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RESEARCH ARTICLE

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

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Aims In AFFIRM-AHF, intravenous ferric carboxymaltose (FCM) reduced heart failure (HF) hospitalisations and improved quality of life versus placebo in iron-deficient patients stabilised after an acute HF episode. This analysis explored the effects of FCM versus placebo in patients with ischaemic and non-ischaemic HF aetiology.

Methods and results We included 1082 patients from AFFIRM-AHF: 590 with ischaemic HF (defined as investigator-reported ischaemic HF aetiology and/or prior acute myocardial infarction and/or prior coronary revascularisation) and 492 with non-ischaemic HF. The prevalences of male sex, comorbidities, and history of HF were higher in the ischaemic versus non-ischaemic HF subgroup. Annualised event rates for the primary composite outcome of total HF hospitalisations and cardiovascular death with FCM versus placebo were 65.3 versus 100.6 per 100 patient-years in the ischaemic HF subgroup (rate ratio [RR] 0.65, 95% confidence interval [CI] 0.47–0.89, $p = 0.007$) and 58.3 versus 52.5 in the non-ischaemic HF subgroup (RR 1.11, 95% CI 0.75–1.66, $p = 0.60$) ($p_{interaction} = 0.039$). An interaction between HF aetiology and treatment effect was also observed for the secondary outcome of total HF hospitalisations ($p_{interaction} = 0.038$). A nominal increase in quality of life, assessed using the 12-item Kansas City Cardiomyopathy Questionnaire, was observed with FCM versus placebo, within each subgroup.

Conclusions Heart failure hospitalisations and cardiovascular deaths occurred at a higher rate in patients with ishaemic versus those with non-ischaemic HF and were reduced by FCM versus placebo only in ischaemic patients. Further studies are needed to assess the role of aetiology in FCM efficacy.

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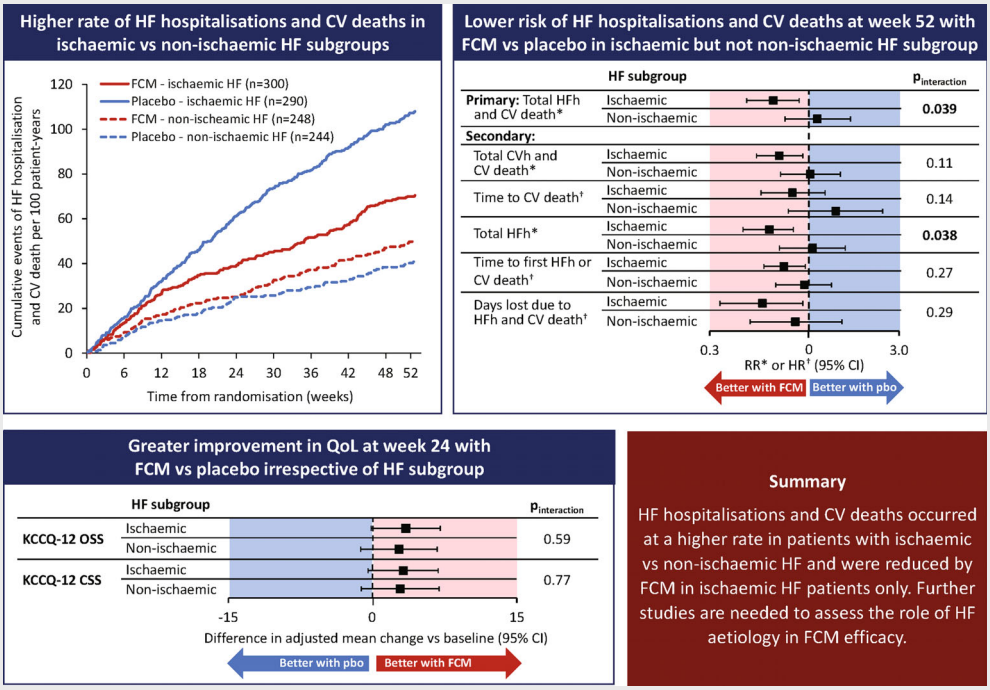
Graphical Abstract



AFFIRM-AHF subgroup analysis exploring the association between ischaemic vs non-ischaemic HF aetiology and treatment outcomes with FCM vs placebo in patients stabilised following an acute HF episode who have iron deficiency. *RR for recurrent event analyses. †HR for time to event analyses. CI, confidence interval; CSS, clinical summary score; CV, cardiovascular; CVh, cardiovascular hospitalisation; FCM, ferric carboxymaltose; HF, heart failure; HFh, heart failure hospitalisation; HR, hazard ratio; KCCQ-12, 12-item Kansas City Cardiomyopathy Questionnaire; OSS, overall summary score; pbo, placebo; QoL, quality of life; RR, risk ratio.

Keywords Acute heart failure • Iron deficiency • Ferric carboxymaltose • Ischaemic heart failure • AFFIRM-AHF

Introduction

Iron deficiency is a frequent comorbidity in heart failure (HF) with a prevalence of up to 50% in patients with stable chronic HF[1] and an even higher prevalence in those hospitalised for acute HF (AHF).[2,3] Iron deficiency is associated with reduced quality of life (QoL) and is an independent predictor of worse outcomes and poorer survival in patients with HF,[4] irrespective of anaemia status.[5–7]

Coronary artery disease and myocardial ischaemia represent major causes of HF.[8,9] In contrast, non-ischaemic HF comprises a broad, heterogeneous group of patients with different aetiologies, including hypertensive, valvular, idiopathic and congenital heart disease.[10,11] Several studies have shown that patients with an ischaemic aetiology of HF have a worse prognosis than those with non-ischaemic HF aetiology.[12–15]

In the AFFIRM-AHF trial, which included hospitalised patients with iron deficiency and a left ventricular ejection fraction (LVEF) <50% who had stabilised after an episode of AHF, treatment with intravenous (IV) ferric carboxymaltose (FCM) reduced the risk of HF hospitalisations and improved QoL, with no apparent effect on the risk of cardiovascular (CV) death alone.[16] Here, we report the results of a subgroup analysis exploring the effects of FCM versus placebo in patients with ischaemic and non-ischaemic HF aetiology.

Methods

AFFIRM-AHF trial design

Details of the AFFIRM-AHF trial design have been reported previously.[16,17] In brief, AFFIRM-AHF was an international, multicentre, double-blind, placebo-controlled, phase 4, randomised clinical trial. Eligible patients were aged ≥18 years and had been hospitalised with signs or symptoms characteristic of AHF and elevated natriuretic peptide levels, treated with a minimum of 40 mg IV furosemide (or equivalent IV diuretic), and had concomitant iron deficiency (defined as serum ferritin <100 ng/ml, or ferritin 100–299 ng/ml with transferrin saturation [TSAT] <20%) and an LVEF <50%. Patients were randomised (1:1)

to IV FCM or placebo, with the first dose administered shortly before hospital discharge. Efficacy and safety outcome assessments were performed at weeks 4, 6, 12, 24, 36 and 52. The trial was conducted in accordance with the Declaration of Helsinki,[18] the International Conference on Harmonisation Good Clinical Practice guidelines,[19] and local and national regulations and ethics committees. All patients provided written informed consent before any study-specific procedures were performed. The AFFIRM-AHF trial was registered at ClinicalTrials.gov (NCT02937454).

Study endpoints and clinical assessments

The primary endpoint in AFFIRM-AHF was a composite of total HF hospitalisations and CV death up to 52 weeks after randomisation. Secondary efficacy outcomes were the composite of total CV hospitalisations and CV death; CV death; total HF hospitalisations; time to first HF hospitalisation or CV death; and days lost due to HF hospitalisations or CV death, all evaluated up to 52 weeks after randomisation. Other endpoints included disease-specific QoL (assessed using the self-administered 12-item Kansas City Cardiomyopathy Questionnaire [KCCQ-12], overall summary score [OSS] and clinical summary score [CSS]). Safety endpoints included the occurrence of adverse events (according to the Medical Dictionary for Regulatory Activities [MedDRA]) and changes in iron parameters (serum ferritin and TSAT) assessed from baseline to week 52. An independent data safety monitoring board reviewed the safety data of study participants on a continuing basis.

Definitions of ischaemic heart failure aetiology

A comparison of outcomes in patients with ischaemic versus non-ischaemic HF (defined according to investigator-reported HF aetiology) was pre-specified in the study protocol. In this subgroup analysis, the definition of ischaemic HF was expanded *post hoc* to investigator-reported ischaemic HF aetiology and/or prior acute myocardial infarction and/or prior coronary revascularisation at baseline, in order to capture all patients with evidence of ischaemic heart disease. Non-ischaemic HF was defined as investigator-reported non-ischaemic HF aetiology with no prior acute myocardial infarction and/or prior coronary revascularisation at baseline.

Statistical analyses

This subgroup analysis included all randomised patients from the AFFIRM-AHF modified intention-to-treat (mITT) population for whom the HF aetiology was documented at index hospitalisation. Patients were stratified into two subgroups: those with ischaemic HF and those with non-ischaemic HF, according to the aforementioned definitions.

The treatment effect of FCM versus placebo was analysed within each subgroup using a negative binomial model for all recurrent primary and secondary efficacy endpoints (reported as event rate ratios [RRs] with 95% confidence intervals [CIs])[20] and a Cox regression model for time to first event secondary endpoints (reported as hazard ratios [HRs] with 95% CIs). Both analyses were adjusted for baseline covariates (sex, age, HF aetiology, HF duration, and country), and interaction between treatment group and HF aetiology. Interaction *p*-values ($p_{interaction}$) for the effect of ischaemic versus non-ischaemic HF on treatment outcomes at week 52 were generated for all primary and secondary efficacy endpoints.

Primary and secondary efficacy outcomes were also compared between the ischaemic HF and non-ischaemic HF subgroups overall, as well as between the placebo arms of each subgroup, to examine the effect of HF aetiology on outcomes in patients with untreated iron deficiency following an AHF episode. A pre-COVID-19 sensitivity analysis was performed to evaluate the potential impact of the initial outbreak of the COVID-19 pandemic on the primary and secondary efficacy outcomes in both subgroups. As previously described,[16] this analysis censored all patients in each country on the date when its first COVID-19 patient case was reported.

Disease-related QoL was reported as model-adjusted mean change from baseline in KCCQ-12 OSS and CSS for each visit, with estimates based on a mixed-effect model for repeated measurements that included terms for baseline score, subgroup of ischaemic aetiology of HF, treatment visit and baseline covariates within an unstructured covariance matrix. $P_{interaction}$ values for the effect of ischaemic versus non-ischaemic HF on treatment outcomes were generated for KCCQ-12 OSS and CSS estimated treatment differences at week 24.

An exploratory subgroup analysis that further stratified patients with ischaemic and non-ischaemic HF by prior HF status (documented prior HF vs. *de novo* HF) was also performed to evaluate the potential impact of these combined variables on primary, secondary and QoL outcomes.

Mean (standard deviation [SD]) changes from baseline in serum ferritin and TSAT at weeks 6, 12, 24 and 52 were compared between FCM and placebo arms within each subgroup using ANOVA. Safety endpoint analyses were performed on all patients for whom HF aetiology was known at index hospitalisation and who had started study treatment (safety analysis set). For all analyses presented, *p*-values <0.05 were considered statistically significant. SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA; 2000–2004) was used to conduct all analyses.

Results

Baseline characteristics

Of the 1108 patients in the AFFIRM-AHF mITT analysis set, the HF aetiology at index hospitalisation could be determined in 1082 (97.7%) patients, who were included in this subgroup analysis. Among them, 590 patients (54.5%) had ischaemic HF (FCM: $n = 300$; placebo: $n = 290$) and 492 (45.5%) had non-ischaemic HF (FCM: $n = 248$; placebo: $n = 244$).

Baseline characteristics of patients with ischaemic and non-ischaemic HF are summarised in *Table 1*. Compared with non-ischaemic HF patients, ischaemic HF patients were more frequently male, with a generally higher proportion of comorbidities (e.g. dyslipidaemia, diabetes, chronic kidney disease), and more often had a history of HF at the time of the index hospitalisation (83.1% vs. 58.5%; $p < 0.0001$). Patients with ischaemic HF also had lower mean LVEF (31.8% vs. 33.8%; $p = 0.0010$), haemoglobin (12.0 vs. 12.4 g/dl; $p = 0.0008$) and TSAT levels (14.2% vs. 15.4%; $p = 0.0154$) at baseline. There was no significant difference between the ischaemic and non-ischaemic HF subgroups for New York Heart Association (NYHA) class or for serum ferritin and natriuretic peptide levels. Within each subgroup, baseline characteristics of patients in the FCM and placebo arms were generally balanced (online supplementary *Table S1*). Among patients with

Table 1 Baseline demographics and clinical characteristics for patients with ischaemic and non-ischaemic heart failure in the modified intention-to-treat population

	Ischaemic HF (n = 590)	Non-ischaemic HF (n = 492)	p-value
Age, years	71.6 (9.5)	70.4 (12.4)	0.06
Male sex, *n* (%)	391 (66.3)	209 (42.5)	<0.0001
Race, *n* (%)			0.0128
White	549 (93.1)	477 (97.0)	
Asian	38 (6.4)	10 (2.0)	
Other	3 (0.5)	5 (1.0)	
Comorbidities, *n* (%)			
Current smoking	60 (10.2)	42 (8.5)	<0.0001
Hypertension	509 (86.3)	409 (83.1)	0.1514
Dyslipidaemia	392 (66.4)	191 (38.8)	<0.0001
Diabetes	310 (52.5)	149 (30.3)	<0.0001
Atrial fibrillation or flutter	310 (52.5)	296 (60.2)	0.0019
Previous myocardial infarction	442 (74.9)	0	NA
Angina pectoris	143 (24.2)	25 (5.1)	<0.0001
Previous stroke	73 (12.4)	45 (9.1)	0.09
Previous coronary revascularisation	401 (68.0)	0	NA
Chronic kidney disease	286 (48.5)	154 (31.3)	<0.0001
Systolic blood pressure, mmHg	118.9 (15.5)	120.6 (15.0)	0.07
Diastolic blood pressure, mmHg	70.8 (10.0)	73.9 (10.1)	<0.0001
Heart rate, bpm	72.2 (12.0)	76.8 (13.7)	<0.0001
BMI, kg/m^2	27.6 (5.1)	28.7 (6.3)	0.0035
New York Heart Association class, *n* (%)			0.31
I	15 (2.5)	6 (1.2)	
II	262 (44.5)	220 (45.0)	
III	290 (49.2)	250 (51.1)	
IV	22 (3.7)	13 (2.7)	
Left ventricular ejection fraction[a], %	31.8 (9.6)	33.8 (9.8)	0.0010
Left ventricular ejection fraction, *n* (%)			0.0108
<25%	129 (21.9)	92 (18.7)	
25% to <40%	297 (50.4)	222 (45.1)	
40% to <50%	163 (27.7)	178 (36.2)	
HF history, *n* (%)			<0.0001
De novo at index hospitalisation	100 (16.9)	204 (41.5)	
Documented HF prior to index hospitalisation	490 (83.1)	288 (58.5)	
Device therapy			
ICD	103 (17.5)	28 (5.7)	<0.0001
CRT	40 (6.8)	22 (4.5)	0.10
Non-ischaemic HF aetiology, *n* (%)			NA
Hypertensive	0	202 (41.1)	
Valvular	0	88 (17.9)	
Idiopathic	0	129 (26.2)	
Congenital	0	4 (0.8)	
Other	0	69 (14.0)	
Pharmacotherapy[b], *n* (%)			
ACEI	297 (50.3)	261 (53.0)	0.3745
ARB	92 (15.6)	99 (20.1)	0.0517
ARNI	46 (7.8)	24 (4.9)	0.0520
Aldosterone antagonists	382 (64.7)	333 (67.7)	0.3096
Beta-blocker	486 (82.4)	404 (82.1)	0.9116
Digitalis glycosides	92 (15.6)	89 (18.1)	0.2733
Loop diuretic	515 (87.3)	409 (83.1)	0.0538

Table 1 (Continued)

	Ischaemic HF (n = 590)	Non-ischaemic HF (n = 492)	p-value
Laboratory test results			
NT-proBNP, pg/ml, median (IQR)	4957 (2826–9000)	4600 (2719–7310)	0.82
Brain natriuretic peptide, pg/ml, median (IQR)	1197 (820–1753)	1000 (735–1715)	0.38
Hb, g/dl	12.0 (1.6)	12.4 (1.6)	0.0008
Hb category, *n* (%)			0.0281
<10 g/dl	69 (11.7)	42 (8.6)	
≥10 to ≤14 g/dl	450 (76.3)	366 (74.5)	
>14 g/dl	71 (12.0)	83 (16.9)	
Anaemia, *n* (%)			
Males: Hb <13 g/dl	254 (43.1)	102 (20.8)	0.0002
Females, non-pregnant: Hb <12 g/dl	113 (19.2)	124 (25.3)	0.0051
Serum ferritin, ng/ml	88.2 (67.0)	83.0 (62.5)	0.19
Serum ferritin <100 ng/ml, *n* (%)	405 (68.6)	366 (74.5)	0.0498
TSAT, %	14.2 (7.0)	15.4 (9.0)	0.0154
TSAT <20%, *n* (%)	507 (86.5)	394 (80.6)	0.0084
eGFR, ml/min/1.73 m^2	39.9 (11.1)	41.3 (12.1)	0.15

Data are mean (standard deviation) unless otherwise specified and are based on the number of patients in the modified intention-to-treat population with available data per treatment group. Percentages might not add to 100% due to rounding.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CRT, cardiac resynchronisation therapy; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HF, heart failure; ICD, implantable cardioverter defibrillator; IQR, interquartile range; NA, not applicable; NT-proBNP, N-terminal pro-brain natriuretic peptide; TSAT, transferrin saturation.

[a]Measured within 12 months prior to screening.

[b]Any medication that is current on the first day of study drug administration.

non-ischaemic HF, several specific HF aetiologies were identified, with hypertension being the most common (41.1%), followed by idiopathic cardiomyopathy (26.2%), and valvular heart disease (17.9%).

Primary and secondary outcomes

Over the 52-week study, the primary composite outcome of total HF hospitalisations and CV death occurred in 246/590 (41.7%) patients with ischaemic HF and in 137/492 (27.8%) patients with non-ischaemic HF. The annualised event rate for the primary endpoint was higher in the ischaemic HF subgroup compared with the non-ischaemic HF subgroup (82.4 vs. 55.6 events per 100 patient-years; RR 1.48, 95% CI 1.12–1.96, p = 0.005) (*Figure 1A*). Higher annualised event rates in patients with ischaemic versus non-ischaemic HF were also observed for the other recurrent event-based secondary endpoints, including the composite of total CV hospitalisations and CV death (RR 1.49, 95% CI 1.16–1.92, p = 0.002) and total HF hospitalisations (RR 1.47, 95% CI 1.12–1.92, p = 0.005). Regarding time to first event outcomes, the occurrence of CV death at week 52 (HR 1.29, 95% CI 0.89–1.87, p = 0.187) (*Figure 1B*) and of HF hospitalisation or CV death at week 52 (HR 1.31, 95% CI 1.04–1.65, p = 0.020) (*Figure 1C*) was more frequent among patients with ischaemic versus non-ischaemic HF, although statistical significance was not reached for CV death alone. Patients with ischaemic HF were also shown to have a poorer outcome than those with non-ischaemic HF when the analysis was restricted to those on placebo (online supplementary *Figure S1*).

Impact of ischaemic versus non-ischaemic heart failure on the treatment effect of ferric carboxymaltose

The annualised event rates for the primary composite outcome of total HF hospitalisations and CV death with FCM versus placebo were 65.3 versus 100.6 per 100 patient-years among patients with ischaemic HF (RR 0.65, 95% CI 0.47–0.89, p = 0.007, for FCM vs. placebo) and 58.3 versus 52.5 per 100 patient-years for patients with non-ischaemic HF (RR 1.11, 95% CI 0.75–1.66, p = 0.60) (*Figure 2*). The interaction for the effect of HF aetiology on the primary outcome was statistically significant ($p_{interaction}$ = 0.039).

Among secondary outcomes, a significant interaction between HF aetiology and treatment effect was observed for total number of HF hospitalisations ($p_{interaction}$ = 0.038), whereas no significant subgroup effect was observed for the remaining secondary outcomes of total CV hospitalisations and CV death, time to CV death, time to first HF hospitalisations or CV death, and days lost due to HF hospitalisation and CV death (all $p_{interaction}$ >0.05). For the primary and secondary outcomes, findings of the pre-COVID-19 sensitivity analysis by HF aetiology subgroup were similar to those observed in the main analysis (online supplementary *Figure S2*).

Disease-specific quality of life

At baseline, the mean (SD) KCCQ-12 OSS for patients with ischaemic and non-ischaemic HF was 43.6 ± 21.0 and 38.9 ± 20.0, respectively, while the mean KCCQ-12 CSS was 44.7 ± 24.8 and

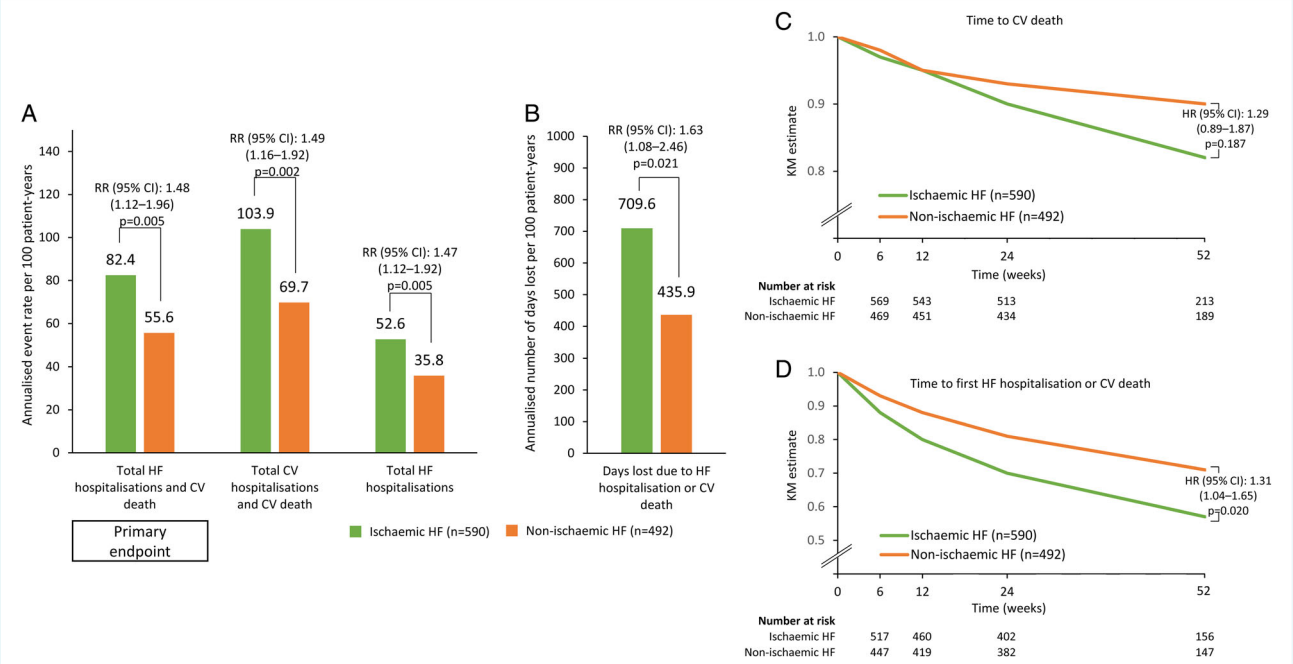


Figure 1 (*A*) Annualised event rates per 100 patient-years for recurrent event-based primary and secondary outcomes; (*B*) annualised number of days lost per 100 patient-years; (*C*) Kaplan–Meier (KM) estimates for time to cardiovascular (CV) death; (*D*) KM estimates for time to first hospitalisation or death in the ischaemic versus non-ischaemic heart failure (HF) aetiology subgroups (modified intention-to-treat population). Annualised event rate ratio (RR) for ischaemic HF versus non-ischaemic HF subgroups analysed using a negative binomial model. Hazard ratio (HR) for ischaemic versus non-ischaemic HF subgroups analysed using Cox regression model. Both models were adjusted for the following baseline covariates: sex, age, HF history, country and subgroup of ischaemic aetiology of HF. Respective number of patients with ischaemic versus non-ischaemic HF at baseline were 590 and 492. CI, confidence interval.

42.0 ± 21.3, respectively. Although KCCQ-12 OSS and KCCQ-12 CSS increased from baseline in both the FCM and placebo arms of patients with ischaemic and non-ischaemic HF, nominally greater increases were seen with FCM versus placebo in each subgroup from approximately week 4, with the difference in adjusted mean change between treatment arms reaching significance ($p < 0.05$) in the non-ischaemic HF subgroup at weeks 6 and 12 for OSS and at weeks 4 and 6 for CSS (*Figure 3*). At week 24, the difference in adjusted mean change in KCCQ-12 OSS between FCM and placebo arms was 3.43 (95% CI −0.18–7.04) in the ischaemic HF subgroup and 2.73 (−1.28–6.73) in the non-ischaemic HF subgroup, with no significant interaction between HF aetiology and treatment effect ($p_{interaction} = 0.588$); similar findings were observed for the KCCQ-12 CSS (*Figure 3*).

Further exploratory subgroup analyses

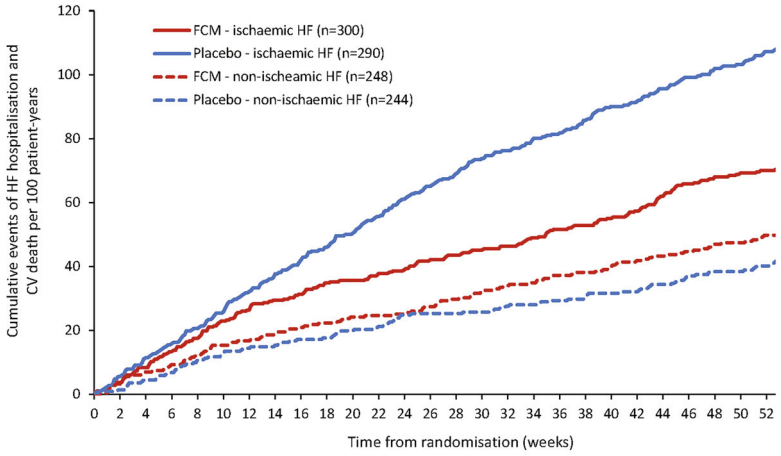
Further stratification of patients in the ischaemic and non-ischaemic HF subgroups according to prior HF history showed that the effect of FCM versus placebo on clinical event and QoL outcomes was greatest in the subgroup with ischaemic HF and history of HF, with a RR of 0.59 (95% CI 0.42–0.83; $p = 0.002$) for the primary outcome, a RR of 0.57 (95% CI 0.41–0.78; $p < 0.001$) for total HF hospitalisations, and a difference in adjusted mean change in KCCQ-12 OSS of 5.28 (95% CI 1.34–9.22; $p = 0.009$) (online supplementary *Figure S3*). Indeed, the effect of FCM versus placebo was statistically significant ($p < 0.05$) for all outcomes assessed in this subgroup, except time to CV death (online supplementary *Figure S3*). Nevertheless, $p_{interaction}$ values for the impact of both HF aetiology and prior HF history on treatment effect were not significant for any of the outcomes.

Iron parameters

At baseline, there was no significant difference in mean serum ferritin levels between patients with ischaemic and non-ischaemic HF (88.2 vs. 83.0 ng/ml; $p = 0.19$), although mean TSAT (14.2% vs. 15.4%; $p = 0.0154$) and haemoglobin (12.0 vs. 12.4 g/dl; $p = 0.0008$) levels were lower in those with ischaemic HF (*Table 1*). Compared with the non-ischaemic HF patients, anaemia was more common in males (43.1% vs. 20.8%, $p = 0.0002$) and less common in females (19.2% vs. 25.3%, $p = 0.0051$) with ischaemic HF (*Table 1*).

The increase from baseline in serum ferritin and TSAT levels was significantly greater with FCM versus placebo within each of the ischaemic and non-ischaemic HF patient subgroups (*Figure 4*). In patients on placebo, the increase from baseline in serum ferritin and TSAT levels were numerically larger in patients with non-ischaemic compared with ischaemic HF aetiology (online supplementary *Figure S4*).

A



Number at risk					
FCM - ischaemic HF	300	265	238	214	87
Placebo - ischaemic HF	290	252	222	188	69
FCM - non-ischaemic HF	248	221	207	192	75
Placebo - non-ischaemic HF	244	226	212	190	72

B

	Subgroup	Patients with ≥1 events, n (%) FCM	Placebo	Annualised event rate per 100 patient-years FCM	Placebo	RR or HR* [95% CI]	p-value	$p_{interaction}$
Primary outcome								
Total HF hospitalisations and CV death	Overall population			57.2	72.5	RR: 0.79 (0.62–1.01)	0.059	NA
	Ischaemic HF	110 (36.7)	136 (46.9)	65.3†	100.6†	RR: 0.65 (0.47–0.89)†	0.007	0.039
	Non-ischaemic HF	69 (27.8)	68 (27.9)	58.3†	52.5†	RR: 1.11 (0.75–1.66)†	0.604	
Secondary outcomes								
Total CV hospitalisations and CV death	Ischaemic HF	131 (43.7)	155 (53.4)	86.5†	123.4†	RR: 0.70 (0.53–0.93)†	0.015	0.11
	Non-ischaemic HF	74 (29.8)	80 (32.8)	70.5†	69.1†	RR: 1.02 (0.71–1.47)†	0.912	
Time to CV death	Ischaemic HF	47 (15.7)	55 (19.0)	NA	NA	HR: 0.82 (0.56–1.22)‡	0.335	0.14
	Non-ischaemic HF	29 (11.7)	20 (8.2)	NA	NA	HR: 1.39 (0.78–2.46)‡	0.261	
Total HF hospitalisations	Ischaemic HF	85 (28.3)	118 (40.7)	40.2†	65.3†	RR: 0.62 (0.45–0.83)†	0.002	0.038
	Non-ischaemic HF	56 (22.6)	57 (23.4)	34.3†	32.7†	RR: 1.05 (0.70–1.56)†	0.818	
Time to first HF hospitalisation or CV death	Ischaemic HF	110 (36.7)	136 (46.9)	NA	NA	HR: 0.74 (0.58–0.96)‡	0.022	0.27
	Non-ischaemic HF	69 (27.8)	68 (27.9)	NA	NA	HR: 0.95 (0.67–1.32)‡	0.743	
Days lost due to HF hospitalisation and CV death	Ischaemic HF	NA	NA	528.0†	934.4†	RR: 0.57 (0.34–0.93)†	0.026	0.29
	Non-ischaemic HF	NA	NA	404.4†	473.3†	RR: 0.85 (0.49–1.50)†	0.582	

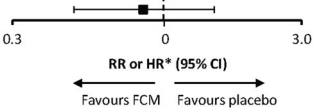


Figure 2 Subgroup analyses showing (*A*) cumulative primary outcome events (total heart failure [HF] hospitalisations and cardiovascular [CV] death) over time and (*B*) relative rate/risk for primary and secondary outcomes at week 52 with ferric carboxymaltose (FCM) versus placebo by HF aetiology (modified intention-to-treat population). *Rate ratio (RR) or hazard ratio (HR) for FCM versus placebo in each subgroup. †Annualised event rate per 100 patient-years and RR analysed using a negative binomial model. ‡HR for treatment difference analysed using Cox regression model. Negative binomial model and Cox regression model were adjusted for baseline covariates: sex, age, HF aetiology, HF duration, country, and included interaction between treatment group and HF aetiology. Respective number of patients with ischaemic and non-ischaemic HF at baseline were 265 and 282 for FCM, and 257 and 275 for placebo. CI, confidence interval; NA, not applicable.

Safety

Adverse events for patients with ischaemic and non-ischaemic HF aetiology are reported in *Table 2*. In both the FCM and placebo treatment arms, the overall incidence of treatment-emergent adverse events (TEAEs) and serious TEAEs were numerically higher in patients with ischaemic HF than with non-ischaemic HF. Adverse events by system organ class are shown in online supplementary *Table S2*.

Discussion

This pre-specified subgroup analysis of AFFIRM-AHF confirmed the poorer clinical outcomes of patients with an ischaemic versus non-ischaemic HF aetiology. There was a reduction in the primary outcome of total HF hospitalisations and CV death with IV FCM versus placebo in iron-deficient patients with ischaemic HF, but not in those with non-ischaemic HF. In the ischaemic HF subgroup, administration of FCM also improved the majority of the secondary

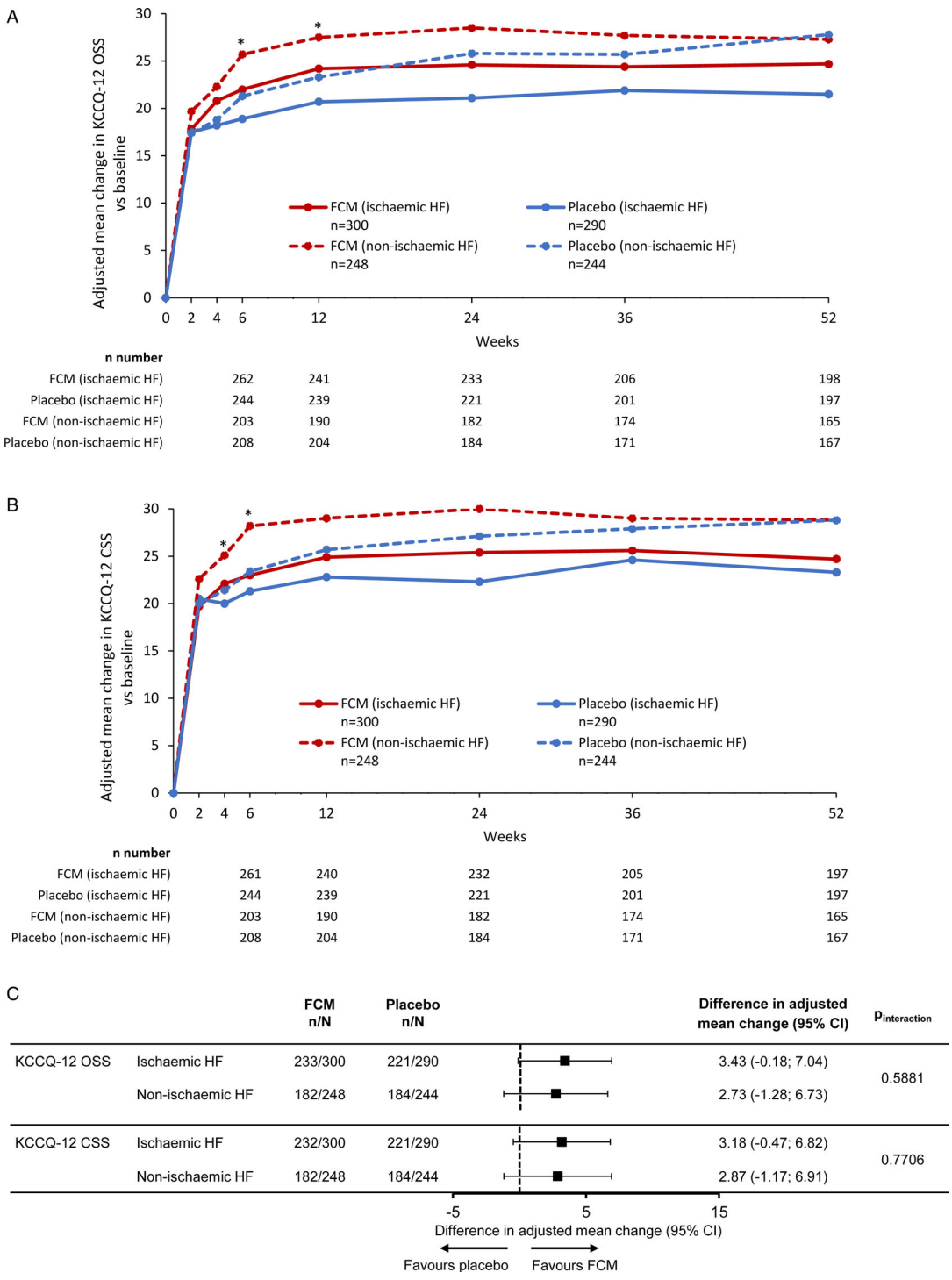
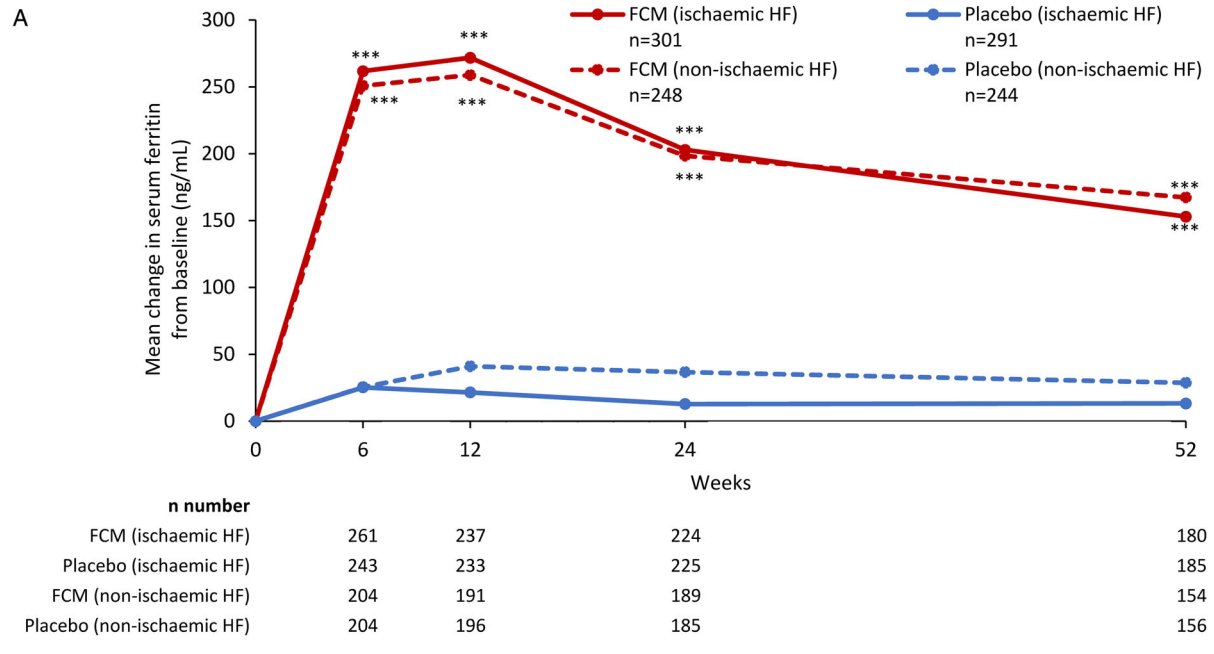
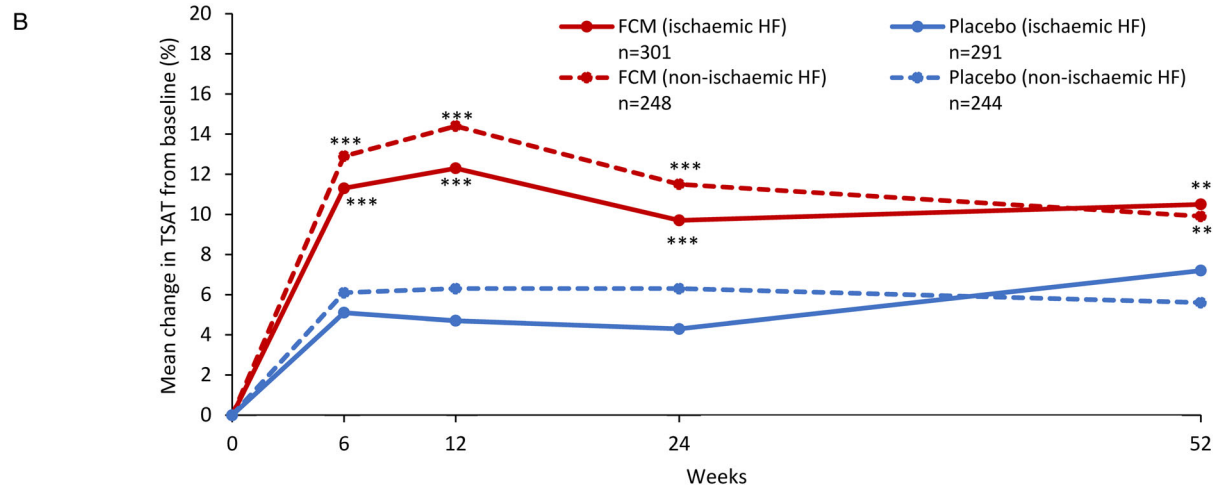


Figure 3 Adjusted mean change from baseline to week 52 in the 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12) (*A*) overall summary score (OSS) and (*B*) clinical summary score (CSS) by heart failure (HF) aetiology and treatment arm, and (*C*) interaction of HF aetiology with ferric carboxymaltose (FCM) treatment effect at week 24 (modified intention-to-treat population). *$p < 0.05$ for difference in change versus baseline with FCM versus placebo within the non-ischaemic HF subgroup only (no significance seen in the ischaemic HF subgroup). Estimates are from analysis based on mixed-effect model of repeated measures (MMRM) using unstructured covariance matrix: change score = baseline score + subgroup of ischaemic aetiology of HF (sensitivity analysis) + visit + treatment + visit × treatment + subgroup of ischaemic aetiology of HF (sensitivity analysis) × visit + subgroup of ischaemic aetiology of HF (sensitivity analysis)*treatment + subgroup of ischaemic aetiology of HF (sensitivity analysis) × visit × treatment + baseline covariates. CI, confidence interval.



n number				
FCM (ischaemic HF)	261	237	224	180
Placebo (ischaemic HF)	243	233	225	185
FCM (non-ischaemic HF)	204	191	189	154
Placebo (non-ischaemic HF)	204	196	185	156



n number				
FCM (ischaemic HF)	257	232	222	177
Placebo (ischaemic HF)	238	231	221	182
FCM (non-ischaemic HF)	205	187	187	154
Placebo (non-ischaemic HF)	201	192	183	154

Figure 4 Mean change from baseline to week 52 in (*A*) serum ferritin and (*B*) transferrin saturation (TSAT) by heart failure (HF) aetiology (safety analysis set). $^{**}p < 0.01$, $^{***}p < 0.0001$ for ferric carboxymaltose (FCM) versus placebo within each subgroup.

endpoints versus placebo, including reducing HF hospitalisations and CV hospitalisation and CV death, reducing the number of days lost due to HF hospitalisation and CV death, and increasing the time without HF hospitalisation or CV death. Nominally greater improvements in QoL were seen with FCM versus placebo, irrespective of HF aetiology.

The present subgroup analysis is the first to show an interaction between HF aetiology and the effect of FCM treatment on clinical event outcomes in patients with HF. Previous studies consistently demonstrated the benefit of FCM versus placebo for improving symptoms, QoL and clinical outcomes in patients with iron deficiency and HF, irrespective of HF aetiology.[21,22] However, these clinical trials included mostly patients with ischaemic heart disease, with 80% and 83% of patients reported as having ischaemic HF aetiology in, respectively, FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure) and

Table 2 Summary of adverse events (safety analysis set)

Adverse events	Ischaemic HF (n = 590)				Non-ischaemic HF (n = 492)			
	FCM (n = 301)		Placebo (n = 291)		FCM (n = 248)		Placebo (n = 244)	
	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n
All TEAEs	212 (70.4)	799	217 (74.6)	873	139 (56.0)	430	132 (54.1)	412
Related to study drug	10 (3.3)	13	0	0	2 (0.8)	2	2 (0.8)	2
Leading to treatment discontinuation	37 (12.3)	42	52 (17.9)	59	23 (9.3)	28	23 (9.4)	25
Leading to hospitalisation	140 (46.5)	316	160 (55.0)	398	82 (33.1)	162	90 (36.9)	150
Leading to study discontinuation	58 (19.3)	70	61 (21.0)	78	37 (14.9)	44	29 (11.9)	36
Serious TEAEs	153 (50.8)	355	174 (59.8)	439	92 (37.1)	185	98 (40.2)	173
Related to study drug	1 (0.3)	3	0	0	0	0	2 (0.8)	2
Fatal TEAEs	58 (19.3)	70	61 (21.0)	78	38 (15.3)	45	29 (11.9)	36
Related to study drug	0	0	0	0	0	0	0	0

Adverse events coded using Medical Dictionary for Regulatory Activities version 23.0.
FCM, ferric carboxymaltose; HF, heart failure; TEAE, treatment-emergent adverse event.

CONFIRM-HF (Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure).[21,22] Thus, the analyses may have been underpowered to detect such an effect, due to the small number of patients and low event rate in the non-ischaemic subgroup. Conversely, patients enrolled in AFFIRM-AHF were more heterogeneous in terms of HF aetiology than those in the FAIR-HF and CONFIRM-HF trials, with almost half having non-ischaemic HF.

The previously reported results in the overall AFFIRM-AHF study indicated a reduction in HF hospitalisations and an improvement in QoL with FCM versus placebo in patients with AHF and iron deficiency, with no effect on CV death.[16,23] In the current subgroup analysis, FCM resulted in early (from week 4) improvements in QoL in ischaemic and non-ischaemic HF patients, with no significant interaction of HF aetiology with treatment effect. Although FCM appeared to lack efficacy for reducing clinical events in patients with non-ischaemic HF, with a significant interaction of HF aetiology with treatment effect observed, this should be caveated by the typical limitations of subgroup analyses, and these observations must be considered as hypothesis-generating only.[24,25]

Multiple reasons may underlie the apparent lack of FCM efficacy for reducing clinical events in the non-ischaemic subgroup. Firstly, patients with non-ischaemic HF had better outcomes and fewer endpoint events than those with ischaemic HF (42.8 vs. 78.7 primary endpoint events per 100 patient-years in the placebo arms of each subgroup); independently of treatment, their event rate was lower than that of the ischaemic HF patients receiving FCM. Thus, the almost halved primary event rate in the non-ischaemic HF subgroup, compared with the ischaemic HF subgroup, may have reduced the likelihood of observing a treatment benefit with FCM versus placebo. Previous studies have shown that ischaemic versus non-ischaemic heart disease increases the risk of death by 16–50% in various HF populations.[12–14] The current analysis found an increase in the risk of HF hospitalisation and CV death by 84% in the placebo-treated patients with iron deficiency and an ischaemic HF aetiology, compared with those with non-ischaemic HF aetiology. The particularly large effect of ischaemic HF on prognosis in the AFFIRM-AHF population may be due also to a higher proportion of comorbidities in the ischaemic subgroup (e.g. diabetes, chronic kidney disease) and to the acute rather than chronic setting of the present study with a higher frequency of new-onset (*de novo*) HF in the non-ischaemic subgroup compared with the ischaemic subgroup (42% vs. 17%).[16] New-onset HF is associated with significantly lower mortality rates after hospitalisation and a greater likelihood of improvement with oral, guideline-directed medical therapy, compared with acutely decompensated chronic HF.[26–28] Secondly, patients with non-ischaemic HF were extremely heterogeneous, including also patients with valvular or congenital heart disease. In these cases, HF aetiology and/or associated comorbidities may have been the principal driver of outcomes, implying lower sensitivity to detect the effects of FCM administration. Thirdly, patients with non-ischaemic compared with ischaemic HF had higher TSAT and haemoglobin levels at baseline and had a numerically larger increase from baseline in KCCQ-12 OSS and CSS scores and in serum ferritin levels in the placebo group, consistent with a milder severity of HF and less need for iron repletion therapy. Consistently, Hirsch *et al.*[29] previously reported that cardiac iron concentrations (which are associated with cardiac energy production) are higher in HF patients with less severe disease than in those with more severe disease.

While further exploratory analyses showed the interaction between history of HF, HF aetiology and FCM efficacy was not statistically significant, the greatest effect of FCM versus placebo was observed in patients with ischaemic HF and a history of HF, suggesting that FCM may be most beneficial in this sub-population. However, this analysis was not sufficiently powered to draw robust conclusions and further exploration in larger data sets is needed. Indeed, the small subgroup populations, low incidence of clinical events in the non-ischaemic subgroup (lower than that of ischaemic patients receiving FCM), and the greater tendency

towards a spontaneous improvement in non-ischaemic patients, mean that the AFFIRM-AHF data cannot provide definitive conclusions regarding the efficacy of FCM in patients with AHF of non-ischaemic aetiology.

Study limitations

The main limitations of this analysis were those pertaining to subgroup analyses, which commonly have limited statistical power and can only be considered as hypothesis-generating.[24,25] As such, the lack of significant effect of FCM versus placebo on clinical outcomes in patients with non-ischaemic HF would require further exploration, also in terms of the effect of baseline characteristics on outcomes; unfortunately this is not possible in the context of the AFFIRM-AHF clinical trial because of the low subgroup patient numbers. Although a comparison of outcomes in ischaemic and non-ischaemic HF subgroups was pre-specified in the AFFIRM-AHF protocol, a *post hoc* deviation from the protocol definition of ischaemic HF was necessary to ensure the clinical validity of the analysis.

Conclusions

This exploratory subgroup analysis of the AFFIRM-AHF trial showed that FCM significantly reduced total HF hospitalisations and CV death versus placebo in iron-deficient AHF patients with ischaemic HF aetiology, but not in those with non-ischaemic HF aetiology. Improvements in QoL with FCM versus placebo were, however, similar irrespective of HF aetiology. Due to limitations associated with subgroup analyses, the current data do not permit definitive conclusions regarding the role of HF aetiology in determining the efficacy of FCM treatment in iron-deficient patients following an AHF episode.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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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.

2. Cohen-Solal A, Damy T, Terbah M, Kerebel S, Baguet JP, Hanon O, et al. High prevalence of iron deficiency in patients with acute decompensated heart failure. *Eur J Heart Fail*. 2014;**16**:984–91.
3. Van Aelst LNL, Abraham M, Sadoune M, Lefebvre T, Manivet P, Logeart D, et al. Iron status and inflammatory biomarkers in patients with acutely decompensated heart failure: early in-hospital phase and 30-day follow-up. *Eur J Heart Fail*. 2017;**19**:1075–6.
4. von Haehling S, Ebner N, Evertz R, Ponikowski P, Anker SD. Iron deficiency in heart failure: an overview. *JACC Heart Fail*. 2019;**7**:36–46.
5. Jankowska EA, Kasztura M, Sokolski M, Bronisz M, Nawrocka S, Oleskowska-Florek W, et al. Iron deficiency defined as depleted iron stores accompanied by unmet cellular iron requirements identifies patients at the highest risk of death after an episode of acute heart failure. *Eur Heart J*. 2014;**35**:2468–76.
6. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J*. 2010;**31**:1872–80.
7. Rangel I, Goncalves A, de Sousa C, Leite S, Campelo M, Martins E, et al. Iron deficiency status irrespective of anemia: a predictor of unfavorable outcome in chronic heart failure patients. *Cardiology*. 2014;**128**:320–6.
8. Sama IE, Woolley RJ, Nauta JF, Romaine SPR, Tromp J, ter Maaten JM, et al. A network analysis to identify pathophysiological pathways distinguishing ischaemic from non-ischaemic heart failure. *Eur J Heart Fail*. 2020;**22**:821–33.
9. Severino P, D'Amato A, Pucci M, Infusino F, Birtolo LI, Mariani MV, et al. Ischemic heart disease and heart failure: role of coronary ion channels. *Int J Mol Sci*. 2020;**21**:3167.
10. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al.; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;**24**:4–131.
11. Piepoli MF, Adamo M, Barison A, Bestetti RB, Biegus J, Böhm M, et al. Preventing heart failure: a position paper of the Heart Failure Association in collaboration with the European Association of Preventive Cardiology. *Eur J Heart Fail*. 2022;**24**:143–68.
12. Gajanana D, Shah M, Junpapart P, Romero-Corral A, Figueredo VM, Bozorgnia B. Mortality in systolic heart failure revisited: ischemic versus non-ischemic cardiomyopathy. *Int J Cardiol*. 2016;**224**:15–7.
13. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction. *Circulation*. 2009;**119**:3070–7.
14. Silverdal J, Sjöland H, Bollano E, Pivodic A, Dahlström U, Fu M. Prognostic impact over time of ischaemic heart disease vs. non-ischaemic heart disease in heart failure. *ESC Heart Fail*. 2020;**7**:264–73.
15. Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT, et al. Significance of ischemic heart disease in patients with heart failure and preserved, midrange, and reduced ejection fraction: a nationwide cohort study. *Circ Heart Fail*. 2017;**10**:e003875.
16. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, et al.; AFFIRM-AHF Investigators. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet*. 2020;**396**:1895–904.
17. Ponikowski P, Kirwan BA, Anker SD, Dorobantu M, Drozdz J, Fabien V, et al. Rationale and design of the AFFIRM-AHF trial: a randomised, double-blind, placebo-controlled trial comparing the effect of intravenous ferric carboxymaltose on hospitalisations and mortality in iron-deficient patients admitted for acute heart failure. *Eur J Heart Fail*. 2019;**21**:1651–8.
18. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;**310**:2191–4.
19. International Conference on Harmonisation Good Clinical Practice guidelines. https://www.ich.org/page/efficacy-guidelines (10 August 2022).
20. Claggett B, Pocock S, Wei LJ, Pfeffer MA, McMurray JJV, Solomon SD. Comparison of time-to-first event and recurrent-event methods in randomized clinical trials. *Circulation*. 2018;**138**:570–7.
21. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al.; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009;**361**:2436–48.
22. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al.; CONFIRM-HF Investigators. 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.
23. Jankowska EA, Kirwan BA, Kosiborod M, Butler J, Anker SD, McDonagh T, et al. The effect of intravenous ferric carboxymaltose on health-related quality of life in iron-deficient patients with acute heart failure: the results of the AFFIRM-AHF study. *Eur Heart J*. 2021;**42**:3011–20.
24. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet*. 2000;**355**:1064–9.
25. Khan MS, Khan MAA, Irfan S, Siddiqi TJ, Greene SJ, Anker SD, et al. Reporting and interpretation of subgroup analyses in heart failure randomized controlled trials. *ESC Heart Fail*. 2021;**8**:26–36.
26. Butt JH, Fosbøl EL, Gerds TA, Andersson C, McMurray JJV, Petrie MC, et al. Readmission and death in patients admitted with new-onset versus worsening of chronic heart failure: insights from a nationwide cohort. *Eur J Heart Fail*. 2020;**22**:1777–85.
27. Senni M, Wachter R, Witte KK, Straburzynska-Migaj E, Belohlavek J, Fonseca C, et al.; TRANSITION Investigators. Initiation of sacubitril/valsartan shortly after hospitalisation for acutely decompensated heart failure in patients with newly diagnosed (de novo) heart failure: a subgroup analysis of the TRANSITION study. *Eur J Heart Fail*. 2020;**22**:303–12.
28. Younis A, Mulla W, Goldkorn R, Klempfner R, Peled Y, Arad M, et al. Differences in mortality of new-onset (de-novo) acute heart failure versus acute decompensated chronic heart failure. *Am J Cardiol*. 2019;**124**:554–9.
29. Hirsch VG, Tongers J, Bode J, Berliner D, Widder JD, Escher F, et al. Cardiac iron concentration in relation to systemic iron status and disease severity in non-ischaemic heart failure with reduced ejection fraction. *Eur J Heart Fail*. 2020;**22**:2038–46.