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Original Article

Effect of ferric carboxymaltose on hospitalization and mortality outcomes in chronic heart failure: A meta-analysis

Jamshed Dalal[a], Vijay Katekhaye[b], Rishi Jain[c,*]

[a] Centre for Cardiac Sciences, Kokilaben Dhirubhai Ambani Hospital, Rao Saheb Achutrao Patwardhan Marg, Four Bunglows, Andheri West, Mumbai, Maharashtra 400053, India
[b] Dev Clinic, Opp. Bhosala Vedh School, Ayachit Mandir Road, Mahal, Nagpur, Maharashtra 440032, India
[c] Medical Services Dept., Emcure Pharmaceuticals Ltd., Survey No. 255/2, Phase-I, M.I.D.C., Hinjawadi, Pune, Maharshtra 411057, India

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ABSTRACT

Introduction: Iron administration especially intravenous iron therapy is associated with improvements in exercise capacity and quality of life in patients with chronic heart failure (CHF). Our aim was to assess effect of ferric carboxymaltose (FCM) on hospitalization and mortality outcomes in CHF.
Materials and methods: A literature search across PUBMED, Google Scholar and trials database www.clinicaltrials.gov was conducted to search for randomized controlled trials (till August 2016) comparing FCM to placebo in CHF with or without anaemia. Published human studies in English language which reported data on mortality and hospitalization rates were included. Primary outcome was rates of HF hospitalizations and secondary outcomes were hospitalization due to any cardiovascular (CV) cause, death due to worsening HF and any CV death.
Results: From 17 studies identified, two were included in final analysis (n = 760; 455 in FCM and 305 in placebo arms). We observed significantly lower rates of hospitalization for worsening HF in FCM arm [Risk Ratio (RR) 0.34, 95% confidence interval (CI) 0.19, 0.59, p = 0.0001] as well as for any CV hospitalizations [RR 0.49, 95% CI 0.35, 0.70; p < 0.0001] (figure). No heterogeneity in studies was seen for these two outcomes (I^2 = 0%, p > 0.05). No significant treatment effect with FCM was noted in mortality from worsening HF (RR 0.41, 95% CI 0.02, 7.36; p = 0.55) or any CV death (RR 0.80, 95% CI 0.40, 1.57; p = 0.51).
Conclusion: FCM reduces hospitalization rates in CHF but may not reduce mortality outcome. This finding needs further evaluation in a large, prospective, randomized controlled trial.

1. Introduction

Chronic heart failure (CHF) is associated with adverse short-term and long-term consequences which lead to poor health related quality of life (QoL).[1,2] Various factors determine the clinical course of HF patients.[3,4] Iron deficiency is known to occur with a greater frequency in HF, is associated with unfavourable clinical outcome and has prognostic significance.[5–7] Anemia in CHF is associated with increases in left ventricular (LV) mass, increased markers of HF like natriuretic peptides, and higher number of repeat hospitalizations.[8–10] In a meta-analysis of anemia and mortality in HF by Gorenveld et al.,[11], presence of anaemia was found to increase risk of death in HF compared to non-anaemic population (46.8% Vs 29.5%) in a follow-up of six months.

Development of anaemia in HF is multifactorial. Defective erythropoiesis predominates in HF besides contribution from renal dysfunction and neurohormonal and pro-inflammatory cytokine activation leading to iron deficiency (ID) state.[12] Further, defective iron absorption, and reduced re-absorption of recycled iron contribute to ID. ID is significantly prevalent worldwide including developing countries like India.[13] Study in Indian population reported ID in 76% HF cases and 48.7% had absolute deficiency.[14] Development of ID even in absence of anaemia is known to reduce aerobic performance, and result in exercise intolerance.[15]

Treatment of ID is associated with improvement in cardiac function, clinical symptoms, peak oxygen consumption, increase exercise tolerance, along with improved cardiac remodelling.[16,17,18] A meta-analysis involving 370 patients being treated by intravenous iron therapy reported improved outcome in terms of QoL, improved exercise tolerance suggested by increase in 6 min walk

* Corresponding author.
E-mail addresses: jjdalal@hotmail.com (J. Dalal), katekhayevijay23@gmail.com (V. Katekhaye), drrishijain@gmail.com (R. Jain).

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distance (6MWD) and lower rates of hospitalizations.[19] Given a choice, intravenous iron may always be preferred considering problems with oral iron absorption and gastrointestinal intolerance.[20] In fact, the 2016 European Society of Cardiology (ESC) CHF guidelines recommend intravenous iron – ferric carboxymaltose (FCM) in symptomatic HF with reduced ejection fraction (EF) to relieve symptoms and improve exercise capacity and QoL.[21] As suggested from literature evidence and recommendation from guideline, intravenous iron benefits HF in terms of symptomatic improvements. However, it remains unclear whether this benefit translates to reduction in endpoints such as HF hospitalizations and deaths. Although, a previous meta-analysis from Moore and colleagues[22] with FCM is available, it was for anaemia from all causes and assessed changes in haematological parameters. Here, we performed a systematic review and a meta-analysis exploring the effect of intravenous iron therapy with FCM on hospitalization and mortality outcomes in HF.

2. Methods

2.1. Search strategy

We searched the PUBMED, and Google scholar databases and international clinical trial registry – http://www.clinicaltrials.gov; for RCTs of FCM in CHF. RCTs published till August 2016 were searched using the following search terms: Ferric carboxymaltose OR FCM AND chronic heart failure OR CHF.

2.2. Trials selection

In this meta-analysis, we included human trials where the control group was given a placebo, trial duration of minimum 12-weeks, and the data on hospitalization and mortality for heart failure or any cardiovascular (CV) cause were available irrespective of study included anaemic population or not. We excluded trials that were performed in patients under age of 18, in pregnant patients and in patients with active bleeding. Only published RCTs in English language were included. Other languages were excluded for technical and cost-related reasons.

2.3. Extraction of data

Two investigators extracted the trials data and assessed quality of the trial independently as per guidelines published by the Cochrane Collaboration.[23] Any discrepancy in views of two investigators was resolved by the opinion of third investigators and finalized by majority view. Characteristics of trials included in the meta-analysis are described in Table 1.

2.4. Quality assessment

Quality assessment was performed by two authors independently who assessed trials in following domains: i) random sequence generation, ii) allocation concealment, iii) blinding of participants and personnel, iv) blinding of outcome assessment, v) incomplete outcome data reporting, and v) selective outcome reporting. Each of these domains were graded for biases as low risk, unclear risk, lack of information or uncertainty, or high risk as per the standard criteria published from Cochrane collaboration.[23]

Table 1
Characteristics of the included studies.

Characteristics	FAIR-HF[26]	CONFIRM-HF[25]
Total patients randomized	459	304
Active drug and dose	IV FCM (200 mg)	IV FCM (500–1000 mg)
Placebo	Saline	Saline
Patients randomized	N = 304 to FCM N = 155 to saline	N = 152 to FCM N = 152 to saline
Iron dosage in therapy phase	200 mg weekly	500–1000 mg weekly
Iron dosage in maintenance phase	200 mg every 4 weeks	500 mg every 12 weeks
Follow up duration	26 weeks	52 weeks
Haematological criteria for inclusion		
• TSAT (%)	<20%	<20%
• Ferritin (ng/mL)	<100 (or 100–299 if TSAT <20%)	<100 (or 100–300 if TSAT <20%)
• Hb (gm/dL)	9.5 to 13.5	<15
Cardiac criteria for inclusion		
• LVEF (%)	<40% for NYHA II, <45% for NYHA III	≤ 45%
• NYHA class	II to III	II to III
• BNP and/or Nt-pro-BNP	–	>100 pg/mL and/or >400 pg/mL
Mean age (years) of participants	67.8 ± 10.3 in FCM arm 67.4 ± 11.1 in placebo arm	68.8 ± 9.5 in FCM arm 69.5 ± 9.3 in placebo arm
Female (%)	52.3% in FCM arm 54.8% in placebo arm	45% in FCM arm 49% in placebo arm
eGFR (ml/min/1.73 m^2)	63.8 ± 21.2 in FCM arm 64.8 ± 25.3 in placebo arm	66.4 ± 21.7 in FCM arm 63.5 ± 20.9 in placebo arm

FAIR-HF: the Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF), CONFIRM-HF: Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure, IV: Intravenous, FCM: ferric carboxymaltose, TSAT: transferrin saturation, Hb: haemoglobin, NYHA: Ney York Heart Association, LVEF: left ventricular ejection fraction, BNP: brain natriuretic peptide, Nt-Pro-BNP: N-terminal-pro-brain natriuretic peptide, eGFR: estimated glomerular filtration rate.

2.5. Outcomes assessed

The primary outcome that we examined was hospitalization due to worsening HF whereas the secondary outcomes were hospitalization due to any CV cause, death due to worsening HF and any CV death. It was not mandatory for trials to have these outcomes as either primary or secondary outcomes of the study for the inclusion in meta-analysis.

2.6. Analysis

Meta-analysis was conducted using the Cochrane Program Review Manager (RevMan) version 5.3. Risk ratios (RR) were determined for dichotomous outcomes in each trial with 95% confidence intervals (CI) providing uncertainty limits of each result. Random effects model was used for assessment. We evaluated heterogeneity in the results of the trials using χ^2 and I^2 tests.

3. Results

From the described databases, we identified 17 studies. Of these, three were eligible studies on FCM in CHF.[24–26] Two of them met the inclusion criteria.[25,26] while one was excluded on the grounds of retrospective study design.[24] Study flow chart is shown in Fig. 1. Two RCTs included amounted to 760 participants (455 in FCM and 305 in placebo arms). Table 1 represents the characteristics of studies included in analysis. The dose of iron ranged from 200 mg to 1000 mg. Follow up duration of patients was for 24–52 weeks. Patients included in both trials had similar characteristics with New York Heart Association (NYHA) functional class II or III, a left ventricular ejection fraction of $\leq$40% or $\leq$45% and iron deficiency defined by ferritin levels below 100 μg/L or 100–299 μg/L, if the transferrin saturation was <20%. Anaemia was defined as hemoglobin concentration $\leq$12 gm/dL in both studies.

3.1. Assessment of risk of bias

In both RCTs, allocation generation was adequate. None of the trial reported on allocation concealment. Both were double blind studies except study personnel involved in preparation and administration of study drug including at least one study physician (not involved in study assessments) since FCM is easily distinguishable from saline placebo. Both studies employed either black syringes or curtain masking injection site to keep patients blinded. Outcome assessment was blinded and there was no selective reporting. Risk of bias results are summarized in Table 2.

3.2. Primary outcome

3.2.1. Hospitalization for worsening HF

Compared to placebo, FCM was associated with significant reduction in hospitalization due to HF (RR 0.30, 95% CI 0.19, 0.59; p = 0.0001). There was no heterogeneity in studies (I^2 = 0%, p = 0.71) as shown in Fig. 2a.

3.3. Secondary outcomes

3.3.1. Hospitalization for any CV cause

Alike primary outcome, FCM was associated with significantly lower risk of hospitalizations for any CV cause than placebo (RR 0.49, 95% CI 0.35, 0.70, p < 0.0001). With this outcome, as well, there was no heterogeneity in studies (I^2 = 0%, p = 0.73) as shown in Fig. 2b.

3.3.2. Death due to worsening HF

Though there was no significant heterogeneity between studies observed for this outcome (I^2 = 68%, p = 0.08), treatment with FCM was found to have no significant effect on mortality from worsening HF (RR 0.49, 95% CI 0.02, 7.36; p = 0.55). However, point estimate was still in favor of FCM (Fig. 2c).

3.3.3. Death due to any CV cause

Though FCM was not effective in reducing deaths due to any CV cause than placebo (RR 0.80, 95% CI 0.40, 1.57; p = 0.51), point estimate was favouring FCM over placebo. No heterogeneity in studies was evident (I^2 = 0%, p = 0.45) as seen in Fig. 2d.

3.4. Adverse events

In FAIR-HF trial,[26] premature discontinuation of FCM and placebo was reported in 5.3% and 9% participants respectively. No

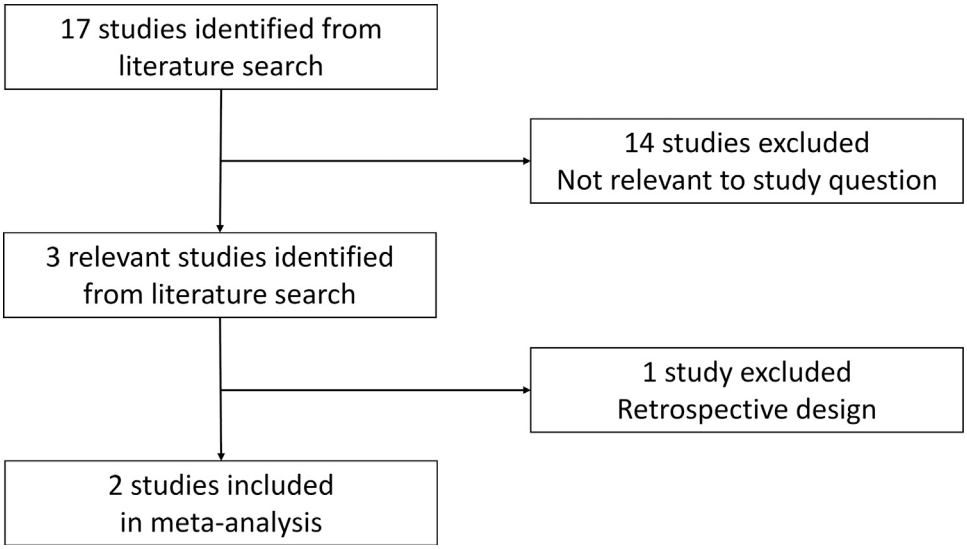

Fig. 1. PRISMA study flow chart.

Table 2
Risk of bias assessment.

Bias assessment parameters	FAIR-HF[26]	Risk category	CONFIRM-HF[25]	Risk category
Random sequence generation	Yes	Low	Yes	Low
Allocation concealment	Yes	Low	Yes	Low
Blinding of participants and personnel	Yes	Low	Yes	Low
Blinding of outcome assessment	Yes	Low	Yes	Low
Incomplete outcome data	No	Low	No	Low
Selective reporting	No	Low	No	Low

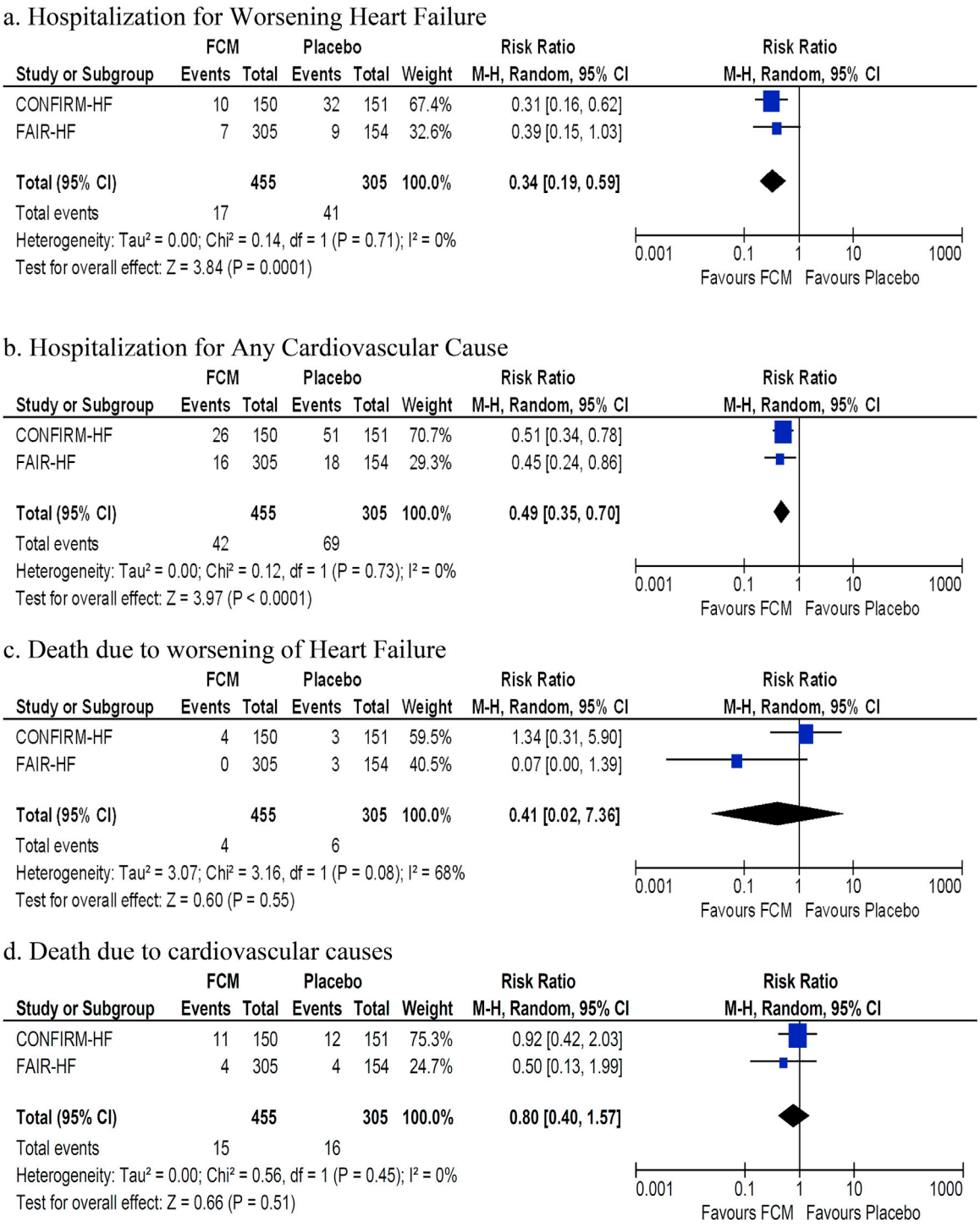

Fig. 2. Forest plot of FCM against placebo for hospitalization and mortality outcomes.

allergies were reported in patient. Injection site reactions were reported in six cases (four skin discoloration and two local pain). No laboratory abnormalities were significantly different in two groups except for iron related indices.

In CONFIRM-HF trial,[25] event leading drug withdrawal were seen in 9.2% of FCM group and 12.5% of placebo group participants. Local site adverse events were reported in 5.9% and 1.3% patients from two groups respectively. No significant differences were observed in any major organ system events.

4. Discussion

In this systematic review, we attempted to assess effect of intravenous iron – FCM – in hospitalization and mortality outcomes in HF. The results from this meta-analysis suggests that FCM treatment reduces hospitalizations associated with worsening HF or any CV cause related hospitalizations with relatively safe use over 52 weeks. The improvement in symptoms observed in both trials included is culminating in to the benefits related to hospitalizations in HF. This effect was observed with no heterogeneity in trials ($I^2 = 0\%$ in both outcomes). This benefit was seen in all patients who may or may not be anaemic. However, mortality benefits were not evident, though the point estimates were slightly in favor of FCM over placebo. This could be due to very few number of mortality outcomes in both the trials.[25,26]

Clinical improvement with FCM in HF is seen irrespective presence of anaemia.[27] As we did not restrict analysis by anaemia and included all cases, the observed benefits of FCM are not only related to correction of anaemia but might as well involve non-haematological mechanisms. Replenishment of iron is known to improve aerobic exercise tolerance, improvement in symptoms of fatigue, dyspnoea on exertion, QoL and 6MWD.[19] Further, in patients treated with intravenous iron, improvements in posterior wall thickness, LV end diastolic volume and diameter, LV end systolic volume and diameter, and LV mass index have been reported.[18] Though not included in our analysis, a retrospective study evaluating 70 cases observed that FCM compared to placebo (12.9% Vs 51.4%, $p < 0.001$) was associated with significantly lower rate of emergency consultations and admission to hospital for acute decompensation of HF in mean follow up of nearly 20 months.[24] Interesting to note, a recent study EFFECT-HF (Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure) (n = 174) reported significant improvement in peak oxygen uptake (peak VO_2), NYHA class and quality of life with FCM added to standard care than standard care alone over 6 months.[28] These findings strengthen the evidence that FCM lowers rates of hospitalizations due to worsening of HF.

Although we observed no difference in mortality due to worsening heart failure or any other CV cause in FCM and placebo groups, it needs to be remembered that the duration of these trials was short (up to 52 weeks). To detect mortality benefits, longer duration studies are therefore warranted. Presence of point estimate in favor of FCM shows it can offer mortality benefits as well probably translating from its effect on reducing hospitalization due to worsening of HF or any CV cause.

Although safety assessment was not plan of analysis, a review of both trials suggested no significant differences in occurrence of side effects with FCM compared to placebo. Except for expected haematological changes, there was no difference in any specific organ related events. We need to keep in mind that individual studies may be underpowered to detect rare and serious events like anaphylaxis. Intravenous iron is known to be safe and better tolerated than oral iron.

Thus, a compelling evidence and recommendation from guidelines prompts routine use of intravenous iron therapy with FCM in HF cases.[29]

5. Limitations

Our analysis was limited by the availability of trials with FCM in HF. Despite no heterogeneity in trials, mortality results did not reach statistical significance probably because of short duration of trials and low number of mortality events. Another important limitation is that the outcomes assessed in our analysis were not the primary outcomes of included trials. This means studies were underpowered to detect the difference in the outcomes we studied. Further, comparison of different IV iron preparations is needed to provide comparative utility of these preparations in HF.

6. Conclusion

Treatment with IV iron preparation – ferric carboxymaltose – is effective in reducing hospitalizations due to worsening HF and from any CV cause but not effective in reducing mortality. Better safety and tolerability with FCM provides us with an important therapeutic agent for HF and the benefits in anaemic and non-anaemic population calls for its routine use with monitoring of haematological parameters. As the outcomes assessed in this meta-analysis were not based on primary outcomes of trials, our findings need to be taken with caution and we therefore suggest a well-designed, large, long-term RCT to ascertain mortality and morbidity benefits of FCM in HF.

Conflict of interest

Dr Jamshed Dalal and Dr Vijay Katekhaye have nothing to declare. Dr Rishi Jain is a full-time salaried employee of Emcure Pharmaceuticals Ltd., Pune, India.

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