	14 (3%)	8 (1%)
Class II	255 (46%)	240 (44%)
Class III	272 (49%)	277 (50%)
Class IV	16 (3%)	22 (4%)
LVEF†, %	32·6% (9·6)	32·7% (10·0)
LVEF category†		
<25%	104 (19%)	122 (22%)
25–39%	288 (52%)	243 (44%)
40–49%	166 (30%)	184 (33%)
Ischaemic cause of heart failure	265 (47%)	257 (47%)
Previous history of heart failure	405 (73%)	385 (70%)
Device therapy		
Implantable cardioverter-defibrillator	67 (12%)	64 (12%)
Cardiac resynchronisation therapy	33 (6%)	30 (5%)
(Table 1 continues in next column)		
(Continued from previous column)		
Heart failure history		
Newly diagnosed at index hospitalisation	153 (27%)	165 (30%)
Hospitalisation for heart failure in previous 12 months	152 (27%)	153 (28%)
Hospitalisation for heart failure >12 months before index hospitalisation	253 (45%)	232 (42%)
Pharmacotherapy		
Angiotensin converting enzyme inhibitor	293 (53%)	283 (51%)
Angiotensin receptor blocker	97 (17%)	100 (18%)
Angiotensin receptor neprilysin inhibitor	35 (6%)	36 (7%)
Mineralocorticoid receptor antagonist	376 (67%)	352 (64%)
β blocker	453 (81%)	461 (84%)
Digitalis glycosides	83 (15%)	101 (18%)
Loop diuretic	483 (87%)	465 (85%)
Laboratory test results		
NT-proBNP, pg/mL	4743 (2781–8128)	4684 (2785–8695)
BNP, pg/mL	1068 (802–1715)	1204 (803–1955)
Haemoglobin, g/dL	12·3 (1·6)	12·1 (1·6)
Anaemia	292 (52%)	312 (57%)
Ferritin, ng/mL	83·9 (62·2)	88·5 (68·6)
Ferritin <100 ng/mL	408 (73%)	380 (69%)
Transferrin saturation, %	15·2% (8·3)	14·2% (7·5)
Transferrin saturation <20%	457 (82%)	469 (85%)
eGFR <60 mL/min per 1·73 m²	292 (52%)	288 (52%)
Phosphorus, mg/dL	3·65 (0·727)	3·83 (0·975)

Data are mean (SD), n (%), or median (IQR). Percentages might not add to 100% because of rounding. NYHA=New York Heart Association. LVEF=left ventricular ejection fraction. NT-proBNP=N-terminal prohormone of brain natriuretic peptide. BNP=brain natriuretic peptide. eGFR=estimated glomerular filtration rate. *Baseline NYHA data were missing for one patient in the ferric carboxymaltose group and three patients in the placebo group. †LVEF was measured within a maximum of 12 months before randomisation. Baseline LVEF data were missing for one patient in the placebo group.

Table 1: **Baseline characteristics**

The management and follow-up of patients was affected by the COVID-19 pandemic. The impact of COVID-19 cases, related changes in health-care services provided, and the potential consequences of COVID-19 on heart failure epidemiology[18,19] have been acknowledged as a serious and unpredictable threat to the conduct of clinical trials.[20–22] Based on recommendations by the Heart Failure Association of the European Society

	Ferric carboxymaltose (n=558)		Placebo (n=550)		Rate ratio (95% CI)	p value
	Number of events	Rate per 100 patient-years	Number of events	Rate per 100 patient-years		
Modified intention-to-treat analysis						
Total heart failure hospitalisations* and cardiovascular death	293	57·16	372	72·51	0·79 (0·62–1·01)	0·059
Total cardiovascular hospitalisations* and cardiovascular death	370	76·04	451	95·13	0·80 (0·64–1·00)	0·050
Total heart failure hospitalisations*	217	31·72	294	43·15	0·74 (0·58–0·94)	0·013
Days lost due to heart failure hospitalisations and cardiovascular death†	NA	369·00	NA	548·40	0·67 (0·47–0·97)	0·035
COVID-19 sensitivity analysis‡						
Total heart failure hospitalisations* and cardiovascular death	274	55·24	363	73·48	0·75 (0·59–0·96)	0·024
Total cardiovascular hospitalisations* and cardiovascular death	350	75·07	440	97·35	0·77 (0·62–0·97)	0·024
Total heart failure hospitalisations*	202	31·19	287	44·30	0·70 (0·55–0·90)	0·005

NA=not applicable. *Total hospitalisations included first and recurrent events. If a patient was hospitalised for heart failure and died within 24 h of admission or if a patient was hospitalised for a cardiovascular reason and died within 24 h of admission, this was counted as one event. †Number of days lost due to heart failure hospitalisations or cardiovascular death corresponds to the total number of days in hospital for heart failure from randomisation to censoring (follow-up). Days lost due to cardiovascular death is added to the number of days lost due to heart failure hospitalisation. The total number of days lost is divided by the total patient-years of follow-up in each treatment group multiplied by 100. ‡Patients were censored in each country on the date when its first COVID-19 patient was reported in the respective country.

Table 2: **Recurrent event outcomes**

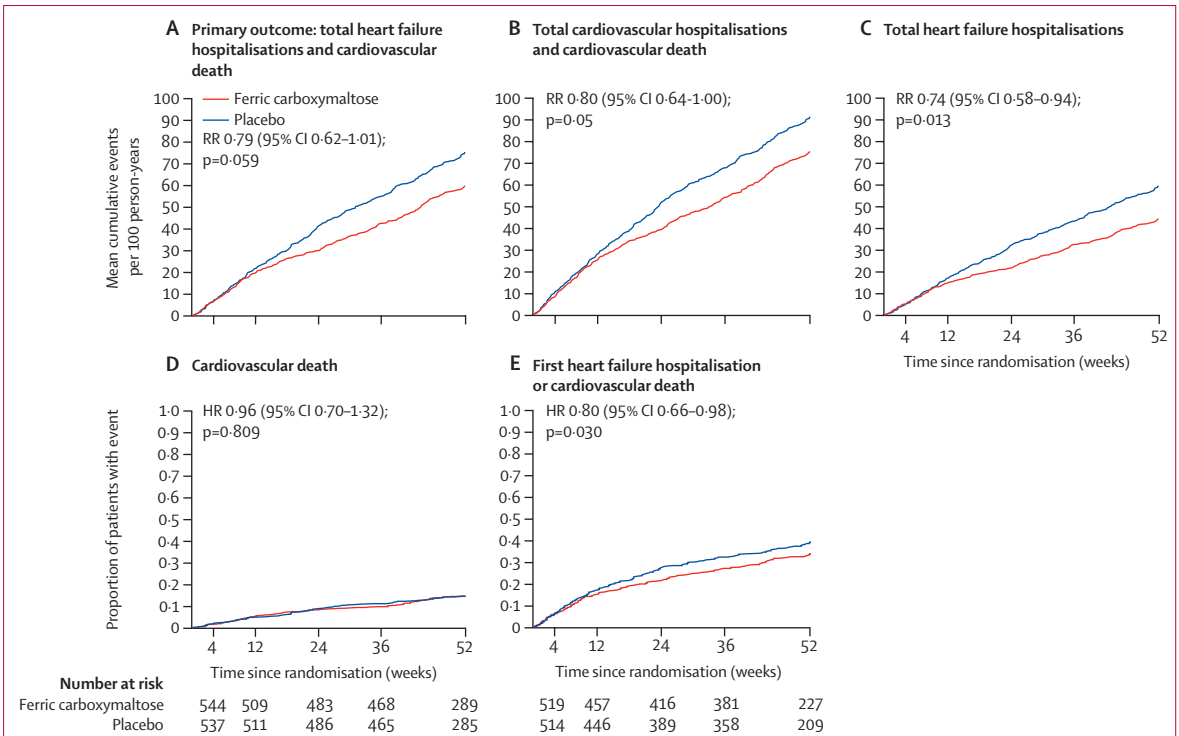

Figure 2: **Primary and secondary outcomes**
RR=rate ratio. HR=hazard ratio.

	Ferric carboxymaltose (n=558)		Placebo (n=550)		Hazard ratio (95% CI)	p value
	Number of events (%)	Rate per 100 patient-years	Number of events (%)	Rate per 100 patient-years		
Modified intention-to-treat analysis						
First heart failure hospitalisation or cardiovascular death	181 (32%)	37·40	209 (38%)	47·10	0·80 (0·66–0·98)	0·030
Cardiovascular death	77 (14%)	15·90	78 (14%)	16·10	0·96 (0·70–1·32)	0·81
COVID-19 sensitivity analysis*						
First heart failure hospitalisation or cardiovascular death	175 (31%)	44·59	205 (37%)	52·20	0·79 (0·65–0·97)	0·023
Cardiovascular death	73 (13%)	16·13	76 (14%)	16·78	0·94 (0·68–1·29)	0·69

*Patients were censored in each country on the date when the first patient with COVID-19 was reported in the respective country.

Table 3: **Time to first event outcomes**

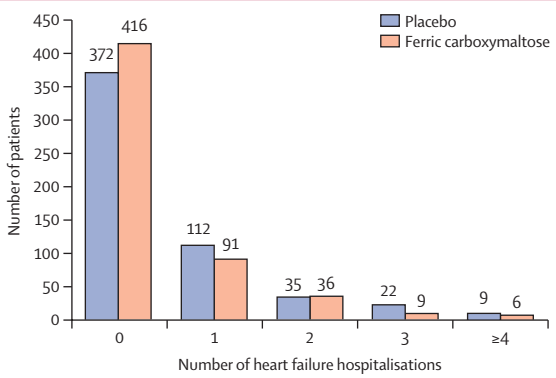

Figure 3: **Distribution of heart failure hospitalisations per patient**

of Cardiology[20] and the European Medicines Agency[21] and the US Food and Drug Administration,[23] the statistical analysis plan included a pre-COVID-19 sensitivity analysis, censoring patients in each country at the date when its first COVID-19 patient was reported. The analyses were prespecified in the statistical analysis plan before locking the database.

An independent data safety monitoring board reviewed the safety data of study participants on a continuing basis. The composition of all AFFIRM-AHF committees is listed in the appendix (pp 9–11). The analyses were done according to the prespecified statistical analysis plan by Cytel (Geneva, Switzerland), and replicated by the sponsor's statistician (VF) and an independent statistician at the University Medical Center Göttingen, Germany (TF). This study is registered with ClinicalTrials.gov, NCT02937454.

Role of the funding source

Vifor Pharma, PP, B-AK, and EAJ participated in the conception and design of the study, collection and assembly of data, data analysis, and data interpretation. All authors had full access to all the study data and accept responsibility for the decision to submit for publication.

Results

Between March 21, 2017, and July 30, 2019, 1525 patients at 121 sites in 15 countries were screened. 1132 patients were randomly assigned to receive either ferric carboxymaltose (n=567) or placebo (n=565). Study treatment was started in 1110 patients and at least one post-randomisation value was available for 1108 patients (figure 1). Patient characteristics and medications at baseline were balanced between treatment groups (table 1). At trial closure (July 24, 2020), fatal and non-fatal outcomes were known for all except 45 patients (27 in the ferric carboxymaltose group and 16 in the placebo group withdrew consent, and one patient in the ferric carboxymaltose group and one patient in the placebo group were lost to follow-up). The distribution of recruitment by country and geographical region is presented in the appendix (p 17).

293 primary events (57·2 per 100 patient-years) occurred in 558 patients in the ferric carboxymaltose group and 372 (72·5 per 100 patient-years) occurred in 550 patients in the placebo group (RR 0·79, 95% CI 0·62–1·01, p=0·059; table 2, figure 2A).

370 total cardiovascular hospitalisations and cardiovascular deaths occurred in the ferric carboxymaltose group and 451 occurred in the placebo group (RR 0·80, 95% CI 0·64–1·00, p=0·050; table 2, figure 2B). 217 total heart failure hospitalisations occurred in the ferric carboxymaltose group and 294 occurred in the placebo group (0·74; 0·58–0·94, p=0·013; table 2, figure 2C). The incidence of cardiovascular death was 77 (14%) of 558 in the ferric carboxymaltose group and 78 (14%) of 550 in the placebo group (HR 0·96, 95% CI 0·70–1·32, p=0·81; table 3, figure 2D). Sensitivity analyses adjusting for the competing risk of cardiovascular death provided similar results (data not shown).

The composite of first heart failure hospitalisation or cardiovascular death occurred in 181 (32%) of 558 patients in the ferric carboxymaltose group and in 209 (38%) of 550 patients in the placebo group (HR 0·80, 95% CI 0·66–0·98, p=0·030; table 3, figure 2E). The frequency distribution of patients

experiencing one or more heart failure hospitalisation is shown in figure 3.

Fewer days were lost due to heart failure hospitalisations and cardiovascular death for patients assigned to ferric carboxymaltose as compared with placebo (369 days per 100 patient-years *vs* 548 days per 100 patient-years; RR 0·67, 95% CI 0·47–0·97, p=0·035; table 2). The effect of ferric carboxymaltose on the primary composite outcome was consistent across prespecified subgroups (figure 4). There were 295 total cardiovascular hospitalisations in the ferric

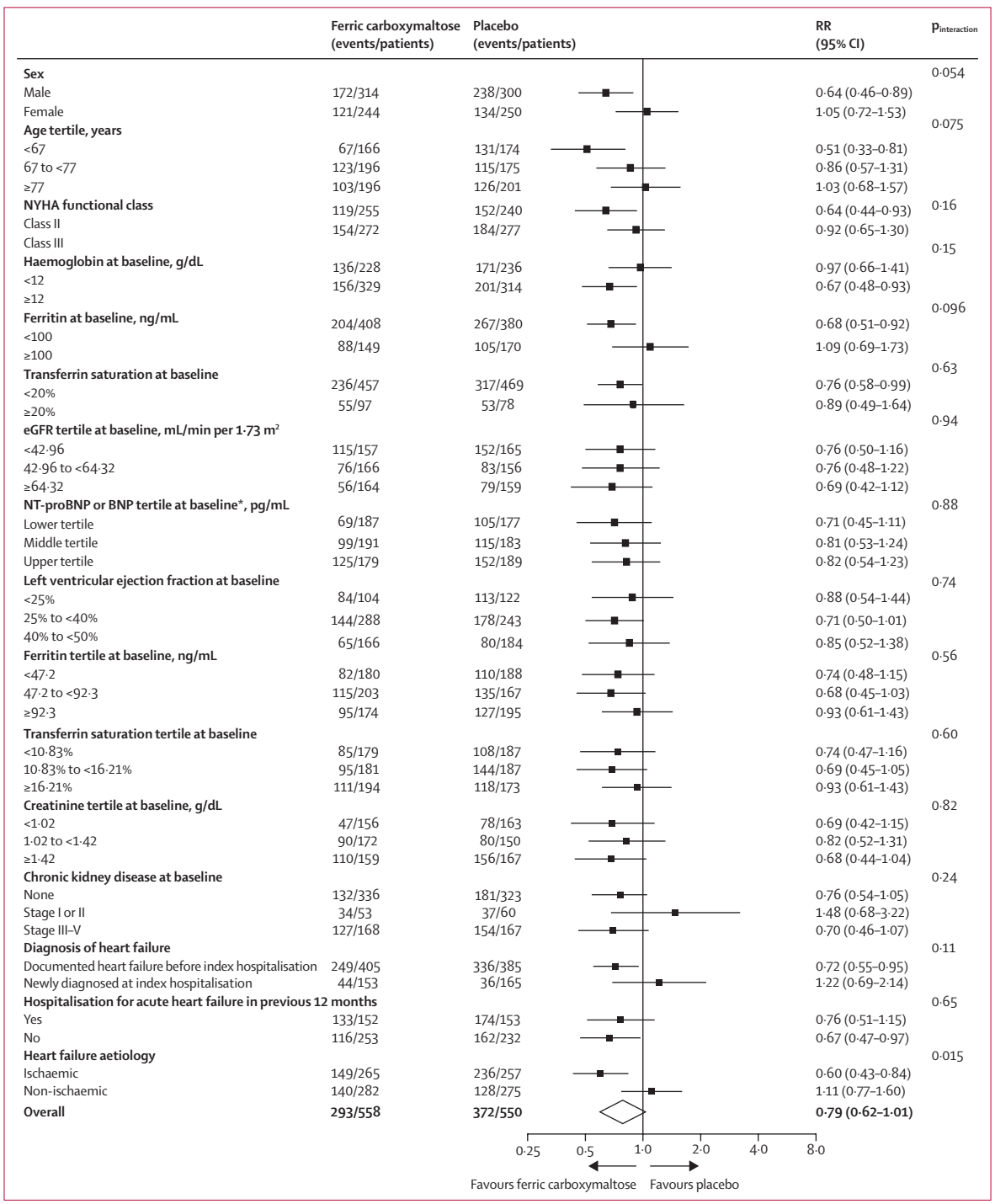

Figure 4: **Forest plot of recurrent heart failure hospitalisations and cardiovascular mortality by subgroup in the modified intention-to-treat population**
BNP=brain natriuretic peptide. eGFR=estimated glomerular filtration rate. NYHA=New York Heart Association. NT-proBNP=N-terminal prohormone of brain natriuretic peptide. RR=rate ratio. *If patients had both measurements at baseline, NT-proBNP was used.

carboxymaltose group and 374 in the placebo group (0·77, 0·62–0·95, p=0·015; appendix p 18).

The overall incidence of investigator-reported adverse events, serious adverse events, and adverse events leading to study discontinuation or drug withdrawal were similar in both groups (appendix p 27). Serious adverse events occurred in 250 (45%) of 559 patients in the ferric carboxymaltose group and 282 (51%) of 551 patients in placebo group. The most frequently reported event category was cardiac disorders; 224 (40%) patients assigned to ferric carboxymaltose experienced 391 cardiac disorder events and 244 (44%) patients assigned to placebo experienced 453 cardiac disorder events. Study treatment was discontinued prematurely for 157 (28%) of 558 patients assigned to ferric carboxymaltose and 160 (29%) of 550 assigned to placebo (modified intention-to-treat population). Throughout the treatment phase (ie, up to week 24), 80% of patients assigned to ferric carboxymaltose received either one or two administrations of study treatment. 53% of patients assigned to placebo received either three or four administrations. The mean total dose of ferric carboxymaltose administered during the trial was 1352 mg (SD 568).

Change from baseline to week 52 in haemoglobin was 0·8 g/dL (SD 1·8) in the ferric carboxymaltose group and 0·3 g/dL (1·7) in the placebo group. Compared with the placebo group, both serum ferritin and transferrin saturation increased in the ferric carboxymaltose group by week 6 and remained significantly higher at week 52 (appendix pp 24–25). At week 6, the mean change from baseline in serum phosphate was –0·2 mg/dL (SD 0·9) in the ferric carboxymaltose and –0·1 mg/dL (1·0) in the placebo group. From week 12 to week 52, the magnitude of change (from baseline) for serum phosphate was similar between the two groups (appendix p 26).

In the pre-COVID-19 sensitivity analysis, 274 primary events (202 heart failure hospitalisations and 73 cardiovascular deaths) occurred in 558 patients in the ferric carboxymaltose group and 363 primary events (287 heart failure hospitalisations and 76 cardiovascular deaths) occurred in 550 patients in the placebo group (RR 0·75, 95% CI 0·59–0·96, p=0·024; table 2, appendix p 19). The secondary outcomes of total cardiovascular hospitalisations and cardiovascular deaths, total heart failure hospitalisations, cardiovascular death, and first heart failure hospitalisation or cardiovascular death are shown in tables 2 and 3 and the appendix (pp 20–23).

Discussion

The findings of AFFIRM-AHF show that, compared with placebo, treatment with ferric carboxymaltose, initiated at hospital discharge in stabilised patients with acute heart failure and concomitant iron deficiency, resulted in an RR for the combined endpoint of total heart failure hospitalisations and cardiovascular death of 0·79 (95% CI 0·62–1·01, p=0·059) which falls just short of conventional 5% statistical significance. The total number of heart failure hospitalisations was significantly lower in the ferric carboxymaltose group compared with the placebo group. Statistically significant treatment benefits of ferric carboxymaltose compared with placebo were seen for the time to first heart failure hospitalisation or cardiovascular death, and for days lost due to heart failure hospitalisation and cardiovascular death. Patients assigned to ferric carboxymaltose received an average total dose of 1352 mg ferric carboxymaltose, up to the maximum treatment period of 24 weeks.

Iron is an essential micronutrient involved in cellular energy and metabolism of both haematopoietic and extrahaematopoietic tissues and is thus critical for maintaining body homoeostasis. Iron deficiency in acute heart failure is characterised by depleted body iron stores accompanied by unmet cellular iron requirements for maintenance of energetic homoeostasis at the periphery, thus impacting negatively on the haematopoietic and non-haematopoietic pathways.[10,24,25] We showed that in this high-risk population of patients with stabilised acute heart failure and concomitant iron deficiency, the total number of heart failure hospitalisations was reduced with ferric carboxymaltose treatment compared with placebo, irrespective of anaemia status (ie, anaemic or non-anaemic), providing further evidence that ferric carboxymaltose benefits patients beyond the correction of anaemia.

Our findings suggest a consistent treatment effect across several predefined subgroups for the primary outcome of total heart failure hospitalisations and cardiovascular death. We note that cause of heart failure could be an effect modifier. This might be a topic for future research, given that non-ischaemic heart failure aetiology comprises a heterogeneous group of patients, in whom the pathophysiological consequences of iron deficiency are not yet well understood.

The AFFIRM-AHF cohort had higher annualised event rates for the combined endpoint of first heart failure hospitalisation or cardiovascular death than in some recently published trials (47·1 per 100 patient-years in the placebo group compared with 40·2 per 100 patient-years in the EVEREST placebo group[26] and 37·3 per 100 patient-years in the ASTRONAUT placebo group[27]). In addition, patients included in this trial (both groups combined) presented with highly elevated plasma NT-proBNP (median 4684 pg/mL compared with 2718 pg/mL in ASTRONAUT[27]). These data suggest that for patients admitted with acute heart failure, the identification and treatment of comorbidities such as iron deficiency should be a routine component of the treatment strategy.

This is one of the first randomised clinical trials reporting results in which data collection, follow-up, and the analyses were potentially affected by the COVID-19 pandemic. The prespecified pre-COVID-19 sensitivity analysis showed a significant benefit of ferric carboxymaltose on the combined endpoint of total heart failure hospitalisations and cardiovascular death. At the

initial outbreak of the COVID-19 pandemic in February to March, 2020, patient follow-up was continuing but all patients had completed their week 24 visit (ie, the last visit for the administration of study treatment in patients in whom iron deficiency persisted). Both patient safety and the potential impact of COVID-19 on the data integrity and completeness of follow-up was discussed in detail between the trial sponsor and steering committee, and several mitigation plans were implemented. For example, patients could be contacted by telephone for the planned study visits instead of returning to the outpatient clinic visit planned by the study protocol. The number of heart failure hospitalisations was reportedly reduced by 40% in Europe between March and June, 2020.[19] We are unable to predict what influence COVID-19 might have had on a treatment effect, but it is plausible that less complete follow-up, fewer hospitalisations, and a general lack of protocol compliance could have diluted the ability to observe treatment differences. Thus, we consider our prespecified COVID-19 sensitivity a judicious analysis.

In patients with iron deficiency, a left ventricular ejection fraction of less than 50%, and who had stabilised after an episode of acute heart failure, treatment with ferric carboxymaltose was safe and reduced the risk of heart failure hospitalisations but had no apparent effect on the risk of cardiovascular death.

Contributors

PP, B-AK, UMG, and EAJ contributed to study design, data collection, and writing of the report. VF and TF contributed to the data analysis. MD, JD, AK, IK, HK, FAM, MMe, DM, JCN, MO, AP, DAP-F, DS, HS, and PvdM contributed to data collection and provision of patients. All authors reviewed the data analyses, contributed to data interpretation and writing of the report, and approved the final version of the submitted report.

Declaration of interests

PP has received research grants and personal fees from Vifor Pharma; and personal fees from Amgen, Bayer, Novartis, Abbott Vascular, Boehringer Ingelheim, Pfizer, Servier, AstraZeneca, Berlin Chemie, Cibiem, Bristol Myers Squibb, and Impulse Dynamics. SDA has received research grants and personal fees from Vifor Int and Abbott Vascular; and personal fees from Bayer, Boehringer Ingelheim, Impulse Dynamics, Novartis, Cardiac Dimensions, Occlutech, and Servier. TM has received personal fees from Vifor Pharma. JD has received research grants from Vifor Pharma. VF, UMG, and KHJ are employees of Vifor Pharma. GF has received personal fees from Servier, Novartis, and Boehringer Ingelheim. AK has received personal fees from Vifor Pharma. FAM has received personal fees from Vifor Pharma, AstraZeneca, and Novartis. MMe has received personal fees from Vifor Pharma, Amgen, AstraZeneca, Abbott Vascular, Bayer, Servier, Edwards Therapeutics, Actelion, LivaNova, and Windtree Therapeutics. DM has received personal fees from Vifor Pharma. JCN has received research grants and personal fees from Vifor Pharma, Bayer, Novartis, and Sanofi; research grants from AstraZeneca, Esperion, CSL Behring, Dalcor, Janssen, and NovoNordisk; and personal fees from Amgen, Daiichi-Sankyo, and Servier. AP has received research grants from Vifor Pharma and Amgen; and research grants and personal fees from Bayer and AstraZeneca. DAP-F has received research grants from Roche Diagnostics, AstraZeneca, and Pfizer; personal fees from Vifor Pharma, Novartis, Servier, Pfizer, AstraZeneca, and Abbot. PvdM has received research grants and personal fees from Vifor Pharma; research grants from AstraZeneca, Ionis, Pfizer, and Corvidia; and personal fees from Novartis and Servier. BSL has received research grants and personal fees from Merck Sharp & Dohme; and personal fees from Vifor Pharma. JC-C has received research grants and personal fees from Vifor Pharma. SvH has received personal fees from Vifor Pharma, Bayer, Boehringer Ingelheim, BRAHMS/ThermoFisher, Grünenthal, Helsinn, Hexal, Novartis, Pharmacosmos, RespiCardia, Roche, and Servier. AC-S has received research grants and personal fees from Menarini; and personal fees from Vifor Pharma, AstraZeneca, Merck, Bayer, We Health, Leo, Boehringer Ingelheim, Sanofi, and Abbott. ND has received research grants and personal fees from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, and Sanofi; and personal fees from Vifor Pharma, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Intercept, Pfizer, Servier, and UCB. WD has received research grants and personal fees from Vifor Pharma; research grants from ZS Pharma; and personal fees from Boehringer Ingelheim, Pfizer, Sphingotec, Bayer, and Medtronic. JB has received personal fees from Vifor Pharma, Abbott, Adrenomed, Amgen, Applied Therapeutics, Array, AstraZeneca, Bayer, Boehringer Ingelheim, CVRx, G3 Pharma, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Sequana Medical, and V-Wave. TF has received personal fees from Vifor Pharma, Novartis, Bayer, Janssen, Roche, Boehringer Ingelheim, Daiichi-Sankyo, Galapagos, Penumbra, Parexel, BiosenseWebster, CSL Behring, Fresenius Kabi, Coherex Medical, and LivaNova. SP has received personal fees from Vifor Pharma. EAJ has received research grants and personal fees from Vifor Pharma; and personal fees from Bayer, Novartis, Abbott, Boehringer Ingelheim, Pfizer, Servier, AstraZeneca, Berlin Chemie, Cardiac Dimensions, Fresenius, and Gedeon Richter. All other authors declare no competing interests.

Data sharing

Data underlying the findings described in this manuscript may be obtained in accordance with Vifor Pharma's data sharing policy. Enquiries can be made to medinfo@viforpharma.com.

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