Original Article

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

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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 (P=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.

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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).\textsuperscript{1,2} Various factors determine the clinical course of HF patients.\textsuperscript{3,4} Iron deficiency is known to occur with a greater frequency in HF, is associated with unfavourable clinical outcome and has prognostic significance.\textsuperscript{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.\textsuperscript{8–10} In a meta-analysis of anemia and mortality in HF by Gorenveld et al.,\textsuperscript{11} presence of anemia 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.\textsuperscript{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.\textsuperscript{13} Study in Indian population reported ID in 76% HF cases and 48.7% had absolute deficiency.\textsuperscript{14} Development of ID even in absence of anaemia is known to reduce aerobic performance, and result in exercise intolerance.\textsuperscript{15}

Treatment of ID is associated with improvement in cardiac function, clinical symptoms, peak oxygen consumption, increase exercise tolerance, along with improved cardiac remodelling.\textsuperscript{16–18}

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
distance (6MWD) and lower rates of hospitalizations.\textsuperscript{19} Given a choice, intravenous iron may always be preferred considering problems with oral iron absorption and gastrointestinal intolerance.\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{23}

| Characteristics                                      | FAIR-HF\textsuperscript{30} | CONFIRM-HF\textsuperscript{32} |
|------------------------------------------------------|-----------------------------|---------------------------------|
| 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                         | 200mg weekly                | 500–1000mg weekly               |
| Iron dosage in maintenance phase                     | 200mg every 4 weeks         | 500mg 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      | 68.8 ± 9.5 in FCM arm            |
| Female (%)                                           | 67.4 ± 11.1 in placebo arm  | 69.5 ± 9.3 in placebo arm        |
|                                                       | 52.3% in FCM arm 54.8% in placebo arm | 45% in FCM arm 49% in placebo arm |
|                                                       | 63.8 ± 21.2 in FCM arm      | 66.4 ± 21.7 in FCM arm           |
|                                                       | 64.8 ± 25.3 in placebo 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 Iiron deficiency in coMbinaton with chronic Heart Failure, IV: Intravenous, FCM: ferric carboxymaltose, TSAT: transferrin saturation, Hb: haemoglobin, NYHA: New 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 \( \chi^2 \) and \( I^2 \) tests.

3. Results

From the described databases, we identified 17 studies. Of these, three were eligible studies on FCM in CHF,\textsuperscript{24–26} while one was excluded on the grounds of retrospective study design.\textsuperscript{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 \(<40\% \) or \(<45\% \) and iron deficiency defined by ferritin levels below 100 \( \mu g/L \) or 100–299 \( \mu g/L \), if the transferrin saturation was \(<20\% \). Anaemia was defined as hemoglobin concentration \(<12 \) g/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,\textsuperscript{26} premature discontinuation of FCM and placebo was reported in 5.3% and 9% participants respectively. No

![Fig. 1. PRISMA study flow chart.](image-url)
Table 2
Risk of bias assessment.

| Bias assessment parameters                     | FAIR-HF²⁶ | Risk category | CONFIRM-HF²⁵ | 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           |

a. Hospitalization for Worsening Heart Failure

| Study or Subgroup   | FCM Events | Total Events | Placebo Events | Total Events | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---------------------|------------|--------------|----------------|--------------|--------------------------------|--------------------------------|
| CONFIRM-HF          | 10         | 150          | 32             | 151          | 0.31 [0.16, 0.62]              |                                |
| FAIR-HF             | 7          | 305          | 9              | 154          | 0.39 [0.15, 1.03]              |                                |
| Total (95% CI)      | 455        | 305          | 100.0%         |              | 0.34 [0.19, 0.59]              |                                |
| Total events        | 17         | 41           |                |              |                                |                                |
| Heterogeneity: τ² = 0.00; χ² = 0.14, df = 1 (P = 0.71); I² = 0% |
| Test for overall effect: Z = 3.84 (P = 0.0001) |

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

b. Hospitalization for Any Cardiovascular Cause

| Study or Subgroup   | FCM Events | Total Events | Placebo Events | Total Events | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---------------------|------------|--------------|----------------|--------------|--------------------------------|--------------------------------|
| CONFIRM-HF          | 26         | 150          | 51             | 151          | 0.51 [0.34, 0.78]              |                                |
| FAIR-HF             | 16         | 305          | 18             | 154          | 0.45 [0.24, 0.86]              |                                |
| Total (95% CI)      | 455        | 305          | 100.0%         |              | 0.49 [0.35, 0.70]              |                                |
| Total events        | 42         | 69           |                |              |                                |                                |
| Heterogeneity: τ² = 0.00; χ² = 0.12, df = 1 (P = 0.73); I² = 0% |
| Test for overall effect: Z = 3.97 (P < 0.0001) |

c. Death due to worsening of Heart Failure

| Study or Subgroup   | FCM Events | Total Events | Placebo Events | Total Events | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---------------------|------------|--------------|----------------|--------------|--------------------------------|--------------------------------|
| CONFIRM-HF          | 4          | 150          | 3              | 151          | 1.34 [0.31, 5.90]              |                                |
| FAIR-HF             | 0          | 305          | 3              | 154          | 0.07 [0.00, 1.39]              |                                |
| Total (95% CI)      | 455        | 305          | 100.0%         |              | 0.41 [0.02, 7.36]              |                                |
| Total events        | 4          | 6            |                |              |                                |                                |
| Heterogeneity: τ² = 3.07; χ² = 3.16, df = 1 (P = 0.08); I² = 68% |
| Test for overall effect: Z = 0.60 (P = 0.55) |

d. Death due to cardiovascular causes

| Study or Subgroup   | FCM Events | Total Events | Placebo Events | Total Events | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---------------------|------------|--------------|----------------|--------------|--------------------------------|--------------------------------|
| CONFIRM-HF          | 11         | 150          | 12             | 151          | 0.92 [0.42, 2.03]              |                                |
| FAIR-HF             | 4          | 305          | 4              | 154          | 0.50 [0.13, 1.99]              |                                |
| Total (95% CI)      | 455        | 305          | 100.0%         |              | 0.80 [0.40, 1.57]              |                                |
| Total events        | 15         | 16           |                |              |                                |                                |
| Heterogeneity: τ² = 0.00; χ² = 0.56, df = 1 (P = 0.45); I² = 0% |
| Test for overall effect: Z = 0.66 (P = 0.51) |
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 (I² = 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
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-
haematomatous 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 VO2), 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 hospitaliza-
tion 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-
aanaemic 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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