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**RESEARCH ARTICLE**

# Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis

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**Aims** Iron deficiency (ID) is a common co-morbidity in patients with heart failure (HF) and has been suggested to be associated with poor prognosis. Recently completed double-blind randomised controlled trials (RCTs) studying HF patients with ID have shown improvements in functional capacity, symptoms and quality of life when treated with i.v. ferric carboxymaltose (FCM). This individual patient data meta-analysis investigates the effect of FCM vs. placebo on recurrent hospitalisations and mortality in HF patients with ID.

**Methods and results** Individual patient data were extracted from four RCTs comparing FCM with placebo in patients with systolic HF and ID. The main outcome measures were recurrent cardiovascular (CV) hospitalisations and CV mortality. Other outcomes included cause-specific hospitalisations and death. The main analyses of recurrent events were backed up by time-to-first-event analyses. In total, 839 patients, of whom 504 were randomised to FCM, were included. Compared with those taking placebo, patients on FCM had lower rates of recurrent CV hospitalisations and CV mortality [rate ratio 0.59, 95% confidence interval (CI) 0.40–0.88; $P = 0.009$]. Treatment with FCM also reduced recurrent HF hospitalisations and CV mortality (rate ratio 0.53, 95% CI 0.33–0.86; $P = 0.011$) and recurrent CV hospitalisations and all-cause mortality (rate ratio 0.60, 95% CI 0.41–0.88; $P = 0.009$). Time-to-first-event analyses showed similar findings, with somewhat attenuated treatment effects. The administration of i.v. FCM was not associated with an increased risk for adverse events.

**Conclusions** Treatment with i.v. FCM was associated with a reduction in recurrent CV hospitalisations in systolic HF patients with ID.

**Keywords** Chronic heart failure • Iron deficiency • Ferric carboxymaltose • Individual patient data meta-analysis

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# Introduction

Despite optimal conventional therapy, many patients with heart failure (HF) remain limited by symptoms, are exercise-intolerant, and are at high risk for repeated hospitalisations and mortality, all of which lead to major public health burdens.[1,2] Co-morbidities are common in patients with chronic HF, irrespective of the presence of preserved or reduced left ventricular ejection fraction (LVEF), and these may also affect outcomes.[3,4]

One such co-morbidity is iron deficiency (ID), which is present in approximately 50% of patients with HF.[5–7] Iron plays a central role in the uptake, transport, storage and metabolism of oxygen, erythropoiesis and cellular immune response.[8,9] The regulation of systemic iron balance, which is determined by the combination of dietary iron absorption, utilisation and excretion, is essential to maintain fundamental cellular functions, particularly in cells that are characterised by high energy demands, such as skeletal and cardiac myocytes.[8,10–12] At the cellular level, ID is thought to decrease enzymatic activity of both the Krebs cycle and the respiratory chain in the mitochondria. As a consequence, ID can lead to disturbance in the energetic metabolism of cells.[13]

In HF patients, ID is associated with reduced exercise capacity, impaired quality of life (QoL) and poor prognosis, irrespective of whether anaemia is present or not.[5,14–18] Two recently published randomised controlled trials (RCTs) investigating patients with systolic HF and ID, which compared the effects of i.v. iron as ferric carboxymaltose (FCM) with placebo, demonstrated important improvements in functional capacity, symptoms and QoL.[19,20] The clinical and prognostic significance of ID in HF is now well recognised.[7,21,22] However, the available information on the effects of i.v iron on morbidity and mortality is limited while no such information is available for the effects of oral iron on these outcomes.[23]

The aim of this meta-analysis using individual patient data was to explore the effect of i.v. FCM relative to placebo on recurrent hospitalisations and mortality rates, focusing on recurrent cardiovascular (CV) hospitalisations. Composite outcomes that consider only the first event (i.e. time-to-first-event analyses) are suboptimal for evaluating the progression of chronic diseases such as HF. Hospitalisations for worsening HF are an indication of worsening condition. Taking all such hospitalisations into account is more representative of disease progression and more accurately estimates the effect of treatment on the true burden of disease. It is well known that an increase in such hospitalisations is associated with an increased risk for CV mortality. Any censoring attributable to CV mortality is not independent of the recurrent event process. Recurrent event analysis investigating this outcome must therefore account for the competing risk for CV mortality. Data from all double-blind RCTs comparing i.v. FCM with placebo in patients with systolic HF and ID which were closed by 30 June 2016 are included in this analysis.[19,20,24,25]

# Methods

## Study design and inclusion criteria

Four double-blind RCTs investigating the effects of i.v. FCM versus placebo on clinical outcomes, QoL and symptoms in ambulatory after systolic chronic HF patients with ID that had been closed by 30 June 2016. Data from these four trials, designated FER-CARS-01, FAIR-HF (NCT00520780),[19] EFFICACY-HF (NCT00821717) and CONFIRM-HF (NCT01453608),[20] are included in this meta-analysis. The main study design features are shown in *Table 1*. All four studies were approved by the appropriate regulatory authorities and ethics committees, and all patients who participated in the individual RCTs provided written informed consent. The four RCTs were conducted in strict compliance with the guidelines for Good Clinical Practice of the International Council for Harmonisation (ICH GCP) and with the Declaration of Helsinki. The risk for bias from the four RCTs included in this meta-analysis was limited because the four trials were randomised, double-blinded, investigated similar patient populations and used the same iron preparation (i.e. i.v. FCM). A detailed statistical analysis plan (SAP) was prepared a priori for this meta-analysis. All four studies included were designed and undertaken by academic executive committees in conjunction with the sponsor. Authors had full access to all data and had final responsibility for the decision to submit for publication.

## Outcome measures

For the purpose of this meta-analysis, the main outcome was predefined as the composite of recurrent CV hospitalisations and CV mortality. Other outcomes included the composites of HF hospitalisations and CV mortality, CV hospitalisations and all-cause mortality, and HF hospitalisations and all-cause mortality, in addition to the individual composite components. All outcomes were assessed in recurrent event analyses and backed up by time-to-first-event analyses.

## Definition of outcomes

For each RCT, reasons for hospitalisations and cause of mortality were independently adjudicated in a blinded manner by a committee using predefined criteria detailed in an adjudication charter developed for that RCT. The same criteria were used across the four RCTs. The adjudicated outcomes were used in this analysis. All hospitalisations and deaths were adjudicated irrespective of the investigator's reported term. For the purpose of this analysis, all adjudications for 'worsening HF' and 'other CV' were combined for the count of 'any CV hospitalisation'. Cause of death was adjudicated as one of the following: '(worsening of) HF'; 'other CV'; 'non-CV'; 'serious (study) drug reaction', and 'insufficient data to adjudicate'.[26] For the purpose of this analysis, safety outcomes focused on the incidence and frequency of reported adverse events (AEs).

## Statistical analysis

All analyses used individual patient data and are fully documented in a prespecified SAP. The main outcome analysis was conducted using the full analysis set (FAS). Event rates (including recurrent hospitalisations) were analysed using a log-link negative binomial regression model. The model included fixed covariates of treatment, haemoglobin (Hb) at baseline, region and random effect for study. Length of observation was logged and included as an offset variable. Rate ratios, associated 95% confidence intervals (CIs) and *P*-values were obtained from the model. The interaction term between study and treatment was tested on a separate model to further assess the treatment effect across studies. Statistical heterogeneity across the studies was quantified using the $I^2$ statistic.

**Table 1 Design features of the randomised controlled trials included in this meta-analysis**

| | FER-CARS-01 | FAIR-HF | EFFICACY-HF | CONFIRM-HF |
|---|---|---|---|---|
| Patient population | Ambulatory, optimally treated, systolic CHF with ID, NYHA class II/III, eGFR < 60 mL/min/1.73 $m^2$ | Ambulatory, optimally treated, systolic CHF with ID, NYHA class II/III | Ambulatory, optimally treated, systolic CHF with ID, NYHA class II/III | Ambulatory, optimally treated, systolic CHF with ID, NYHA class II/III |
| Randomisation | 2:2:1 (FCM:IS:placebo) | 2:1 (FCM:placebo) | 1:1 (FCM:placebo) | 1:1 (FCM:placebo) |
| Patients, *n* (FAS) FCM/placebo | 30/27[a]/15 | 304/155 | 20/14[b] | 150/151 |
| Comparator | i.v. FCM vs. IS vs. placebo[c] | i.v. FCM vs. placebo[c] | i.v. FCM vs. placebo[c] | i.v. FCM vs. placebo[c] |
| Study duration | 12 weeks | 24 weeks | 24 weeks | 52 weeks |
| Calculation of iron repletion dose | Ganzoni formula using the mean of two baseline Hb values | Ganzoni formula using the mean of two baseline Hb values | Ganzoni formula using the mean of two baseline Hb values | Determined by baseline Hb values and screening body weight |
| Correction phase duration (i.e. until iron repletion) | Weekly i.v. injections for minimally 3, maximally 9 weeks | Weekly i.v. injections for maximally 4 weeks | Weekly i.v. injections for minimally 3, maximally 9 weeks | Maximally two i.v. injections over a 6-week period |
| Correction phase dosing regimen (i.e. until iron repletion) | 200 mg/100 mg iron: FCM or placebo | 200 mg/100 mg iron: FCM or placebo | 200 mg/100 mg iron: FCM or placebo | 500 mg/1000 mg iron: FCM or placebo |
| Maintenance phase | 4-weekly 200 mg iron i.v. injection (FCM/placebo) up to 24 weeks after randomisation | 4-weekly 200 mg iron i.v. injection (FCM/placebo) up to 12 weeks after randomisation | 4-weekly 200 mg iron i.v. injection (FCM/placebo) up to 24 weeks after randomisation | 3-monthly 500 mg iron i.v. injection (FCM/placebo) up to 36 weeks after randomisation, if ID still present |
| Primary endpoint(s) | PGA at week 12 and NYHA class from baseline to week 12 | PGA at week 24 and NYHA class from baseline to week 24 | Change in 6MWT and NYHA class from baseline to week 24 | Change in 6MWT from baseline to week 24 |

6MWT, 6-minute walk test; CHF, chronic heart failure; eGFR, estimated glomerular filtration rate; FAS, full analysis set; FCM, ferric carboxymaltose; Hb, haemoglobin; ID, iron deficiency; IS, iron sucrose; NYHA, New York Heart Association; PGA, patient global assessment.
Ganzoni formula of total iron deficit [mg]: body weight [kg] × (150 − actual Hb [g/L]) × 0.24 + 500 [mg]. Iron repletion dose, correction of iron deficiency.
[a]Patients randomised to i.v. IS ($n = 27$) were not included in this meta-analysis.
[b]EFFICACY-HF was discontinued as a result of recruitment issues.
[c]Placebo, i.v. normal saline.

Time-to-first-event analyses were performed using Cox models fitted with fixed effects of treatment, Hb at baseline, region and random study effect. As a sensitivity analysis, a joint frailty model was fitted to jointly examine hospitalisation and death rates. The model assumed Poisson and log-logistic distributions for hospitalisation and time to death, respectively, conditional on the frailty terms, with individual frailties following a gamma distribution. Rates of HF hospitalisation followed a negative binomial distribution, and time to CV mortality followed a Lomax distribution as described by Rogers *et al.*[27]

Adverse event incidences were presented as the total number of events, patients with at least one event and the event rate per 100 patient-years. The joint frailty model analysis was performed using R Version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria). All other analyses were performed using SAS Version 9.3 (SAS Institute, Inc., Cary, NC, USA).

# Results

As of 30 June 2016, four double-blind RCTs comparing FCM with placebo were closed. In total, 844 patients (507 FCM and 337 placebo) had been randomised in the four RCTs. Data for 839 patients (504 FCM and 335 placebo) were included in this analysis in the FAS, and data for 842 (507 FCM and 335 placebo) were included in the safety set.

## Baseline characteristics

*Table 2* shows the baseline characteristics and concomitant medications for the pooled dataset. The baseline characteristics were well balanced by treatment allocation, other than New York Heart Association (NYHA) class, in which, compared with the placebo pool, a higher proportion of patients allocated to FCM were in NYHA class III (70% and 61%, respectively, in the FCM and placebo groups).

## Follow-up

The overall mean duration of observation was 31 weeks. The proportion of patients in whom study treatment was stopped prematurely was similar in the two groups (9.5% and 10.7% in the FCM and placebo groups, respectively). The mean ± standard deviation (SD) FCM dose needed to correct the ID was 1327 ± 329 mg.

**Table 2 Baseline characteristics**

| Variable | FCM pool ($n = 504$) | Placebo pool ($n = 335$) |
|---|---|---|
| Demographics | | |
| Baseline age, years, mean ± SD | 68.0 ± 10.1 | 68.3 ± 10.3 |
| Female, *n* (%) | 246 (49%) | 169 (50%) |
| White European ethnicity, *n* (%) | 502 (100%) | 334 (100%) |
| Clinical features/physical findings | | |
| NYHA class, *n* (%) | | |
| II | 146 (29%) | 128 (38%) |
| III | 354 (70%) | 205 (61%) |
| IV | 4 (1%) | 2 (1%) |
| LVEF, mean ± SD | 33.3 ± 6.9 | 34.5 ± 7.1 |
| BMI, kg/m$^2$, mean ± SD | 27.9 ± 4.7 | 28.3 ± 5.4 |
| 6MWT, distance, m, mean ± SD | 277 ± 105 | 284 ± 106 |
| Cardiovascular risk factors, *n* (%) | | |
| Hypertension | 411 (82%) | 283 (84%) |
| Dyslipidaemia | 258 (51%) | 182 (54%) |
| Diabetes mellitus | 148 (29%) | 93 (28%) |
| Smoking | 145 (29%) | 92 (27%) |
| Medical history, *n* (%) | | |
| Atrial fibrillation | 179 (36%) | 126 (38%) |
| Myocardial infarction | 270 (54%) | 183 (55%) |
| Angina pectoris | 300 (60%) | 194 (58%) |
| Stroke | 46 (9%) | 37 (11%) |
| Coronary revascularisation | 116 (23%) | 73 (22%) |
| Laboratory test results | | |
| Hb, g/dL, mean ± SD | 12.08 ± 1.34 | 12.20 ± 1.34 |
| Hb <12 g/dL, *n* (%) | 228 (45%) | 142 (42%) |
| Ferritin, ng/mL, mean ± SD | 54.8 ± 52.3 | 59.9 ± 56.6 |
| Ferritin <100 ng/mL, *n* (%) | 448 (89%) | 292 (87%) |
| TSAT, %, mean ± SD | 18.5 ± 14.1 | 17.5 ± 8.5 |
| TSAT ≤20%, *n* (%) | 338 (67%) | 220 (66%) |
| eGFR (CKD-EPI), mL/min/1.73 m$^2$, mean ± SD | 62.9 ± 21.3 | 63.1 ± 22.6 |
| eGFR <60 mL/min/1.73 m$^2$, *n* (%) | 216 (43%) | 156 (47%) |
| Concomitant treatments, *n* (%) | | |
| Diuretics | 465 (92%) | 307 (92%) |
| ACE inhibitor or angiotensin receptor blocker | 473 (93%) | 313 (93%) |
| Beta-blocker | 438 (86%) | 294 (88%) |
| Aldosterone antagonists | 278 (55%) | 174 (52%) |
| Digitalis glycoside | 94 (19%) | 80 (24%) |
| Warfarin | 52 (10%) | 37 (11%) |
| Lipid-lowering therapy | 272 (54%) | 195 (58%) |

6MWT, 6-minute walk test; ACE, angiotensin-converting enzyme; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula; eGFR, estimated glomerular filtration rate; FCM, ferric carboxymaltose; Hb, haemoglobin; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SD, standard deviation; TSAT, transferrin saturation.

The overall mean ± SD cumulative FCM dose administered was 1679 ± 522 mg.

## Outcomes

*Table 3* and *Figure 1* show the results for recurrent hospitalisations and mortality. Compared with placebo, FCM significantly reduced rates of recurrent CV hospitalisations and CV mortality (rate ratio 0.59, 95% CI 0.40–0.88; $P = 0.009$), recurrent HF hospitalisations and CV mortality (rate ratio 0.53, 95% CI 0.33–0.86; $P = 0.011$), recurrent CV hospitalisations and all-cause mortality (rate ratio 0.60, 95% CI 0.41–0.88; $P = 0.009$), and recurrent HF hospitalisations and all-cause mortality (rate ratio 0.54, 95% CI 0.34–0.87; $P = 0.011$). *Figure 2* depicts the extent of the contribution of each trial to the overall estimate for the main outcome of recurrent CV hospitalisations and CV mortality.

*Table 4* shows the data for the time-to-first-event analyses. Compared with those in the placebo group, the occurrence of HF hospitalisations or CV mortality was less frequent in patients assigned to FCM (hazard ratio 0.55, 95% CI 0.35–0.88; $P = 0.012$), as was that of HF hospitalisations or all-cause mortality (hazard ratio 0.56, 95% CI 0.36–0.88; $P = 0.013$). Kaplan–Meier plots for the time-to-first-event analysis are shown in the supplementary material online (*Figure S1*).

The median duration for a HF hospitalisation was 10 days (minimum: 3 days; maximum: 31 days) for patients randomised to FCM and 12 days (minimum: 1 day; maximum: 165 days) for patients randomised to placebo.

## Prespecified subgroup analysis

*Figure 3* depicts the prespecified subgroup analyses performed for the key subgroups (in tertiles) [Hb, serum ferritin and transferrin saturation (TSAT)] for the composite outcomes of recurrent CV hospitalisations and CV mortality, recurrent HF hospitalisations and CV mortality, and recurrent CV hospitalisations and all-cause mortality. A substantially lower effect was observed for the three composite outcomes in the subgroup with TSAT of ≥20.1%.

## Safety reporting

The proportion of patients who experienced at least one AE (serious or non-serious) was similar in both treatment groups, with incidence rates of 105.4 and 95.8 per 100 patient-years at risk in the FCM and placebo groups, respectively. The proportions of patients who withdrew from study treatment as a result of an AE were 6.3% in patients allocated to FCM and 10.1% in patients allocated to placebo (*Table 5*). No serious or severe hypersensitivity reactions were reported and the nature, type, intensity and frequency of AEs were similar between the two treatment groups across the four RCTs.

## Sensitivity analysis

A random-effects model analysis was performed and the overall rate ratios were consistent with the direction and size of those calculated by the fixed-effects model. The leave-one-out cross-validation method was used on the model to investigate the validity and robustness of the meta-analysis. The results of this validation did not change the overall results.

# Discussion

The main finding of the present meta-analysis is that treatment with i.v. iron (FCM) is associated with lower rates of recurrent CV hospitalisations and CV mortality in ambulatory, stable, systolic

**Table 3 Recurrent event outcomes**

| Outcomes | Total events, *n* (incidence per 100 patient-years of follow-up) | | RR (95% CI) | *P*-value |
|---|---|---|---|---|
| | FCM pool (*n* = 504) | Placebo pool (*n* = 335) | | |
| CV hospitalisations and CV mortality | 69 (23.0) | 92 (40.9) | 0.59 (0.40–0.88) | 0.009 |
| HF hospitalisations and CV mortality | 39 (13.0) | 60 (26.7) | 0.53 (0.33–0.86) | 0.011 |
| CV hospitalisations and all-cause mortality | 71 (23.7) | 94 (41.8) | 0.60 (0.41–0.88) | 0.009 |
| HF hospitalisations and all-cause mortality | 41 (13.7) | 62 (27.6) | 0.54 (0.34–0.87) | 0.011 |
| All-cause hospitalisations and all-cause mortality | 108 (36.1) | 118 (52.5) | 0.73 (0.52–1.01) | 0.060 |
| HF hospitalisations | 22 (7.3) | 43 (19.1) | 0.41 (0.23–0.73) | 0.003 |
| CV hospitalisations | 52 (17.4) | 75 (33.3) | 0.54 (0.36–0.83) | 0.004 |
| All-cause hospitalisations | 89 (29.7) | 99 (44.0) | 0.71 (0.50–1.01) | 0.056 |

CI, confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure; RR, rate ratio.

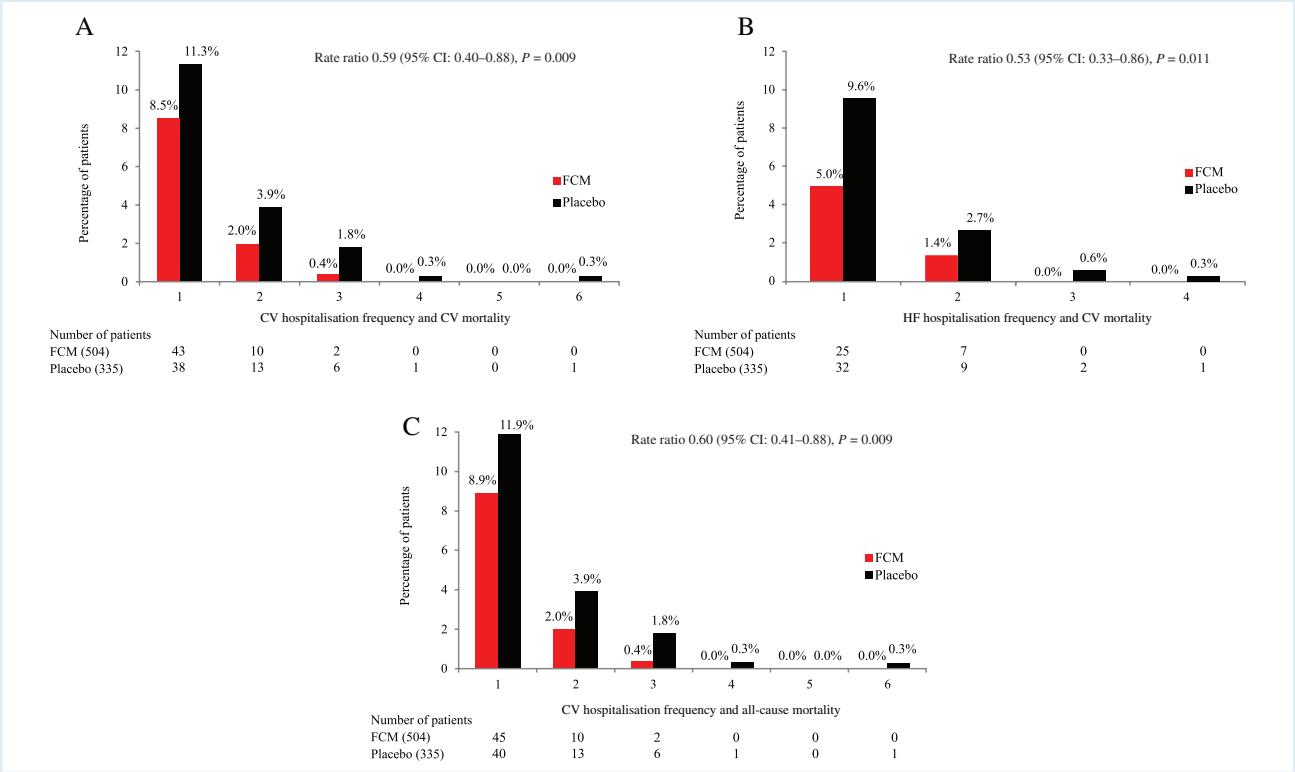


**Figure 1** Recurrent event analyses for (*A*) cardiovascular (CV) hospitalisations and CV mortality, (*B*) heart failure (HF) hospitalisations and CV mortality, and (*C*) CV hospitalisations and all-cause mortality. CI, confidence interval; FCM, ferric carboxymaltose.

HF patients with ID. Treatment with i.v. FCM was not associated with an increased risk for AEs compared with placebo. This is the first meta-analysis using individual patient data obtained from four closed RCTs using i.v. iron (FCM) in HF populations with ID.

Recent meta-analyses investigating the effects of treatment with i.v. iron on hospitalisations and mortality using published data showed similar benefits of iron treatment with respect to HF hospitalisations and the combination of HF hospitalisations and death.[28–31]

However, the criteria used to determine ID differed between the RCTs included, as did the i.v. iron therapy and doses used.[28–31] Furthermore, the use of erythropoietin-stimulating agents (ESAs) was allowed in several of these RCTs. Only one of the meta-analyses analysed recurrent HF hospitalisations.[29]

In the present meta-analysis, we included individual patient data from four RCTs that used the same iron preparation (i.v. FCM). The patient populations included were similar and the same criteria were used to determine the presence of ID across the four RCTs.

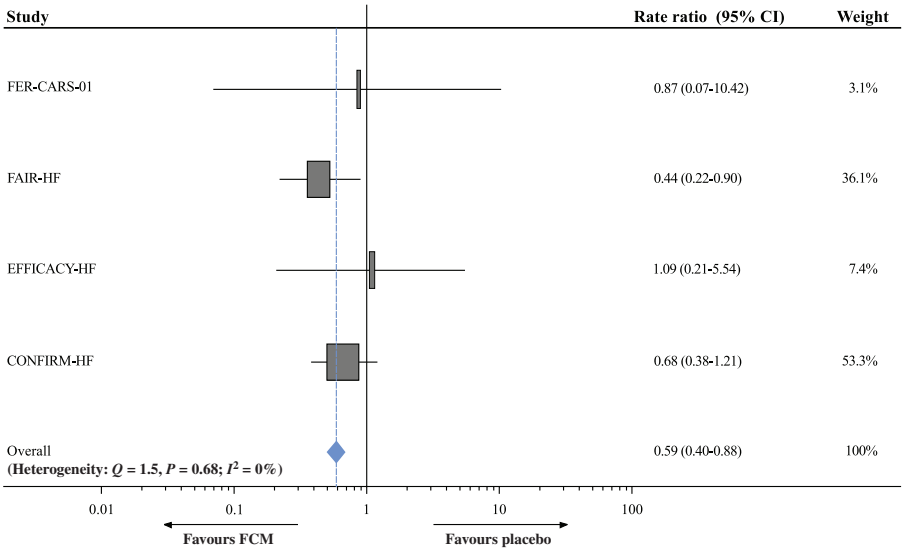


**Figure 2** Rate ratios for cardiovascular hospitalisations and cardiovascular mortality for the individual randomised controlled trials included in this meta-analysis. CI, confidence interval; FCM, ferric carboxymaltose.

**Table 4 Time-to-first-event outcomes**

| Outcomes | Patients with event, *n* (incidence per 100 patient-years at risk) | | HR (95% CI) | *P*-value |
|---|---|---|---|---|
| | FCM pool (*n* = 504) | Placebo pool (*n* = 335) | | |
| CV hospitalisation or CV mortality | 55 (18.4) | 59 (26.2) | 0.70 (0.48–1.02) | 0.062 |
| HF hospitalisation or CV mortality | 32 (10.7) | 44 (19.6) | 0.55 (0.35–0.88) | 0.012 |
| CV hospitalisation or all-cause mortality | 57 (19.0) | 61 (27.1) | 0.70 (0.49–1.02) | 0.060 |
| HF hospitalisation or all-cause mortality | 34 (11.4) | 46 (20.4) | 0.56 (0.36–0.88) | 0.013 |
| All-cause hospitalisation or all-cause mortality | 81 (27.0) | 75 (33.3) | 0.81 (0.59–1.12) | 0.199 |
| HF hospitalisation | 19 (6.3) | 34 (15.1) | 0.42 (0.24–0.74) | 0.003 |
| CV hospitalisation | 43 (14.4) | 52 (23.1) | 0.61 (0.40–0.91) | 0.017 |
| All-cause hospitalisation | 68 (22.7) | 67 (29.8) | 0.75 (0.53–1.06) | 0.099 |
| CV mortality | 17 (5.7) | 17 (7.6) | 0.84 (0.43–1.66) | 0.620 |
| All-cause mortality | 19 (6.3) | 19 (8.4) | 0.84 (0.44–1.61) | 0.604 |

CI, confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure; HR, hazard ratio.

This allowed for a more accurate, granular and robust assessment of the relative effects of the administration of i.v. iron (i.e. FCM) on recurrent hospitalisations and mortality compared with the other recently performed meta-analyses.[28–31]

Although ID is recognised as a common and important co-morbidity in HF, neither screening for ID nor its subsequent treatment are yet part of the routine standard of care in this patient population. There is therefore a need to increase awareness among general practitioners and cardiologists to both identify and subsequently initiate treatment with i.v. iron (FCM), which has been shown to have a positive impact on clinical outcome, physical performance and QoL in this patient population.[19–21] This is reflected in the recently updated European Society of Cardiology (ESC) HF Guidelines 2016, which recommend screening for ID in HF patients (recommendation IC) and, in addition, to consider using i.v. FCM in symptomatic systolic HF patients with ID (recommendation IIaA).[21]

There is limited evidence of clinically meaningful benefits using oral iron preparations to treat ID in HF patients. Oral iron is both poorly absorbed and badly tolerated because of adverse gastrointestinal effects, particularly in patients with chronic diseases, such as HF.[32] There are also limited data concerning the efficacy and safety of other i.v. iron preparations in the treatment of ID in HF patients. Only three small controlled studies have investigated the efficacy and safety of i.v. iron sucrose in systolic HF patients with ID.[33–35] The iron sucrose trials enrolled 23, 11 and 20 patients, respectively, and the results showed initial benefits in improving symptoms, QoL and functional capacity. A larger RCT

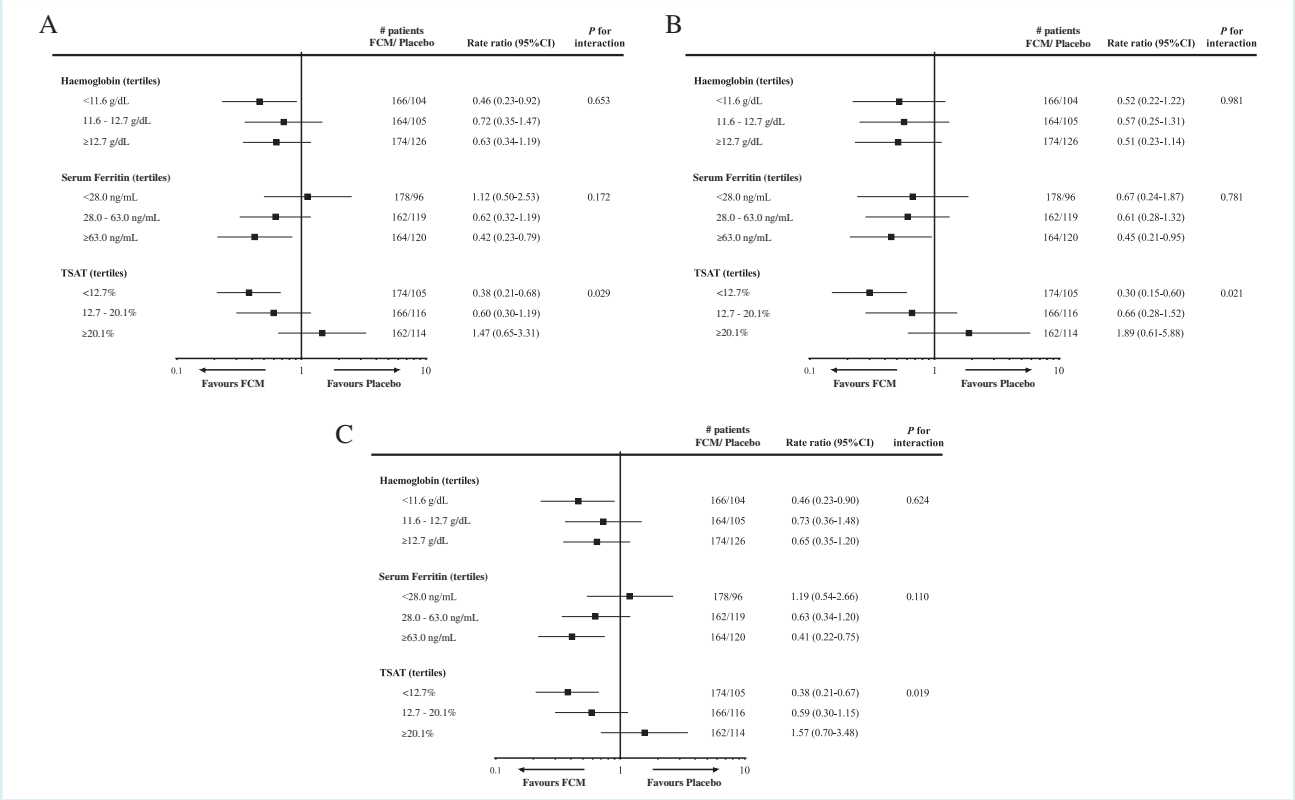


**Figure 3** Subgroup analyses for (*A*) recurrent cardiovascular hospitalisations and cardiovascular mortality, (*B*) recurrent heart failure hospitalisations and cardiovascular mortality, and (*C*) recurrent cardiovascular hospitalisations and all-cause mortality. CI, confidence interval; FCM, ferric carboxymaltose; TSAT, transferrin saturation.

**Table 5 Investigator-reported adverse events**

| Safety reporting | FCM pool ($n = 507$) | | Placebo pool ($n = 335$) | |
|---|---|---|---|---|
| | Patients with event, *n* (%) | Incidence/100 patient-years at risk | Patients with event, *n* (%) | Incidence/100 patient-years at risk |
| AEs | 317 (62.5%) | 105.4 | 215 (64.2%) | 95.8 |
| Serious AEs | 86 (17.0%) | 28.6 | 79 (23.6%) | 35.2 |
| AEs leading to study drug withdrawal | 32 (6.3%) | 10.6 | 34 (10.1%) | 15.1 |
| Study drug-related AEs | 50 (9.9%) | 16.6 | 20 (6.0%) | 8.9 |
| Serious drug-related AEs | 0 | 0 | 1 (0.3%) | 0.4 |
| Study drug-related AEs leading to study drug withdrawal | 7 (1.4%) | 2.3 | 3 (0.9%) | 1.3 |

AE, adverse event; FCM, ferric carboxymaltose.

[Oral Iron Repletion Effects on Oxygen Uptake in Heart Failure (IRONOUT)] recently reported that oral iron did not replenish depleted iron stores and, as a consequence, did not improve peak $VO_2$ or any clinically relevant outcomes in HF with reduced ejection fraction (HFrEF) patients with ID.[36] The authors concluded that the IRONOUT results do not support the use of oral iron supplementation in HFrEF patients with ID.[36]

The current treatment recommendations for HF include the prescription of beta-blockers, ACE inhibitors and/or angiotensin receptor blockers, and diuretics. These treatments play a critical role in the management of HF. Just over 90% of patients included in the four RCTs analysed in this meta-analysis were prescribed at least one of these drugs and could thus be considered as being 'optimally treated'. However, despite the optimisation of HF treatments in systolic HF, post-discharge mortality and readmission rates for HF in patients with HF remain unacceptably high. This confirms that other HF co-morbidities should be considered in the process of defining overall treatment strategies for HF patients.[21]

In the exploratory pre-planned subgroup analysis, the reductions in recurrent CV hospitalisations and CV mortality, in recurrent HF hospitalisations and CV mortality, and in recurrent CV hospitalisations and all-cause mortality in the FCM vs. placebo groups were larger in patients with TSAT in the two lower tertiles (i.e. TSAT of <12.7% and TSAT of 12.7–20.1%). Although these findings should be interpreted with caution, they do warrant the targeting of further research to better understand the role of TSAT in the definition of ID. Such research is currently ongoing.

The FAIR-HF[19] and CONFIRM-HF[20] trials contributed approximately 90% of the total number of patients included in our meta-analysis. A sensitivity analysis was performed and showed that the overall rate ratios were consistent with the direction and size of those calculated by the fixed-effects model. The results of our meta-analysis are limited by sample size, number of deaths and follow-up duration in the clinical trials included in this analysis, in addition to the relatively small number of outcomes observed in the control group. We also recogonise that subgroup analyses in meta-analyses pose methodological challenges and should be viewed with caution.

Meta-analyses may provide useful information concerning treatment-related outcomes and may guide future research. However, prospective RCTs remain the gold standard method and are considered to provide the strongest and most robust evidence concerning an intervention. Four large (>1000 patients in each trial) RCTs evaluating the effects of i.v. iron on mortality and hospitalisations in differing HF populations are being set up or are currently recruiting. In three of these RCTs [FAIR-HF2 (NCT03036462), AFFIRM-AHF (NCT02937454), HEART-FID (NCT03037931)], patients will be randomised to either i.v. FCM or placebo, and in the fourth RCT [IRONMAN (NCT02642562)] patients will be randomised to either i.v. iron isomaltoside or placebo. The results of all these trials are expected within the next 5 years.

# Conclusions

The results of this individual patient data meta-analysis show that treatment of ID with i.v. FCM in ambulatory systolic HF patients with ID may decrease recurrent CV hospitalisations. These findings suggest that i.v. iron therapy may potentially represent a beneficial addition to the standard medical management of HF. An adequately powered RCT is needed to confirm these findings.

# Supplementary Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Kaplan–Meier plots for time-to-first-event analyses.

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