ESC European Society of Cardiology

European Heart Journal (2023) **44**, 5077–5091
https://doi.org/10.1093/eurheartj/ehad586

FASTTRACK CLINICAL RESEARCH
Heart failure and cardiomyopathies

Efficacy of ferric carboxymaltose in heart failure with iron deficiency: an individual patient data meta-analysis

Piotr Ponikowski [1,2]*, Robert J. Mentz [3,4], Adrian F. Hernandez[4,5], Javed Butler [6,7], Muhammad Shahzeb Khan[8], Dirk J. van Veldhuisen [9], Bernard Roubert[10], Nicole Blackman[11], Tim Friede [12], Ewa A. Jankowska [1,2]†, and Stefan D. Anker [13]†

[1]Institute for Heart Diseases, Wroclaw Medical University, Wroclaw, Poland; [2]Institute for Heart Diseases, University Hospital, Wroclaw, Poland; [3]Division of Cardiology, Department of Medicine, Duke University School of Medicine, Durham, NC, USA; [4]Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA; [5]Department of Medicine, Duke University, Durham, NC, USA; [6]Baylor Scott and White Research Institute, Dallas, TX, USA; [7]Department of Medicine, University of Mississippi, Jackson, MS, USA; [8]Division of Cardiology, Duke University Medical Center, Durham, NC, USA; [9]Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [10]Research, Development, and Sciences, CSL Vifor, Glattbrugg, Switzerland; [11]Quantitative Sciences, American Regent, Inc., Shirley, NY, USA; [12]Department of Medical Statistics and DZHK (German Center for Cardiovascular Research), Partner Site Göttingen, University Medical Center Göttingen, Göttingen, Germany; and [13]Department of Cardiology (CVK) of German Heart Center Charité, Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) Partner Site Berlin, Charité Universitätsmedizin, Berlin, Germany

Received 4 August 2023; revised 23 August 2023; accepted 24 August 2023; online publish-ahead-of-print 26 August 2023

See the editorial comment for this article 'Intravenous iron repletion in heart failure: bridging the gap between symptom relief and hard clinical outcomes', by H. Abu-Own *et al.*, https://doi.org/10.1093/eurheartj/ehad746.

Abstract

Background and Aims Whereas a beneficial effect of intravenous ferric carboxymaltose (FCM) on symptoms and exercise capacity among patients with iron deficiency and heart failure (HF) has been consistently demonstrated, the effects of treatment on clinical events remain the subject of research. This meta-analysis aimed to characterize the effects of FCM therapy on hospitalizations and mortality.

Methods Patient-level data from randomized, placebo-controlled FCM trials including adults with HF and iron deficiency with ≥52 weeks follow-up were analysed. The co-primary efficacy endpoints were (i) composite of total/recurrent cardiovascular hospitalizations and cardiovascular death and (ii) composite of total HF hospitalizations and cardiovascular death, through 52 weeks. Key secondary endpoints included individual composite endpoint components. Event rates were analysed using a negative binomial model. Treatment-emergent adverse events were also examined.

Results Three FCM trials with a total of 4501 patients were included. Ferric carboxymaltose was associated with a significantly reduced risk of co-primary endpoint 1 (rate ratio 0.86; 95% confidence interval 0.75–0.98; $P = .029$; Cochran Q: 0.008), with a trend towards a reduction of co-primary endpoint 2 (rate ratio 0.87; 95% confidence interval 0.75–1.01; $P = .076$; Cochran Q: 0.024). Treatment effects appeared to result from reduced hospitalization rates, not improved survival. Treatment appeared to have a good safety profile and was well tolerated.

Conclusions In iron-deficient patients with HF with reduced left ventricular ejection fraction, intravenous FCM was associated with significantly reduced risk of hospital admissions for HF and cardiovascular causes, with no apparent effect on mortality.

* Corresponding author. Tel and Fax: +48 71 733 11 12, Email: piotr.ponikowski@umw.edu.pl
† The last two authors are joint last authors.

Structured Graphical Abstract

Key Question

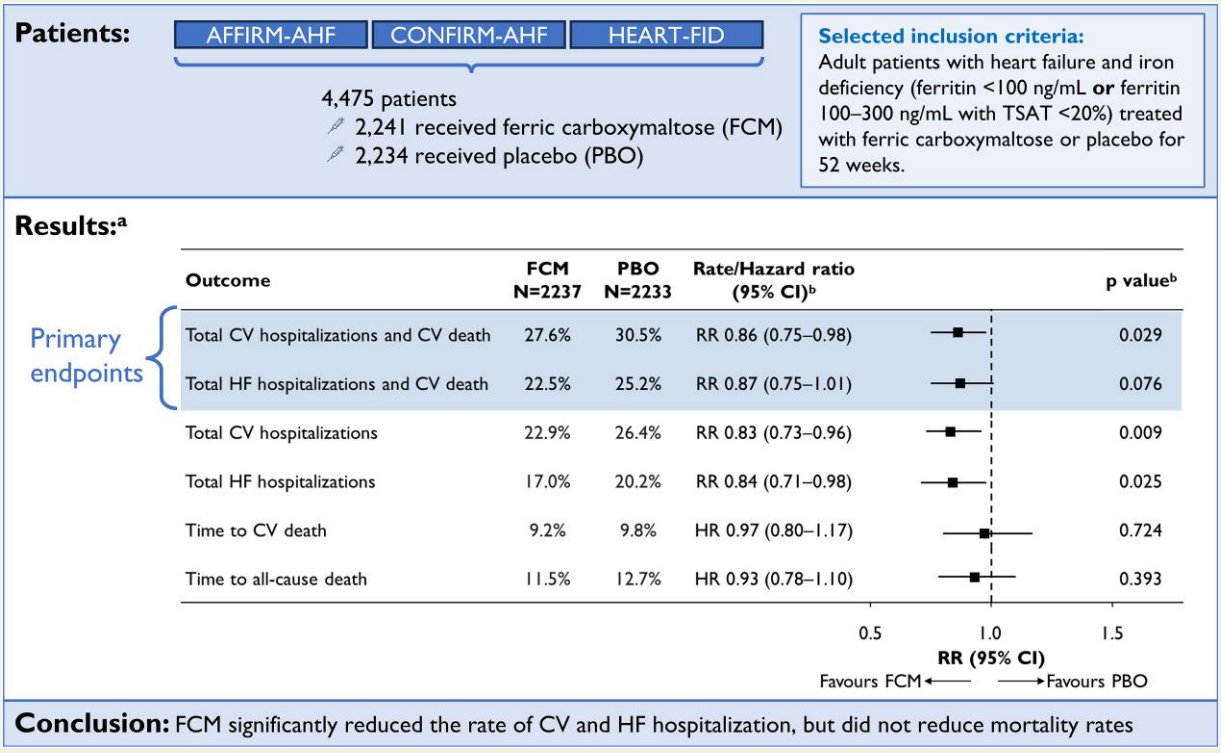
What are the effects of ferric carboxymaltose on clinical events—such as hospitalizations and mortality—over 52 weeks in patients with heart failure and iron deficiency?

Key Finding

Intravenous ferric carboxymaltose was associated with a significantly reduced risk of the composite of cardiovascular death and total cardiovascular hospitalizations and a trend towards a reduction of the composite of cardiovascular death and total heart failure hospitalizations.

Take Home Message

Ferric carboxymaltose reduces the risk of hospital admissions for heart failure and cardiovascular causes in iron-deficient patients with heart failure with reduced left ventricular ejection fraction as shown in pooled analyses of patient-level data from randomized, placebo-controlled trials.



[a]Data are full analysis set. [b]Rate ratios and *P*-values are estimated using a negative binomial model on the number of events, including (fixed covariate) treatment, region, haemoglobin level at baseline, and (random covariate) study. CI, confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure; HR, hazard ratio; PBO, placebo, RR, rate ratio; TSAT, transferrin saturation.

Keywords Heart failure • Acute heart failure • Chronic heart failure • Ferric carboxymaltose • Iron deficiency

Introduction

Iron deficiency (ID) is common in heart failure (HF), with a prevalence of 50%–80%.[1] The presence of ID in HF is associated with reduced exercise capacity, impaired quality of life (QoL), increased hospitalization and rehospitalization rates, and increased mortality.[2–6] Randomized, placebo-controlled trials have consistently demonstrated a beneficial effect of intravenous iron on exercise capacity and QoL in iron-deficient patients with HF and reduced ejection fraction,[7–9] which led to guideline recommendations of intravenous iron administration for improvement of symptoms, exercise capacity, and QoL.[10–13]

Given the size of prior studies and their primary objectives, there has been uncertainty on whether therapy with intravenous iron also reduces the risk of clinical events in HF patients with ID. In the AFFIRM-AHF trial, in 1132 patients hospitalized with acute HF with ejection fraction <50% and ID, treatment with ferric carboxymaltose (FCM) compared with placebo did not demonstrate a significant treatment effect on the primary endpoint of total HF hospitalization and cardiovascular (CV) death [rate ratio (RR) 0.79; 95% confidence interval (CI) 0.62–1.01; $P = .059$].[14] However, FCM therapy was associated with a significant reduction in the risk of total HF hospitalizations (RR 0.74; 95% CI 0.58–0.94; $P = .013$).[14] Similar results were reported in the IRONMAN trial, in which intravenous ferric derisomaltose therapy (used in an open-label fashion) did not significantly reduce the risk of CV death and recurrent HF hospitalizations (RR 0.82; 95% CI 0.66–1.02; $P = .070$).[15] Both trials were affected by the COVID-19 pandemic, and in the prespecified COVID-19 sensitivity analyses, the primary outcome results became statistically significant in both the AFFIRM-AHF

and IRONMAN trials.[14,15] Recently, Mentz[16] published the results of the HEART-FID trial, the largest randomized clinical trial of intravenous iron therapy in the setting of HF to date ($n = 3065$). For the top secondary endpoint, the composite of time to CV death or HF hospitalization over the duration of follow-up, there were fewer events in the FCM group than the placebo group (16.0 vs. 17.3 events per 100 patient-years; 96% CI 0.81–1.06).[16] Of note, there was no apparent statistical difference in HF hospitalizations, but there was a hazard ratio (HR) of 0.86 (96% CI 0.72–1.03) for CV death.

Because of these uncertainties, we conducted a pooled analyses using individual participant data (IPD) from three long-term (with at least 12-month follow-up), placebo-controlled, double-blind randomized clinical trials of FCM therapy in patients with HF and ID.[7,14,16] The use of IPD offers clinical and statistical advantages over a study-level approach to meta-analysis.[17,18]

Methods

We performed a pooled analysis of patient-level data from trials which met the following criteria: (i) adult patients with HF and ID [with the same definition across all three trials: ferritin <100 ng/mL or ferritin 100–300 ng/mL with a transferrin saturation (TSAT) <20%]; (ii) used FCM as an active treatment for ID; (iii) were randomized, double-blind, placebo-controlled trials; (iv) had at least 52 weeks of follow-up; and (v) prospectively recorded clinical outcomes: first and recurrent HF and CV hospitalizations, CV death, and all-cause death. We did not include trials with shorter follow-up periods because they provide limited information on the outcomes of interest.

Three randomized controlled trials met these prespecified criteria: CONFIRM-HF, AFFIRM-AHF, and HEART-FID. The primary results of these studies were published elsewhere.[7,14,16] Individual participant data from all three trials were compiled and provided by CSL Vifor (CONFIRM-HF and AFFIRM-AHF) and American Regent (HEART-FID).

The key characteristics of the prespecified clinical trials are presented in *Table 1*. In brief, the CONFIRM-HF trial included ambulatory HF patients, in New York Heart Association (NYHA) classes II and III and with left ventricular ejection fraction (LVEF) ≤45% and elevated natriuretic peptides[7]; the AFFIRM-AHF trial recruited patients hospitalized for acute HF with LVEF <50%[14]; and the HEART-FID trial enrolled patients with HF and LVEF ≤40% who had recent (within 12 months) hospitalization for HF and/or elevated natriuretic peptides.[16] In each trial, ethics committees approved the trial, and patients provided written informed consent.

To ensure other important trials were not missed, we performed a systematic review of the literature via PubMed (including MEDLINE articles) of randomized controlled clinical trials of FCM therapy in patients with HF and ID published between 19 July 2013 and 18 July 2023 (10 years preceding search date; see online supplementary material). We limited our selection to trials that examined clinical outcomes over at least 52 weeks of follow-up. Although no additional trials of FCM were identified, the IRONMAN trial, a study of ferric derisomaltose therapy, meets some of the above criteria (see Supplementary data online, *Table S1*).[15] To allow for a comprehensive assessment of the long-term effects of intravenous iron therapy on clinical outcomes in patients with HF and ID, we included the results of the IRONMAN trial as a sensitivity analysis (*Figure 1*). Because IPD were not available for this study, it was not included in the primary analysis set. The IRONMAN trial studied patients with HF and LVEF ≤45% who either had current or recent (within 6 months) admission for HF or elevated natriuretic peptides (see Supplementary data online, *Table S2*).[15] Of note, the IRONMAN trial applied a different definition of ID than the FCM trials, namely, serum ferritin <100 ng/mL or TSAT <20%.[15]

Outcomes

The prespecified co-primary efficacy endpoints were (i) a composite of recurrent (total) CV hospitalizations and death for any CV reason (CV death) and (ii) a composite of recurrent (total) HF hospitalizations and CV death. Both endpoints were examined through 52 weeks of follow-up (set with a time window up to 408 days) and based on events adjudicated independently by blinded event committees (see Supplementary data online, *Appendix*). The criteria used for adjudication were prespecified and detailed in an adjudication charter developed for each trial. All three FCM trials used consistent criteria. There is substantial evidence demonstrating that ID is directly involved in multiple pathophysiological pathways across the spectrum of CV disease. Iron deficiency has been previously linked with a risk of thromboatherogenic events.[19] Iron repletion has been shown to improve energy metabolism within skeletal muscles and cardiomyocytes, and, in the PIVOTAL trial, more intense iron supplementation was associated with a reduced risk of both HF hospitalizations and (fatal and non-fatal) myocardial infarctions.[20–22] In order to provide a holistic view of the impact of FCM, we prespecified two equally relevant endpoints, namely, all CV hospitalizations and CV death, and HF hospitalizations and CV death.[19–22]

Table 1 Key characteristics of ferric carboxymaltose trials

	CONFIRM-HF	AFFIRM-AHF	HEART-FID
Randomization	1:1 (FCM:placebo)	1:1 (FCM:placebo)	1:1 (FCM:placebo)
Patients, *n*	150/151	558/550	1532/1533
Centres	Multicentre	Multicentre	Multicentre
Study duration	52 weeks	52 weeks	1.9 years (median)
HF diagnosis and its severity	Ambulatory, optimally treated, systolic CHF with ID, NYHA class II/III	Hospitalization for acute HF, treatment with IV furosemide at a dose of 40 mg, LVEF <50%	Ambulatory, optimally treated, CHF, NYHA classes II–IV, LVEF ≤40% within 24 months or ≤30% within 36 months of screening
Haemoglobin, g/dL	<15	<15	>9.0 and <13.5 (females) or <15.0 (males)
Primary endpoint	Change in 6MWT from baseline to Week 24	Composite of recurrent events of HF hospitalization and cardiovascular death	Composite of death and hospitalization for HF (12 months) and change in 6MWT distance (6 months)

6MWT, 6-min walk test; CHF, chronic heart failure; FCM, ferric carboxymaltose; HF, heart failure; ID, iron deficiency; IV, intravenous; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

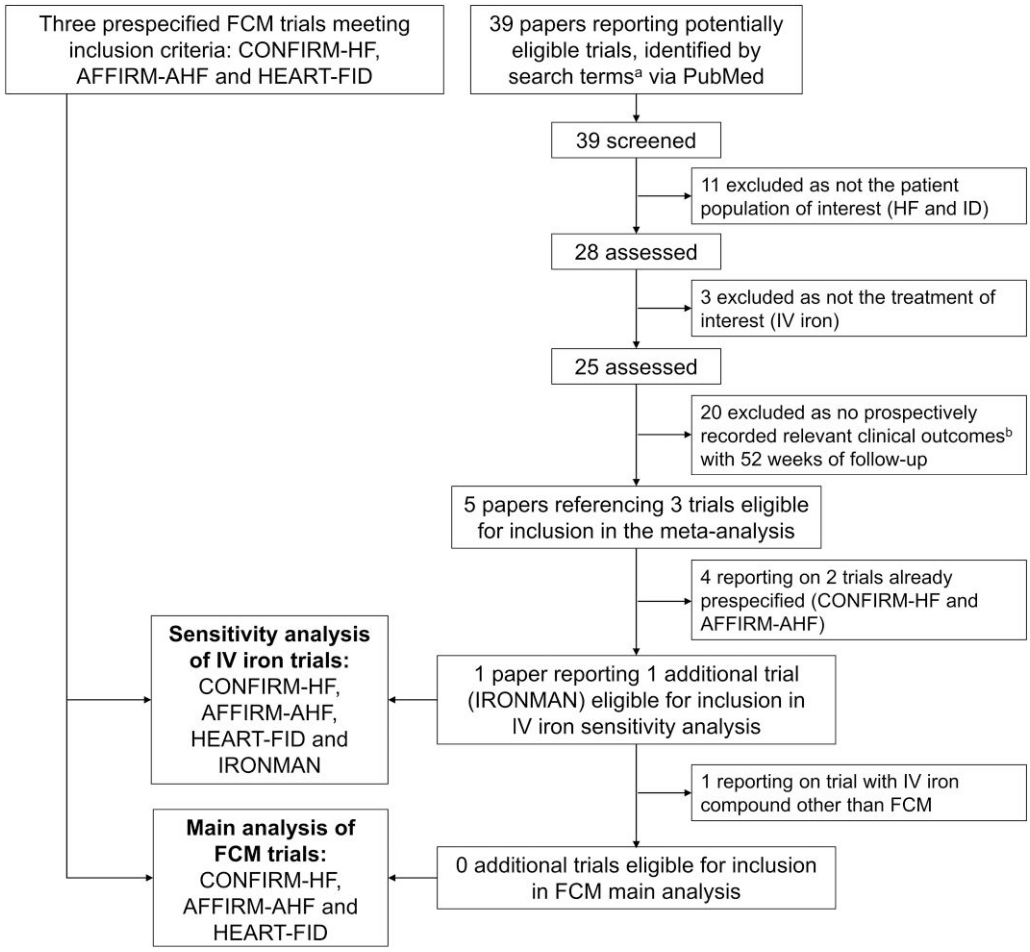


Figure 1 Trial selection. [a]Heart failure AND iron deficiency AND (intravenous iron OR ferric carboxymaltose). [b]First and recurrent heart failure and cardiovascular hospitalizations, cardiovascular death, and all-cause death. CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure; ID, iron deficiency; IV, intravenous.

The key secondary efficacy endpoints were as follows: (i) time to first CV hospitalization or CV death; (ii) time to first HF hospitalization or CV death; (iii) rate of total HF hospitalizations; (iv) time to first HF hospitalization; (v) time to CV death; (vi) time to all-cause death; (vii) total CV hospitalizations; (viii) time to first CV hospitalization; and (ix) total all-cause hospitalization. All secondary endpoints were examined through 52 weeks of follow-up. To characterize the safety of FCM, we examined treatment-emergent adverse events (TEAEs), those events starting or worsening after the first administration of study treatment.

Data analysis

Individual participant data were used for all primary analyses (for the three FCM trials). Efficacy analyses were conducted on the full analysis population defined as all randomly assigned patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment. This mirrors the efficacy populations defined in CONFIRM-HF and AFFIRM-AHF.[7,14] The safety population comprised all randomly assigned patients who received at least one dose of study medication and was used to assess baseline characteristics and analyse the frequency of adverse events.

A negative binomial regression model was used to analyse event rates (including recurrent hospitalizations). The models were adjusted for baseline haemoglobin and region as fixed effects. Study was included as a random effect. The between-trial heterogeneity in the treatment effect was explored by including a treatment by study interaction and a Cochrane *Q* test. Length of observation plus follow-up was logged and included as an offset variable. Rate ratios, associated 95% CIs, and *P*-values were obtained from the model. Forest plots were created for key outcomes to visually explore the heterogeneity of RRs across the trials and to present the summary effect.

The results of time-to-event analyses are presented as HR with 95% CI and associated *P*-values from Cox proportional hazard analyses. The models were adjusted for haemoglobin at baseline and region. To explore between-trial heterogeneity, the study effect was included as a fixed effect.

Subgroup analyses were performed on the primary endpoints of (i) total CV hospitalizations and CV death and (ii) total HF hospitalizations and CV death. Subgroups were created by stratifying patients based on a number of baseline characteristics, including age, sex, HF aetiology, haemoglobin at baseline, serum ferritin at baseline, TSAT at baseline, estimated glomerular filtration rate value at baseline [calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula], and NYHA class. For a *post hoc* subgroup analysis, anaemia was defined as haemoglobin <12 g/dL in women and <13 g/dL in men. Estimates of treatment effect are presented for each subgroup from a model that includes a subgroup by treatment interaction covariate. The *P*-value associated with the test of difference to zero for the coefficient associated with this interaction covariate is also presented. Treatment-emergent adverse events are presented as total number of events and the event rate per 100 patient-years.

We conducted an exploratory analysis to examine the impact of cumulative dose and re-dosing on the treatment effect of FCM. A landmark analysis was run to assess the effect of a re-dosing at 6 months. The landmark time was set at study Day 200 (Day 180 + 2-week window) when the re-dosing of all the subjects who were supposed to be re-dosed should have been completed. For the analysis, subjects who discontinued the study before the landmark time were excluded, and only the events that occurred after study Day 201 were considered. The re-dosing effect was tested between the subjects who received a cumulative dose up to 200 days 1500 mg or less (likely did not receive additional doses) and those with cumulative dose above 1500 mg (re-dosed) and placebo subjects. For the above analyses, a two-sided $P < .05$ was prespecified for overall statistical significance without adjustment for multiple comparisons, and analyses were performed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA). The statistical analysis plan (SAP) is included as Supplementary data online, *Appendix*.

For the sensitivity analyses, we evaluated the effect of intravenous iron therapy (with either FCM or ferric derisomaltose) vs. placebo/usual care on the composite of total HF hospitalizations and CV death. The results of the IRONMAN trial (extracted from the primary publication)[15] were censored at 12 months for consistency with the primary FCM meta-analysis. An additional sensitivity analysis that included the totality of follow-up data available for each of the four trials (median of 2.7 and 1.9 years for IRONMAN[15] and HEART-FID,[16] respectively) was also performed. Reported RRs were converted to the logarithmic scale. Standard errors of the log RR were derived from the reported CIs for the RRs. Following the example of the IRONMAN trial, standardized trial level analyses for the CONFIRM-HF, AFFIRM-AHF, and HEART-FID trials were performed with the semiparametric Lin–Wei–Yang–Ying (LWYY) model,[23] including treatment and region as factors. Whereas analyses of IRONMAN trial data were adjusted for recruitment context (hospital admission or outpatient), such adjustment is not applicable to the FCM trials. Data were combined using the normal–normal hierarchical model for random effects meta-analysis in the Bayesian framework.[24] A uniform prior was used for the treatment effect and a half-normal prior with scale 0.5 for the between-trial heterogeneity tau. The results are summarized by marginal posterior means of the log RR and by marginal posterior medians for tau; both are reported with 95% credible intervals. The Bayesian meta-analyses were performed using the R package bayesmeta.

Results

Study and baseline characteristics

Overall, in the three FCM trials, 4501 patients were randomized to receive either FCM ($n = 2251$) or placebo ($n = 2250$). Study treatment was started in 4475 patients (FCM, $n = 2241$; placebo, $n = 2234$), and at least one post-randomization follow-up data point was available for 4470 patients (FCM, $n = 2237$; placebo, $n = 2233$). Patient characteristics and medication use at baseline appeared balanced between treatment groups (*Table 2*). The total population included 63% males, with mean (SD) age of 69.2 (11.0) years, mean (SD) LVEF of 31.6% (8.1%), and mean (SD) haemoglobin 12.5 (1.5) g/dL. Characteristics were well balanced between the FCM and placebo arms.

Recurrent event efficacy endpoints

Ferric carboxymaltose therapy compared with placebo significantly reduced the co-primary composite endpoint of CV death and total CV hospitalizations (RR 0.86; 95% CI 0.75–0.98; $P = .029$), without evidence of heterogeneity by trial (*Figure 2A*). Similarly, there was a trend towards reduction of the co-primary composite endpoint of CV death and total HF hospitalizations (RR 0.87; 95% CI 0.75–1.01; $P = .076$), without evidence of heterogeneity by trial (*Figure 2B*). A summary of the underlying causes of CV hospitalizations is presented in Supplementary data online, *Table S3*.

Ferric carboxymaltose was associated with a 17% relative rate reduction in total CV hospitalizations (RR 0.83; 95% CI 0.73–0.96; $P = .009$; *Figure 2C*) and a 16% relative rate reduction in total HF hospitalizations (RR 0.84; 95% CI 0.71–0.98; $P = .025$; *Figure 2D*). Ferric carboxymaltose did not impact time to CV death (HR 0.97; 95% CI 0.80–1.17; $P = .72$; *Figure 2E*).

Subgroup analyses

Subgroup analyses examined the effects of FCM therapy on the co-primary endpoints across a number of prespecified subgroups and are summarized in *Figure 3A* (total CV hospitalizations and CV death) and *Figure 3B* (total HF hospitalizations and CV death). Subgroup analyses examining the effects of FCM therapy on CV mortality and all-cause mortality are shown in Supplementary data online, *Figure S1A and B*, respectively.

There was evidence of a significant interaction between TSAT and the composite of CV hospitalization and CV death (interaction $P = .019$) and for CV death (interaction $P = .035$), such that patients in the lowest TSAT tertile (<15%) exhibited a greater treatment effect than those patients with higher baseline TSAT. A similar pattern was observed for the effect of TSAT on total HF hospitalizations and CV death (interaction $P = .095$). Numerically greater treatment effects (i.e. lower RRs) were observed for both co-primary endpoints among patients in the lower haemoglobin tertiles (interaction $P = .099$ for total CV hospitalizations and CV death and interaction $P = .23$ for total HF hospitalizations and CV death). There was also some indication of a potential difference by HF aetiology, indicating more favourable effect of FCM on HF hospitalization and CV death in patients with ischaemic HF aetiology (interaction $P = .08$). Apart from these, the effects of FCM therapy on both primary efficacy endpoints, CV death, and all-cause death were similar across other subgroups examined (*Figure 3*; Supplementary data online, *Figure S1*), and results were generally similar across studies (see Supplementary data online, *Tables S4 and S5*).

Time-to-event efficacy endpoints

Ferric carboxymaltose therapy reduced the time to first CV death or HF hospitalization by 12% (HR 0.88; 95% CI 0.78–0.99; $P = .039$) and the time to first of CV death or CV hospitalization by 11% (HR 0.89; 95% CI 0.80–0.99; $P = .033$). Statistically significant treatment benefits of FCM compared with placebo were also seen for the time to first CV hospitalization (HR 0.85; 95% CI 0.75–0.96; $P = .007$) and time to first HF hospitalization (HR 0.83; 95% CI 0.72–0.95; $P = .006$). There was no significant difference between FCM therapy and placebo for the time to CV death (HR 0.97; 95% CI 0.80–1.17; $P = .724$) and time to all-cause death (HR 0.93; 95% CI 0.78–1.10; $P = .393$) (*Table 3*).

Exploratory analysis

A total of 4089 patients were alive and remained in the trials 6 months after randomization. Of the 2047 patients in the FCM arm, 17% ($n = 357$) received 6-month cumulative FCM doses >1500 mg and had therefore likely received doses beyond the initial dose administered in each trial. Those patients receiving a cumulative FCM dose of no >1500 mg had a risk of CV death or CV hospitalization similar to that of patients receiving placebo (RR 0.95; 95% CI 0.80–1.13; $P = .571$); however, although not reaching statistical significance, the magnitude of treatment effect was greater among those patients who received higher FCM doses and presumably had been re-dosed

Table 2 Baseline demographics and clinical characteristics of ferric carboxymaltose studies (CONFIRM-HF, AFFIRM-AHF, and HEART-FID) (full analysis population)

Baseline characteristics	CONFIRM-HF		AFFIRM-AHF		HEART-FID		Overall	
	FCM ($n = 150$)	PBO ($n = 151$)	FCM ($n = 558$)	PBO ($n = 550$)	FCM ($n = 1529$)	PBO ($n = 1532$)	FCM ($n = 2237$)	PBO ($n = 2233$)
Age, years	68.8 (9.5)	69.5 (9.3)	71.2 (10.8)	70.9 (11.1)	68.6 (10.9)	68.6 (11.2)	69.2 (10.9)	69.2 (11.1)
Sex, *n* (%)								
Male	83 (55)	77 (51)	314 (56)	300 (55)	1023 (67)	1002 (65)	1420 (64)	1379 (62)
Female	67 (45)	74 (49)	244 (44)	250 (45)	506 (33)	530 (35)	817 (37)	854 (38)
Race, *n* (%)								
White	149 (99)	150 (99)	528 (95)	523 (95)	1322 (86)	1324 (86)	1999 (89)	1997 (89)
Black or African American	0 (0)	0 (0)	3 (1)	4 (1)	161 (11)	160 (10)	164 (7)	164 (7)
Asian	0 (0)	1 (1)	26 (5)	22 (4)	19 (1)	21 (1)	45 (2)	44 (2)
Other	1 (1)	0 (0)	1 (<1)	1 (<1)	27 (2)	27 (2)	29 (1)	28 (1)
Co-morbidities, *n* (%)								
Previous myocardial infarction	90 (60)	90 (60)	229 (41)	213 (39)	730 (47)	693 (45)	1049 (52)	996 (50)
Previous stroke	21 (14)	24 (16)	53 (9)	66 (12)	172 (11)	187 (12)	246 (12)	277 (14)
Previous coronary revascularization	46 (31)	39 (26)	195 (35)	206 (37)	746 (49)	723 (47)	987 (48)	968 (48)
Hypertension	130 (87)	130 (86)	468 (84)	471 (86)	1309 (86)	1299 (85)	1907 (88)	1901 (88)
Atrial fibrillation or flutter	66 (44)	73 (48)	314 (56)	305 (55)	676 (44)	664 (43)	1056 (52)	1042 (52)
Diabetes	38 (25)	45 (30)	227 (41)	243 (44)	691 (45)	691 (45)	956 (44)	979 (45)
Dyslipidaemia	98 (65)	98 (65)	300 (54)	292 (53)	991 (65)	988 (65)	1389 (64)	1378 (64)
Smoking	54 (36)	41 (27)	217 (39)	202 (37)	745 (49)	736 (48)	1016 (47)	979 (45)
NYHA classification, *n* (%)								
Class I			14 (3)	8 (1)	2 (<1)	1 (<1)	16 (1)	9 (<1)
Class II	80 (53)	91 (60)	255 (46)	240 (44)	795 (52)	820 (54)	1130 (51)	1151 (52)
Class III	70 (47)	60 (40)	272 (49)	277 (50)	710 (46)	692 (45)	1052 (47)	1029 (46)
Class IV			16 (3)	22 (4)	22 (1)	19 (1)	38 (2)	41 (2)
LVEF, %[a]	40.0 (34.0, 43.0)	39.0 (31.0, 42.0)	34.0 (25.0, 40.0)	35.0 (25.0, 40.0)	33.0 (25.0, 37.0)	32.0 (25.0, 37.0)	33.0 (25.0, 38.0)	33.0 (25.0, 38.0)
Ischaemic HF, *n* (%)	125 (83)	126 (83)	265 (47)	257 (47)	935 (61)	899 (59)	1325 (59)	1282 (57)
Previous history of HF, *n* (%)	150 (100)	151 (100)	405 (73)	385 (70)	1529 (100)	1532 (100)	2084 (93)	2068 (93)

Continued

Table 2 *Continued*

Baseline characteristics	CONFIRM-HF		AFFIRM-AHF		HEART-FID		Overall	
	FCM ($n = 150$)	PBO ($n = 151$)	FCM ($n = 558$)	PBO ($n = 550$)	FCM ($n = 1529$)	PBO ($n = 1532$)	FCM ($n = 2237$)	PBO ($n = 2233$)
Laboratory test results								
NT-proBNP, pg/mL[a]	1453 (476, 2814)	1277 (481, 2929)	4743 (2781, 8128)	4684 (2785, 8695)	1424 (727, 3045)	1424 (710, 2884)	1963 (860, 4254)	1883 (855, 3970)
Hb, g/dL[a]	12.4 (11.4, 13.5)	12.5 (11.4, 13.3)	12.5 (11.1, 13.6)	12.3 (11.0, 13.4)	12.7 (11.7, 13.6)	12.5 (11.6, 13.5)	12.6 (11.5, 13.6)	12.5 (11.4, 13.5)
Anaemia, WHO definition, *n* (%)[b]	79 (52.7)	73 (48.3)	292 (52.4)	312 (56.7)	715 (47.2)	762 (50.1)	1086 (48.9)	1147 (48.4)
Serum ferritin, ng/mL[a]	46.5 (26.9, 78.1)	46.0 (24.9, 78.3)	69.1 (38.7, 104.0)	67.0 (37.4, 117.0)	46.8 (26.6, 71.6)	45.7 (25.0, 71.9)	51.3 (29.0, 79.8)	50.2 (27.7, 82.4)
Serum ferritin <100 ng/mL, *n* (%)	136 (91)	133 (88)	408 (73)	380 (69)	1362 (89)	1353 (88)	1906 (85)	1866 (84)
TSAT, %[a]	17.4 (11.1, 25.3)	17.3 (12.5, 22.4)	13.8 (9.7, 18.1)	13.0 (9.2, 18.0)	23.0 (16.0, 30.0)	22.0 (16.0, 29.0)	19.0 (13.0, 28.0)	19.0 (13.0, 27.0)
TSAT ≤20%, *n* (%)	90 (60)	100 (66)	457 (82)	469 (85)	645 (42)	679 (44)	1192 (53)	1248 (56)
eGFR, mL/min/1.73 m^2[a,c]	69.5 (54.8, 85.8)	64.9 (49.3, 84.1)	53.1 (39.3, 70.6)	52.9 (37.8, 72.8)	57.3 (41.3, 74.1)	59.2 (43.7, 76.5)	57.1 (41.3, 74.1)	58.2 (42.3, 76.0)
eGFR <60 mL/min/1.73 m^2, *n* (%)[c]	54 (36)	65 (43)	292 (52)	288 (52)	797 (52)	749 (49)	1143 (54)	1102 (53)

Data are mean (SD) unless otherwise specified.
eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; FCM, ferric carboxymaltose; Hb, haemoglobin; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; PBO, placebo; SD, standard deviation; TSAT, transferrin saturation; WHO, World Health Organization.
[a]Data are median (upper and lower quartiles).
[b]Defined as <12 g/dL (female) and <13 g/dL (male).
[c]eGFR (CKD-EPI) derived using equations specified in statistical analysis plan (see Supplementary data online, *Appendix* for details).

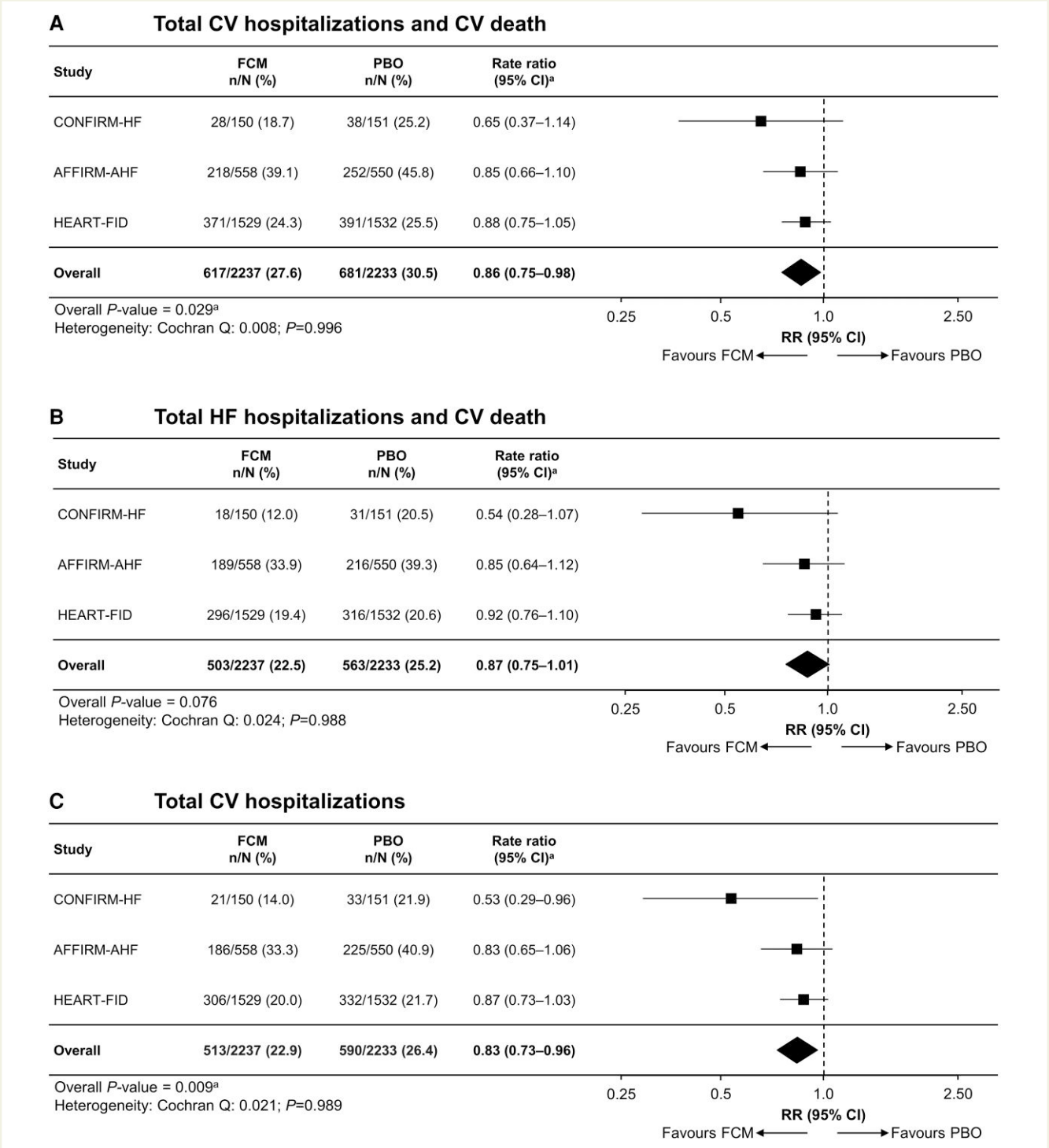


Figure 2 Effect of ferric carboxymaltose vs. placebo on (*A*) total cardiovascular hospitalizations and cardiovascular death, (*B*) total heart failure hospitalizations and cardiovascular death, (*C*) total cardiovascular hospitalizations, (*D*) total heart failure hospitalizations, and (*E*) time to cardiovascular death. [a]Rate ratios and *P*-values are estimated using a negative binomial model on the number of events, including (fixed covariates) treatment, region, haemoglobin level at baseline, and (random covariate) study. [b]The hazard ratio, associated 95% confidence interval, and adjusted Wald *P*-value are from a Cox model fitted with fixed effects of treatment, subgroup, treatment by subgroup, haemoglobin at baseline, region, and a random effect of study, assuming proportional hazards. CI, confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure; PBO, placebo; RR, rate ratio.

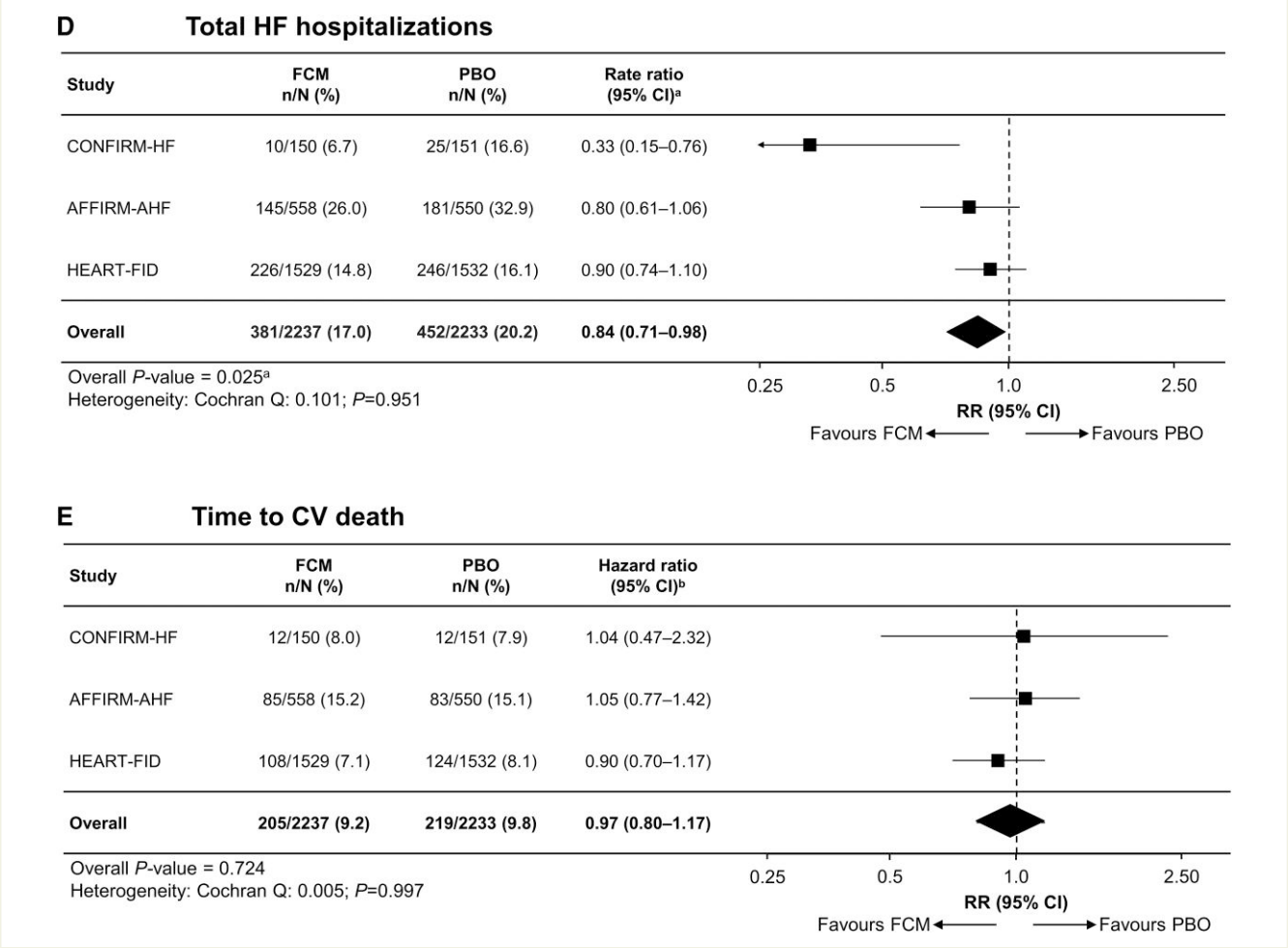


Figure 2 Continued

(RR 0.89; 95% CI 0.64–1.23; $P = .485$) (*Figure 4*). A similar pattern was observed for the endpoint of CV death and HF hospitalization (*Figure 4*).

Safety data

The overall incidences (through Week 52) of investigator-reported serious TEAEs, serious TEAEs leading to death, and serious TEAEs leading to study drug discontinuation were similar in both treatment groups (*Table 4*). No deaths were judged to be the cause of serious treatment-related TEAEs. The rates of serious treatment-emergent infections were 9.9 per 100 patient-years and 9.6 per 100 patient-years in the FCM and placebo groups, respectively.

Sensitivity analyses

Data from the IRONMAN trial ($n = 1063$) were censored at 12 months and incorporated into the FCM data set described above for the composite endpoint of CV death and total hospitalizations for HF. Compared with control (placebo or standard of care), intravenous iron significantly reduced the rates of recurrent HF hospitalizations and CV death at 12 months (RR 0.755; 95% CI 0.529–0.998; tau = 0.16). The forest plot in *Figure 5A* depicts the contribution of each trial as well as the overall estimate for this outcome.

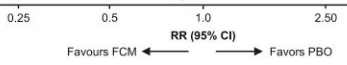
Because both HEART-FID and IRONMAN trials included follow-up periods that extended beyond 1 year, an additional sensitivity analysis was performed to include all available follow-up data. As depicted in *Figure 5B*, the treatment effect associated with intravenous iron was attenuated over the longer follow-up period. Compared with control (placebo or standard of care), intravenous iron reduced the rates of recurrent HF hospitalizations and CV death by 18% (RR 0.822; 95% CI 0.577–1.073; tau = 0.16), although this effect did not reach statistical significance.

Discussion

This study represents the largest pooled analyses using IPD to examine the effects of FCM therapy on clinical outcomes and the first to include the results of the HEART-FID trial. We found that in patients with HF with reduced LVEF and concomitant ID, treatment with intravenous FCM significantly reduced the rate of the composite of CV death and CV hospitalization during 12-month follow-up. There was also a trend towards reduction of the rate of composite of CV death and total HF hospitalizations during 12-month follow-up, which narrowly missed the prespecified level of statistical significance (*Structured Graphical Abstract*). Rate reductions in the primary composite endpoints were mainly driven by treatment effect on HF hospitalizations and CV

A Total CV hospitalizations and CV death

		FCM n/N (%)	PBO n/N (%)	RR (95% CI)[b]	*P*-value[b]	*P*-int
Age, years	<66	209/766 (27.3)	229/784 (29.2)	0.83 (0.66–1.05)	0.114	
	≥66 and <75	187/737 (25.4)	219/706 (31.0)	0.77 (0.61–0.99)	0.038[a]	0.355
	≥75	221/734 (30.1)	233/743 (31.4)	0.99 (0.78–1.25)	0.901	
HF aetiology	Non-ischaemic	222/819 (27.1)	241/868 (27.8)	0.96 (0.77–1.20)	0.745	0.209
	Ischaemic	373/1325 (28.2)	418/1282 (32.6)	0.81 (0.68–0.96)	0.015[a]	
TSAT, %	<20	380/1140 (33.3)	456/1183 (38.5)	0.80 (0.67–0.95)	0.012[a]	0.100
	≥20	232/1079 (21.5)	215/1032 (20.8)	1.00 (0.81–1.23)	0.989	
TSAT, %	<15	222/678 (32.7)	292/697 (41.9)	0.72 (0.57–0.91)	0.006[a]	
	≥15 and <24	216/739 (29.2)	244/790 (30.9)	0.87 (0.69–1.09)	0.223	0.019[a]
	≥24	173/802 (21.6)	135/728 (18.5)	1.17 (0.91–1.50)	0.213	
eGFR, mL/min/1.73 m²	<47.5	251/723 (34.7)	261/677 (38.6)	0.81 (0.65–1.02)	0.071	
	≥47.5 and <68.3	184/700 (26.3)	187/699 (26.8)	0.94 (0.74–1.20)	0.619	0.525
	≥68.3	129/682 (18.9)	165/720 (22.9)	0.77 (0.60–1.00)	0.053	
Haemoglobin, g/dL	<11.9	217/729 (29.8)	271/750 (36.1)	0.73 (0.58–0.92)	0.007[a]	
	≥11.9 and <13.2	195/690 (28.3)	221/752 (29.4)	0.83 (0.65–1.05)	0.122	0.099
	≥13.2	201/803 (25.0)	185/720 (25.7)	1.04 (0.82–1.32)	0.729	
Anaemia, WHO definition[c]	Yes	333/1086 (30.7)	406/1147 (35.4)	0.77 (0.64–0.93)	0.007[a]	0.110
	No	280/1136 (24.6)	271/1075 (25.2)	0.97 (0.79–1.18)	0.725	
NYHA functional class	≤class II	286/1146 (25.0)	319/1160 (27.5)	0.83 (0.68–1.00)	0.052	0.919
	≥class III	331/1090 (30.4)	362/1070 (33.8)	0.84 (0.69–1.02)	0.073	
Ferritin, ng/mL	<100	513/1906 (26.9)	546/1866 (29.3)	0.84 (0.73–0.98)	0.025[a]	0.501
	≥100	100/318 (31.4)	132/361 (36.6)	0.96 (0.68–1.35)	0.807	
Sex	Male	421/1420 (29.6)	481/1379 (34.9)	0.85 (0.72–1.01)	0.061	0.818
	Female	196/817 (24.0)	200/854 (23.4)	0.88 (0.70–1.11)	0.293	
Hospitalization for HF in the prior year	Yes	290/929 (31.2)	329/902 (36.5)	0.83 (0.68–1.01)	0.064	0.759
	No	256/1005 (25.5)	275/1015 (27.1)	0.87 (0.71–1.06)	0.171	
Overall		**617/2237 (27.6)**	**681/2233 (30.5)**	**0.86 (0.75–0.98)**	**0.029[a]**	



B Total HF hospitalizations and CV death

		FCM n/N (%)	PBO n/N (%)	RR (95% CI)[b]	*P*-value[b]	*P*-int
Age, years	<66	165/766 (21.5)	186/784 (23.7)	0.86 (0.66–1.11)	0.233	
	≥66 and <75	153/737 (20.8)	172/706 (24.4)	0.80 (0.61–1.04)	0.099	0.589
	≥75	185/734 (25.2)	205/743 (27.6)	0.97 (0.74–1.26)	0.807	
HF aetiology	Non-ischaemic	194/819 (23.7)	203/868 (23.4)	1.04 (0.81–1.32)	0.771	0.081
	Ischaemic	292/1325 (22.0)	342/1282 (26.7)	0.78 (0.64–0.96)	0.016[a]	
TSAT, %	<20	320/1140 (28.1)	390/1183 (33.0)	0.82 (0.67–1.00)	0.046[a]	0.205
	≥20	177/1079 (16.4)	165/1032 (16.0)	1.00 (0.79–1.26)	0.980	
TSAT, %	<15	186/678 (27.4)	251/697 (36.0)	0.74 (0.57–0.96)	0.021[a]	
	≥15 and <24	178/739 (24.1)	205/790 (25.9)	0.91 (0.71–1.17)	0.468	0.095
	≥24	133/802 (16.6)	99/728 (13.6)	1.12 (0.85–1.49)	0.412	
eGFR, mL/min/1.73 m²	<47.5	217/723 (30.0)	231/677 (34.1)	0.84 (0.65–1.08)	0.176	
	≥47.5 and <68.3	135/700 (19.3)	149/699 (21.3)	0.86 (0.65–1.13)	0.270	0.936
	≥68.3	103/682 (15.1)	124/720 (17.2)	0.90 (0.67–1.21)	0.493	
Haemoglobin, g/dL	<11.9	194/729 (26.6)	243/750 (32.4)	0.75 (0.58–0.97)	0.030[a]	
	≥11.9 and <13.2	156/690 (22.6)	176/752 (23.4)	0.85 (0.65–1.11)	0.230	0.232
	≥13.2	149/803 (18.6)	140/720 (19.4)	1.04 (0.79–1.37)	0.770	
Anaemia, WHO definition[c]	Yes	291/1086 (26.8)	352/1147 (30.7)	0.80 (0.65–0.98)	0.031[a]	0.226
	No	208/1136 (18.3)	207/1075 (19.3)	0.96 (0.77–1.21)	0.741	
NYHA functional class	≤class II	226/1146 (19.7)	258/1160 (22.2)	0.83 (0.67–1.03)	0.092	0.846
	≥class III	277/1090 (25.4)	305/1070 (28.5)	0.86 (0.69–1.06)	0.156	
Ferritin, ng/mL	<100	413/1906 (21.7)	440/1866 (23.6)	0.86 (0.73–1.01)	0.071	0.590
	≥100	86/318 (27.0)	120/361 (33.2)	0.96 (0.66–1.40)	0.838	
Sex	Male	339/1420 (23.9)	396/1379 (28.7)	0.88 (0.73–1.06)	0.167	0.940
	Female	164/817 (20.1)	167/854 (19.6)	0.87 (0.67–1.12)	0.281	
Hospitalization for HF in the prior year	Yes	253/929 (27.2)	285/902 (31.6)	0.88 (0.71–1.09)	0.229	0.768
	No	198/1005 (19.7)	217/1015 (21.4)	0.84 (0.66–1.05)	0.126	
Overall		**503/2237 (22.5)**	**563/2233 (25.2)**	**0.87 (0.75–1.01)**	**0.076**	

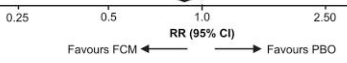


Figure 3 Subgroup analyses for (*A*) total cardiovascular hospitalizations and cardiovascular death and (*B*) total heart failure hospitalizations and cardiovascular death. [a]Significant difference at 5% significance level. [b]Rate ratio and *P*-value are estimated using a negative binomial model on the number of events, including (fixed covariates) treatment, region, haemoglobin level at baseline (where applicable), interaction between subgroup and treatment, and (random covariate) study. [c]Defined as <12 g/dL (female) and <13 g/dL (male). CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FCM, ferric carboxymaltose; HF, heart failure; int, interaction; NYHA, New York Heart Association; PBO, placebo; RR, rate ratio; TSAT, transferrin saturation; WHO, World Health Organization.

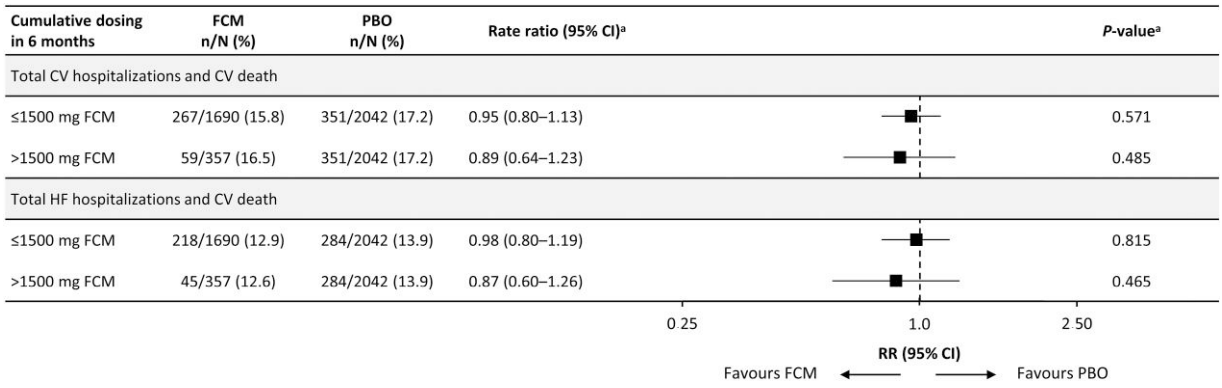


Figure 4 Landmark analysis examining the impact of cumulative dosing during the first 6 months of follow-up on event rates after 6 months. [a]Rate ratio and *P*-value are estimated using a negative binomial model on the number of events, including (fixed covariates) treatment, region, haemoglobin level at baseline (where applicable), and interaction between subgroup and treatment. Population restricted to patients alive at 6 months. Landmark time at 6 months was set to 200 days. CI, confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; PBO, placebo; RR, rate ratio.

Table 3 Secondary endpoints from pooled ferric carboxymaltose studies (CONFIRM-HF, AFFIRM-AHF, and HEART-FID)

	FCM *n* = 2237	PBO *n* = 2233	HR or RR (95% CI)	*P*-value
Time to first CV death and HF hospitalization	503 (22.5)	563 (25.2)	HR 0.88 (0.78–0.99)[a]	.039[a]
Time to first CV death and CV hospitalization	617 (27.6)	681 (30.5)	HR 0.89 (0.80–0.99)[a]	.033[a]
Total HF hospitalizations, *n*	604	734	RR 0.84 (0.71–0.98)[b]	.025[b]
Time to first HF hospitalization	381 (17.0)	452 (20.2)	HR 0.83 (0.72–0.95)[a]	.006[a]
Time to CV death	205 (9.2)	219 (9.8)	HR 0.97 (0.80–1.17)[a]	.724[a]
Time to all-cause death	257 (11.5)	284 (12.7)	HR 0.93 (0.78–1.10)[a]	.393[a]
Total CV hospitalizations, *n*	852	1015	RR 0.83 (0.73–0.96)[b]	.009[b]
Time to first CV hospitalization	513 (22.9)	590 (26.4)	HR 0.85 (0.75–0.96)[a]	.007[a]
Total all-cause hospitalizations, *n*	997	1138	RR 0.87 (0.76–0.99)[b]	.029[b]

Data are *n* (%) unless stated otherwise.
CI, confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure; HR, hazard ratio; PBO, placebo; RR, rate ratio.
[a]Hazard ratio, associated 95% CI, and adjusted Wald *P*-value are from a Cox model fitted with fixed effects of treatment, haemoglobin at baseline, region, and a random effect of study, assuming proportional hazards.
[b]Rate ratio, associated 95% CI, and *P*-value are estimated using a negative binomial model on the number of events, including (fixed covariates) treatment, region, haemoglobin level at baseline, and (random covariate) study.

hospitalizations, with no apparent effect on CV or all-cause mortality. Treatment appeared to be safe and well tolerated. With such a large population ($n > 4500$) across a wide spectrum of CV risk and no evidence of heterogeneity by trial for any of studied endpoints, intravenous administration of FCM in iron-deficient patients with HF with reduced LVEF should be considered to reduce the risk of hospital admissions for HF and CV causes.

This analysis also addresses some previous controversies related to the efficacy of FCM in specific patient subgroups. In brief, we found no evidence for the heterogeneity of treatment effects by sex, age, and baseline serum ferritin, all of which earlier remained controversial based on subgroup analyses from either individual trials or previous meta-analyses.[14,15,25,26] Thus, we conclude that FCM exerts favourable effects on the clinical outcomes across a number of key subgroups, which is in agreement with previous reports.[27,28] It is worthy to note that we found some indication of a potential heterogeneity by HF aetiology, indicating that patients with ischaemic HF aetiology tended to demonstrate greater benefits of FCM therapy regarding the reduction in HF hospitalization and CV death. This intriguing observation has already been noted in the AFFIRM-AHF study[25] and requires further investigations in prospectively designed studies, with robust definition of HF underlying aetiology.

The use of ferritin and TSAT cut-offs (ferritin <100 ng/mL or ferritin 100–300 ng/mL with a TSAT <20%) to define ID has a long history[29] and has generally predicted a positive response to FCM on symptomatic measures. Their predictive value for treatment effects as assessed by hospitalizations and mortality is less clear. In a meta-analysis of IPD that included a smaller population and studies with shorter follow-up duration, Anker *et al.*[26] reported that lower baseline TSAT levels may

Table 4 Safety data

	FCM ($n = 2241$)		Placebo ($n = 2234$)	
	***n* (%) [*E*]**	**Per 100 PY incidence [events]**	***n* (%) [*E*]**	**Per 100 PY incidence [events]**
Any serious TEAE	678 (30.3) [1410]	30.3 [63.1]	706 (31.6) [1465]	31.7 [65.9]
Any serious treatment-related TEAE	6 (0.3) [11]	0.3 [0.5]	3 (0.1) [3]	0.1 [0.1]
Any serious TEAE resulting in death	160 (7.1) [197]	7.2 [8.8]	168 (7.5) [211]	7.6 [9.5]
Any serious treatment-related TEAE resulting in death	0 (0) [0]	0 [0]	0 (0) [0]	0 [0]
Any serious TEAE resulting in withdrawal of study drug	102 (4.6) [125]	4.6 [5.6]	110 (4.9) [130]	4.9 [5.8]
Any non-serious TEAE resulting in withdrawal of study drug	18 (0.8) [21]	0.8 [0.9]	24 (1.1) [28]	1.1 [1.3]
Any serious treatment-related TEAE resulting in withdrawal of study drug	4 (0.2) [7]	0.2 [0.3]	1 (<0.1) [1]	0.0 [0.0]

Medical Dictionary for Regulatory Activities (version 26.0) was used for coding. Percentages are based on the number of subjects in the safety population per treatment group. Treatment emergent is an AE that occurred or increased in severity on or after the first dose of study medication, up to the reference end date. For each category, *n* includes patients only once, even if they experienced multiple AEs in that category. Incidence per 100 PY = 100 × (number of subjects affected)/(total observation time up to Day 408) per treatment group. Events per 100 PY = 100 × (number of events)/(total observation time up to Day 408) per treatment group.
AE, adverse event; *E*, number of events; FCM, ferric carboxymaltose; *n*, number of patients with ≥1 occurrence of the event; PY, patient-years; TEAE, treatment-emergent adverse event.

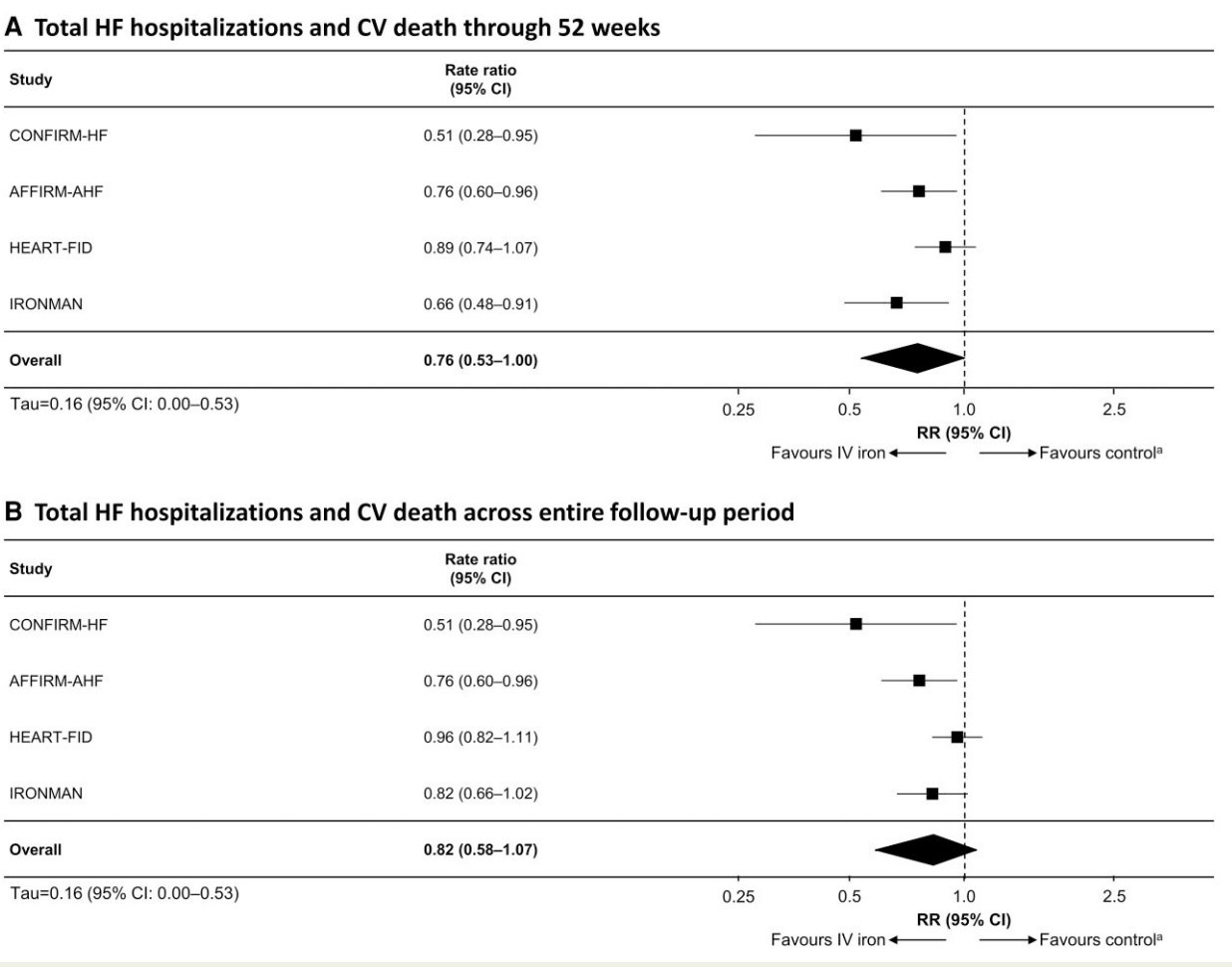


Figure 5 Sensitivity analysis of effect of intravenous iron vs. control (placebo or standard of care) on (*A*) total heart failure hospitalizations and cardiovascular death through 52 weeks and (*B*) total heart failure hospitalizations and cardiovascular death across entire follow-up period. [a]Placebo or standard of care. Standardized trial level analyses were performed using the semiparametric Lin–Wei–Yang–Ying model including treatment and region as factors. Analysis used Bayesian random effects meta-analysis. CI, credible interval; CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure; PBO, placebo; RR, rate ratio.

identify patients who would benefit the most from FCM therapy, whereas in those with TSAT above 20%, the effects of FCM therapy on the outcomes appeared to be negligible. These data align with research from Okonko *et al.*[30] demonstrating that TSAT <20%, but not ferritin-based criteria, predicted 'true' ID as assessed by soluble transferrin receptor (sTFR) levels and TSAT being a more reliable marker of iron status in the pro-inflammatory HF state. Recent meta-analyses that included data from the IRONMAN and AFFIRM-AHF trials reported conflicting results on the impact of TSAT on treatment response.[26,31–33] In our meta-analysis, it appeared that patients in the lowest baseline TSAT tertile (<15%) benefited from FCM therapy (with statistically significant reduction of RR for both primary efficacy outcomes), whereas those with highest TSAT values (i.e. ≥24%) did not. Additionally, there was also an indication of a potential difference in the FCM effect on CV mortality among subgroups split by baseline TSAT with statistically significant reduction of the risk in patients with the lowest values (TSAT <15%) and potentially unfavourable effects in patients with TSAT of 24% or greater. Therapy with FCM tended to be associated with both reduced all-cause and CV mortality in patients with HF and low TSAT. We consider these findings supportive to challenge the current definition of ID in HF as the main indication for intravenous iron therapy. This definition, applied in most clinical trials, is based on serum levels of ferritin and TSAT, but there is ample evidence that it rather poorly reflects depletion of iron in the bone marrow and iron status in the peripheral target tissues, such as myocardium or skeletal muscles.[34–36] In fact, only very low serum ferritin (below 10–15 ng/mL) is specific for an absolute ID, whereas higher ferritin levels reflect a multifaceted milieu of pro-inflammatory activation and cellular damage.[37,38] It may explain the association between higher ferritin and poor prognosis in HF but makes ferritin a rather poor biomarker of ID in HF and indicator for iron repletion therapy. Interestingly, the traditional approach to ID, applied in haematology settings, is based on an assumption that in any case of uncertainty regarding diagnosis of ID, 'genuine ID' is considered *post hoc* only in the cases with positive response to intravenous iron therapy. As ID has been typically linked with anaemia, a favourable response to intravenous iron supplementation has been defined as a certain increase in haemoglobin level. In the HF setting, pathophysiological and clinical implications of ID tend to occur irrespective of haemoglobin level; therefore, one needs to consider different attempts to characterize a positive response to intravenous iron supplementation. It seems that a clinical approach comprising favourable outcomes of being alive and out of hospital due to HF worsening is a desirable concept here. In our meta-analysis including a broad range of patients with HF exposed to intravenous FCM therapy, based on subgroup analyses, baseline TSAT (but not serum ferritin) was the only discriminator of the magnitude of such a response. Clinical benefit from iron repletion was observed in those with low TSAT, whereas those with higher TSAT levels (even if it coincided with low ferritin levels) did not show any benefit because they may not have been 'genuine' ID and therefore may not be appropriate candidates for intravenous iron therapy. The level of TSAT that would be optimal for iron repletion therapy in patients with HF needs to be further established.

In this context, it is also important to highlight the differences that were observed in the effects of FCM on the endpoints across the trials included in this meta-analysis. For instance, there were numerically fewer CV deaths observed with FCM over the follow-up period of the HEART-FID trial [HR (96% CI): 0.86 (0.72–1.03)] which was not observed in prior trials. In AFFIRM-AHF, a significant reduction in HF hospitalizations [RR (95% CI): 0.74 (0.58–0.94)] was observed, but this was not replicated in HEART-FID. These differences may have been due to differences in baseline characteristics, including baseline TSAT levels.

The recommended dosing of FCM varies slightly as approved by regional regulatory agencies, and maximal initial doses varied across studies (CONFIRM-HF and AFFIRM-AHF: 1000 mg Week 0; HEART-FID: 750 mg at Days 0 and 7). It appeared that higher cumulative dose of FCM administered during first 6 months of therapy—likely the result of re-dosing—may be associated with a slightly greater treatment effect after 6 months compared with a lower cumulative dose (although the treatment effect did not reach significance in either dose group). Notably, the treatment effect following a single course of FCM appears to be absent >6 months after therapy. Although these data should be considered as only hypothesis generating, we found them clinically relevant. There are reports that in iron-deficient states, higher doses of intravenous iron may further potentiate beneficial effects of iron repletion. In the PIVOTAL trial in patients with chronic kidney disease undergoing haemodialysis, the use of a high-dose intravenous iron regimen was superior to the use of a low dose and was associated with a lower risk of death or major adverse CV events.[39] Of note, those assigned to receive high-dose iron therapy were less likely to have a myocardial infarction or be hospitalized for HF vs. those in the low-dose iron therapy group.[22,40] Our findings have potential implications for the re-dosing of intravenous iron in HF. Current recommendations (applied in randomized controlled trials and in the HF guidelines) assume regular evaluation of ID biomarkers (namely, ferritin/TSAT), and only if ID is present (as defined by these biomarkers), re-dosing is advised.[7,10–14,16] It may well be that these biomarkers should not be used to predict efficacy of iron repletion but, instead, to monitor safety (only if the level of ferritin/TSAT reaches predefined high levels should the next re-dosing not be recommended). In this context, re-dosing using higher doses of intravenous iron (in the regulatory approved ranges) may also potentially augment favourable effects of correction of ID in HF.

In order to assess all the available data related to long-term effects of intravenous iron therapy on clinical outcomes in patients with HF and ID, we performed a sensitivity analysis that also included the results of the IRONMAN trial. For this trial, IPD were not available, and we used data extracted from the primary publication.[15] The results of the sensitivity analysis including IRONMAN (with ferric derisomaltose) confirmed the findings from FCM trials. In brief, the pooled analysis of 5600 patients showed that therapy with intravenous iron (namely, with FCM or ferric derisomaltose) significantly reduced the rates of recurrent HF hospitalizations and CV death at 12 months (vs. placebo/standard of care). However, for the total follow-up duration, the magnitude of the treatment effect (vs. placebo/standard of care) for the composite of CV death and total HF hospitalizations was reduced, and statistical significance was lost in the Bayesian analysis (with an upper 95% CI of 1.073). We believe, however, that the totality of the data and the results of our meta-analysis support the clinical benefit of intravenous iron therapy in iron-deficient HF patients with reduced LVEF and should inform clinical decision-making and guidelines.

The results of this meta-analysis should be viewed in the context of some limitations. We did not have access to the IPD from the IRONMAN trial; therefore, we could only use aggregated data in the sensitivity analyses for the whole cohort, and data from the IRONMAN trial could not be used for subgroup analyses. In the main analyses, we limited the follow-up to 12 months, because it was a maximal follow-up available for the CONFIRM-HF and AFFIRM-AHF trials. However, in the sensitivity analyses, the totality of evidence regarding the complete follow-up of all trials is presented.

The results of this large meta-analysis provide further support that treatment with FCM significantly reduces recurrent HF and CV hospitalizations. No new safety concerns were raised by the present analysis.

Importantly, our findings support continued research to identify those patients who are most likely to benefit from treatment with intravenous iron, particularly as it relates to the criteria used to identify ID and eligibility for initial and repeat iron doses.

Acknowledgements

Editorial and writing assistance provided by NorthStar Strategic Consulting, LLC, and AXON Communications Inc., both funded by Vifor Pharma Management Ltd. The authors declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

P.P. reports research grants, consulting fees, speaker's bureau for Bayer, MSD, Servier, Novartis, Vifor Pharma Ltd., BMS, Boehringer Ingelheim, Respicardia, AstraZeneca, Berlin Chemie. R.J.M. has received research support and honoraria from Abbott, American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim/Eli Lilly, Boston Scientific, Cytokinetics, Fast BioMedical, Gilead, Innolife, Medtronic, Merck, Novartis, Relypsa, Respicardia, Roche, Sanofi, Vifor, Windtree Therapeutics, and Zoll. A.F.H. reports research grants from American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Merck, Novo Nordisk, Novartis, Pfizer, Verily and consulting from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cytokinetics, Eidos, Intercept, Myokardia, and Novo Nordisk. J.B. reports serving as a consultant to Abbott, American Regent, Amgen, Applied Therapeutic, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiac Dimension, Cardior, CVRx, Cytokinetics, Edwards, Element Science, Innolife, Impulse Dynamics, Imbria, Inventiva, Lexicon, Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Roche, Sequana, SQ Innovation, 3live, and Vifor. MSK declares no competing interests. D.J.v.V. reports research grants from CSL Vifor, paid to his department (not personal payments). B.R. is an employee of CSL Vifor. N.B. is an employee of American Regent, Inc. E.A.J. reports honoraria for lectures, consultancies and/or participation in advisory boards from CSL Vifor, Pharmacosmos, Swixx Biopharma, Novartis, AstraZeneca, Boehringer Ingelheim, Servier, Pfizer, Zoll Respicardia, Bayer, Abbott, Cardiac Dimensions, Takeda, and Sanofi, and was co-PI of the AFFIRM-AHF trial sponsored by Vifor Pharma. T.F. reports personal fees from Aslan, Bayer, BiosenseWebster, Bristol Myers Squibb, CSL Behring, Enanta, Fresenius Kabi, Galapagos, Immunic, IQVIA, Janssen, KyowaKirin, Lilly, LivaNova, Minoryx, Novartis, Recordati, Relaxera, Roche, Servier, Viatris, VICO Therapeutics, and Vifor for statistical consultancies including data monitoring committees, all outside the submitted work. S.D.A. reports grants and personal fees from Vifor and Abbott Vascular, and personal fees for consultancies, trial committee work and/or lectures from Actimed, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bioventrix, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Cytokinetics, Edwards, Farraday Pharmaceuticals, GSK, HeartKinetics, Impulse Dynamics, Novartis, Occlutech, Pfizer, Repairon, Sensible Medical, Servier, Vectorious, and V-Wave.

Data Availability

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

Funding

Funding for the analysis and support of medical writing to was provided by CSL Vifor.

Ethical Approval

Ethical approval was not required.

Pre-registered Clinical Trial Number

None supplied.

References

1. Rocha BML, Cunha GJL, Menezes Falcão LF. The burden of iron deficiency in heart failure: therapeutic approach. *J Am Coll Cardiol* 2018;**71**:782–93. https://doi.org/10.1016/j.jacc.2017.12.027
2. Marchi G, Busti F, Vianello A, Girelli D. Anemia and iron deficiency in heart failure: extending evidences from chronic to acute setting. *Intern Emerg Med* 2021;**16**:167–70. https://doi.org/10.1007/s11739-020-02434-9
3. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, *et al.* Iron deficiency predicts impaired exercise capacity in patients with systolic chronic heart failure. *J Card Fail* 2011;**17**:899–906. https://doi.org/10.1016/j.cardfail.2011.08.003
4. Enjuanes C, Klip IT, Bruguera J, Cladellas M, Ponikowski P, Banasiak W, *et al.* Iron deficiency and health-related quality of life in chronic heart failure: results from a multicenter European study. *Int J Cardiol* 2014;**174**:268–75. https://doi.org/10.1016/j.ijcard.2014.03.169
5. Martens P, Nijst P, Verbrugge FH, Smeets K, Dupont M, Mullens W. Impact of iron deficiency on exercise capacity and outcome in heart failure with reduced, mid-range and preserved ejection fraction. *Acta Cardiol* 2018;**73**:115–23. https://doi.org/10.1080/00015385.2017.1351239
6. Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, *et al.* Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J* 2013;**165**:575–582.e3. https://doi.org/10.1016/j.ahj.2013.01.017
7. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, *et al.* Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J* 2015;**36**:657–68. https://doi.org/10.1093/eurheartj/ehu385
8. van Veldhuisen DJ, Ponikowski P, van der Meer P, Metra M, Böhm M, Doletsky A, *et al.* Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. *Circulation* 2017;**136**:1374–83. https://doi.org/10.1161/circulationaha.117.027497
9. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, *et al.* Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009;**361**:2436–48. https://doi.org/10.1056/NEJMoa0908355
10. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–726. https://doi.org/10.1093/eurheartj/ehab368
11. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2022;**79**:1757–80. https://doi.org/10.1016/j.jacc.2021.12.011
12. Sindone AP, De Pasquale C, Amerena J, Burdeniuk C, Chan A, Coats A, *et al.* Consensus statement on the current pharmacological prevention and management of heart failure. *Med J Aust* 2022;**217**:212–7. https://doi.org/10.5694/mja2.51656
13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, *et al.* 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–200. https://doi.org/10.1093/eurheartj/ehw128
14. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, *et al.* Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre,

double-blind, randomised, controlled trial. *Lancet* 2020;**396**:1895–904. https://doi.org/10.1016/s0140-6736(20)32339-4
15. Kalra PR, Cleland JGF, Petrie MC, Thomson EA, Kalra PA, Squire IB, *et al.* Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. *Lancet* 2022;**400**:2199–209. https://doi.org/10.1016/s0140-6736(22)02083-9
16. Mentz RJ, Garg J, Rockhold FW, *et al*. Ferric carboxymaltose in heart failure with iron deficiency. *N Engl J Med* 2023;**389**:975–986. https://doi.org/10.1016/10.1056/NEJMoa2304968
17. Cooper H, Patall EA. The relative benefits of meta-analysis conducted with individual participant data versus aggregated data. *Psychol Methods* 2009;**14**:165–76. https://doi.org/10.1037/a0015565
18. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010;**340**:c221. https://doi.org/10.1136/bmj.c221
19. Ezeh E, Katabi A, Khawaja I. Iron deficiency anemia as a rare risk factor for recurrent pulmonary embolism and deep vein thrombosis. *Cureus* 2021;**13**:e13721. https://doi.org/10.7759/cureus.13721
20. Hoes MF, Grote Beverborg N, Kijlstra JD, Kuipers J, Swinkels DW, Giepmans BNG, *et al.* Iron deficiency impairs contractility of human cardiomyocytes through decreased mitochondrial function. *Eur J Heart Fail* 2018;**20**:910–9. https://doi.org/10.1002/ejhf.1154
21. Charles-Edwards G, Amaral N, Sleigh A, Ayis S, Catibog N, McDonagh T, *et al.* Effect of iron isomaltoside on skeletal muscle energetics in patients with chronic heart failure and iron deficiency. *Circulation* 2019;**139**:2386–98. https://doi.org/10.1161/CIRCULATIONAHA.118.038516
22. Petrie MC, Jhund PS, Connolly E, Mark PB, MacDonald MR, Robertson M, *et al.* High-dose intravenous iron reduces myocardial infarction in patients on haemodialysis. *Cardiovasc Res* 2023;**119**:213–20. https://doi.org/10.1093/cvr/cvab317
23. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J R Stat Soc B Stat Methodol* 2000;**62**:711–30. https://doi.org/10.1111/1467-9868.00259
24. Friede T, Röver C, Wandel S, Neuenschwander B. Meta-analysis of few small studies in orphan diseases. *Res Synth Methods* 2017;**8**:79–91. https://doi.org/10.1002/jrsm.1217
25. Metra M, Jankowska EA, Pagnesi M, Anker SD, Butler J, Dorigotti F, *et al.* Impact of ischaemic aetiology on the efficacy of intravenous ferric carboxymaltose in patients with iron deficiency and acute heart failure: insights from the AFFIRM-AHF trial. *Eur J Heart Fail* 2022;**24**:1928–39. https://doi.org/10.1002/ejhf.2630
26. Anker SD, Khan MS, Butler J, von Haehling S, Jankowska EA, Ponikowski P, *et al.* Effect of intravenous iron replacement on recurrent heart failure hospitalizations and cardiovascular mortality in patients with heart failure and iron deficiency: a Bayesian meta-analysis. *Eur J Heart Fail* 2023;**25**:1080–90. https://doi.org/10.1002/ejhf.2860
27. Filippatos G, Ponikowski P, Farmakis D, Anker SD, Butler J, Fabien V, *et al.* Association between hemoglobin levels and efficacy of intravenous ferric carboxymaltose in patients with acute heart failure and iron deficiency: an AFFIRM-AHF subgroup analysis. *Circulation* 2023;**147**:1640–53. https://doi.org/10.1161/circulationaha.122.060757
28. Filippatos G, Farmakis D, Colet JC, Dickstein K, Lüscher TF, Willenheimer R, *et al.* Intravenous ferric carboxymaltose in iron-deficient chronic heart failure patients with and without anaemia: a subanalysis of the FAIR-HF trial. *Eur J Heart Fail* 2013;**15**:1267–76. https://doi.org/10.1093/eurjhf/hft099
29. Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, *et al.* Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. *J Am Coll Cardiol* 2008;**51**:103–12. https://doi.org/10.1016/j.jacc.2007.09.036
30. Okonko DO, Mandal AK, Missouris CG, Poole-Wilson PA. Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival. *J Am Coll Cardiol* 2011;**58**:1241–51. https://doi.org/10.1016/j.jacc.2011.04.040
31. Graham FJ, Pellicori P, Kalra PR, Ford I, Bruzzese D, Cleland JGF. Intravenous iron in patients with heart failure and iron deficiency: an updated meta-analysis. *Eur J Heart Fail* 2023;**25**:528–37. https://doi.org/10.1002/ejhf.2810
32. Reinhold J, Burra V, Corballis N, Tsampasian V, Matthews G, Papadopoulou C, *et al.* Effects of intravenous iron replacement therapy on cardiovascular outcomes in patients with heart failure: a systematic review and meta-analysis. *J Cardiovasc Dev Dis* 2023;**10**:116. https://doi.org/10.3390/jcdd10030116
33. Vukadinović D, Abdin A, Emrich I, Tsampasian V, Matthews G, Papadopoulou C, *et al.* Efficacy and safety of intravenous iron repletion in patients with heart failure: a systematic review and meta-analysis. *Clin Res Cardiol* 2023;**112**:954–66. https://doi.org/10.1007/s00392-023-02207-2
34. Sierpinski R, Josiak K, Suchocki T, Wojtas-Polc K, Mazur G, Butrym A, *et al.* High soluble transferrin receptor in patients with heart failure: a measure of iron deficiency and a strong predictor of mortality. *Eur J Heart Fail* 2021;**23**:919–32. https://doi.org/10.1002/ejhf.2036
35. Beverborg N G, Klip IT, Meijers WC, Voors AA, Vegter EL, van der Wal HH, *et al.* Definition of iron deficiency based on the gold standard of bone marrow iron staining in heart failure patients. *Circ Heart Fail* 2018;**11**:e004519. https://doi.org/10.1161/circheartfailure.117.004519
36. Leszek P, Sochanowicz B, Szperl M, Kolsut P, Brzóska K, Piotrowski W, *et al.* Myocardial iron homeostasis in advanced chronic heart failure patients. *Int J Cardiol* 2012;**159**:47–52. https://doi.org/10.1016/j.ijcard.2011.08.006
37. Plays M, Müller S, Rodriguez R. Chemistry and biology of ferritin. *Metallomics* 2021;**13**:mfab021. https://doi.org/10.1093/mtomcs/mfab021
38. Knovich MA, Storey JA, Coffman LG, Torti SV, Torti FM. Ferritin for the clinician. *Blood Rev* 2009;**23**:95–104. https://doi.org/10.1016/j.blre.2008.08.001
39. Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA, *et al.* Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med* 2019;**380**:447–58. https://doi.org/10.1056/NEJMoa1810742
40. Jhund PS, Petrie MC, Robertson M, Mark PB, MacDonald MR, Connolly E, *et al.* Heart failure hospitalization in adults receiving hemodialysis and the effect of intravenous iron therapy. *JACC Heart Fail* 2021;**9**:518–27. https://doi.org/10.1016/j.jchf.2021.04.005