Raghuraman B, et al., Cardiol Cardiovasc Med 2023
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Table 2: Study outcomes

Primary outcome	• Change in the NYHA class from baseline to Week 12 (±1 week).
Secondary outcome	• Mean self-reported PGA score at Week 12 (±1 week). • Number and nature of serious and non-serious adverse events throughout study duration. • Rate of any hospitalization, rate of hospitalization for any cardiovascular reason, and rate of hospitalization due to worsening HF as assessed up to Week 12 (±1 week). • Time to first hospitalization for any reason, time to first hospitalization for any cardiovascular reason and time to first hospitalization due to worsening HF as assessed up to Week 12 (±1 week). • Mean change in the haematological parameters [haemoglobin, serum ferritin, TIBC and TSAT] from baseline to week 12 (±1 week). • Change in the NYHA class and mean self-reported PGA score from baseline at week 4. Change in ejection fraction from baseline to week 12 (±1 week).

NYHA New York Heart Association, PGA Patient Global Assessment, TIBC Total Iron Binding Capacity, TSAT Transferrin Saturation.

Statistical analysis

Data were collected in REDCap and exported to IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. Baseline characteristics were expressed using mean and standard deviation or median with range for continuous variables; frequency and percentage for categorical variables.

Any patient who signed informed consent form and received at least one injection of FCM was included in the descriptive analysis, while only those data available at baseline as well as 12 weeks were included for comparative analysis. Wilcoxon Signed rank test was used to study the change in NYHA class, haematological parameters, self-reported patient global assessment between baseline and 12 weeks. For statistical analysis P value less than 0.05 was considered statistically significant. A convenient sample size of 100 was chosen for the study. The sample size was not based on any calculation.

Results

A total of 98 subjects were enrolled for the study from 4 centres, of which 3 patients were lost to follow-up. The study outline is depicted in Figure 1.

The baseline demographic characteristics and laboratory parameters are mentioned in Table 3 and Table 4 respectively. The mean age of the study participants was 61.08 ± 12.95 years with 58.2% of them being male. Almost 80% of the participants were found to have HF with reduced ejection fraction.

Details about comorbid illness and concomitant medications are described in Figure 2 and Figure 3 respectively. Hypertension was the most common comorbidity observed in 66.30% of the participants. This was followed by diabetes (60.76%) and ischemic heart disease (31.6%).

The efficacy-related endpoints are summarized in Table 5, Table 6, and Table 7. The primary endpoint of the study was change in the patient's symptoms which was evaluated utilising the NYHA classification. A significant improvement in NYHA class from baseline to 12 weeks was

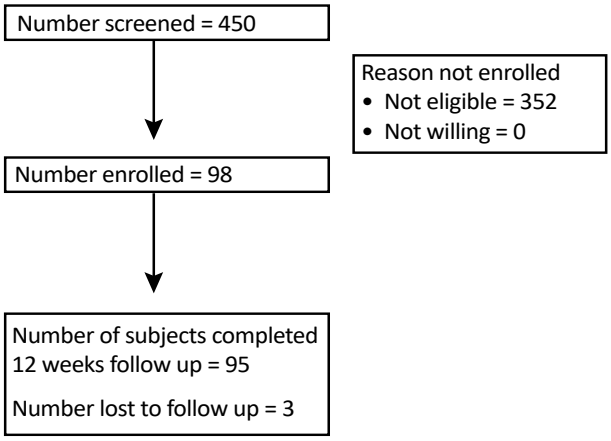

Figure 1: Study flow diagram

Table 3: Baseline Demographic characteristics

Age (years)	61.08 ± 12.95
Gender-Male (%)	57 (58.2%)
Female (%)	41 (41.8%)
Height (cms)	159.6 ± 7.82
Weight (kgs)	63.31 ± 10.68
SBP (mm Hg)	124.36 ± 18.78
DBP (mm Hg)	74.84 ± 11.79
HR (beats/ min)	78.69 ± 13.68
Type of heart failure	
HFrEF	78 (79.6%)
HFpEF	20 (20.4%)
Etiology of Heart failure	
MI	22 (22.4%)
Hypertension	19 (19.4%)
AF	2 (2%)
Valvular heart disease	6 (6.1%)
Cardiomyopathy	31 (31.6%)
Others	18 (18.4%)
Duration of heart failure* (years)	4 (1,8)

SBP Systolic blood pressure, DBP Diastolic blood pressure, HR Heart rate, HFrEF Heart failure with reduced ejection fraction, HFpEF Heart failure with preserved ejection fraction, MI Myocardial infarction, AF Atrial fibrillation. *Represented as Median

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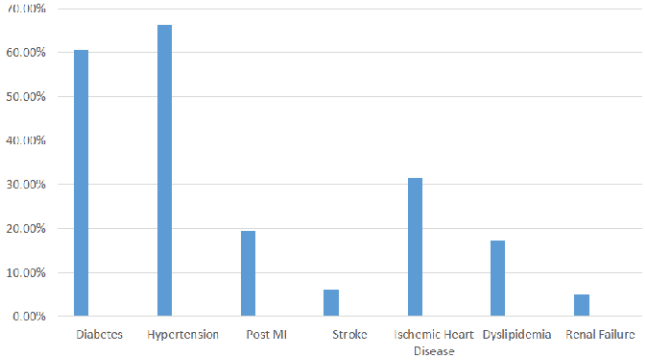
observed in the patients (P< 0.001). At baseline, 56.10% of the participants belonged to NYHA class III which was reduced to 8.40% by end of the study. The haematological parameters also improved significantly from baseline to 12 weeks for haemoglobin (10.69 ± 2.22 g/dL to 11.41 ± 6.68 g/dL; P value= 0.54), serum ferritin (54.70 ± 75.32 mcg/L to 226.72 ± 145 mcg/L; P value < 0.001), TSAT (11.33 ± 3.86% to 24.03 ± 9.78%; P value < 0.001) and TIBC (346.71 ± 58.75 mcg/dL to 294.97 ± 54.43 mcg/dL; P value= 0.002). The self-reported patient global assessment score was used to assess patient response to treatment. There was a significant improvement in the score when the values were compared for week 4 and week 12 (P< 0.001) (Table 7). The changes in ejection fraction from baseline to week 12th is represented in Table 8 where no significant changes were observed (P value = 0.68). No adverse events or hospitalisations were reported during the study period.

Table 4: Baseline laboratory investigations

Parameter	Value
Haemoglobin (g/dL)	10.69 ± 2.22
Serum ferritin (mcg/L)	54.70 ± 45.32
TSAT (%)	11.33 ± 3.86
TIBC (mcg/dL)	346.71 ± 58.75

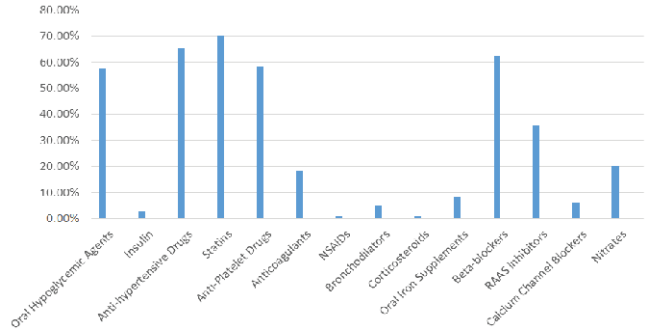
TSAT transferrin saturation, TIBC total iron binding capacity

Figure 2: Comorbidities observed in the study participants.



MI Myocardial infarction

Figure 3: Concomitant medications of the enrolled study participants.



NSAID Non-steroidal anti-inflammatory drugs, RAAS Renin angiotensin aldosterone system

Table 5: Comparison of participants based on NYHA class during the study period

	Baseline	4 weeks	12 weeks	P value
NYHA class	Class II -43 (43.9%)	Class I -10 (10.5%)	Class I -29 (30.5%)	< 0.001*
	Class III -55 (56.1%)	Class II- 65 (68.4%)	Class II-58 (61.1%)	
		Class III 20 (21.1%)	Class III 8 (8.4%)	

* Comparing week 4 with baseline and week 12 with week 4

Table 6: Comparison of change in haematological parameters at the end of the study period

Parameter	Baseline	12 weeks	P value
Haemoglobin (g/dL)	10.69 ± 2.22	11.41 ± 6.68	0.54
Serum ferritin (mcg/L)	54.70 ± 45.32	226.72 ± 145.12	<0.001
TSAT (%)	11.33 ± 3.86	24.03 ± 9.78	< 0.001
TIBC (mcg/dL)	346.71 ± 58.75	294.97 ± 54.43	0.002

TSAT transferrin saturation, TIBC total iron binding capacity

Table 7: Assessment of Self-reported patient global assessment

	Week 4	Week 12	P value
Much improved	15 (15.8%)	32 (33.7%)	< 0.001
Moderately improved	32 (33.7%)	37 (38.9%)	
A little improved	39 (41.1%)	21 (22.1%)	
Unchanged	8 (8.4%)	3 (3.2%)	
A little worse	1 (1.1%)	1 (1.1%)	
Moderately worse	0	1 (1.1%)	
Much worse	0	0	

Table 8: Comparison of change in ejection fraction

	Baseline	12 weeks	P value
Ejection fraction (%) (Mean ±SD)	36.11±6.5	37.22±11.21	0.68

Discussion

The present study reports the effects of IV FCM in chronic HF patients with NYHA class II and III along with ID. The important findings of this study were: (i) There was a significant improvement in NYHA class from baseline to 12 weeks, with 56.1% patients belonging to class III at the baseline as compared to only 8.4% patient at the end of the study period; (ii) Significant improvement in haematological indicators [serum ferritin (P<0.001), TSAT (P< 0.001) and TIBC (P= 0.002)] from baseline to 12 weeks; (iii) Self-reported PGA improved significantly from baseline at week

Raghuraman B, et al., Cardiol Cardiovasc Med 2023
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12 (P< 0.001); (iv) No adverse events or hospitalisations were observed during the study period; and (v) Almost 80% of the study population had heart failure with reduced ejection fraction while 20% had heart failure with preserved ejection fraction. In the iron-sulphur clusters that make up the first three components of the electron transport chain in mitochondria, iron serves as a crucial co-factor for anti-oxidative enzymes [15]. As a result, iron deficiency is identified as a significant comorbidity in the pathological process of heart failure [16, 17]. When iron stores are depleted, an iron deficiency is considered to be "absolute," but it can also be "functional" (or "relative") due to poor iron metabolism, which may be a side effect of inflammatory processes [18]. Ferritin levels are used to identify an iron deficiency in healthy adults, and a cut-off of 30 mcg/l is frequently utilised. The 'normal' range in most laboratories is 30-300 mcg/l, with the mean values being 88 mcg/l for males and 49 mcg/l for women [13]. However, because HF and other chronic disorders are linked to an enhanced activation of both pro- and anti-inflammatory mechanisms, the classification of iron deficiency in these situations is challenging [19]. International HF guidelines define ID as having a serum ferritin level below 100 mcg/L (absolute ID) or having a normal serum ferritin level (100–299 mcg/L) with poor transferrin saturation (<20%) [20]. FCM is the first and only intravenous iron replacement therapy to receive FDA approval for correcting iron deficiency in adult patients with heart failure with reduced ejection fraction [21]. In the current study, iron therapy not only improved the functional capacity of the patients as shown by the primary endpoint of NYHA functional class improvement, but it also had positive effects on patient reported outcomes as assessed by self-reported PGA. The advantage became apparent after 4 weeks and persisted throughout the duration of the study and was statistically significant (P< 0.001). Similar results were reported in FAIR-HF trial as well, where benefits were evident from week 4 onwards and were sustained during the study period [8]. A meta-analysis by Kapoor et al. reported that patients receiving intravenous iron saw significantly fewer hospitalisations and adverse events, as well as improvements in their NYHA class and ejection fraction [22]. Post-intravenous FCM administration, there were no adverse events reported nor did any hospitalisation occur throughout the study period. With no impact on all-cause mortality or CV mortality alone, several studies and meta-analyses have stated that intravenous iron infusion in patients with HF lowers the composite risk of first hospitalisation for HF and CV mortality as well as the risks of first and subsequent hospitalisations for HF [9, 10], [23, 24]. Hospitalisations brought on by HF deterioration are invariably associated with poor outcomes, a reduction in patients' quality of life, and a financial burden on society. Hence, their prevention becomes necessary and new therapies must also be evaluated on these lines. Iron deficiency, which is a frequent occurrence in heart failure is a standalone predictor of worse outcomes [25]. Hence, therapies that improve the iron status in HF patients must be given due importance. The current ESC guidelines recommend that the complete blood count, serum ferritin concentration, and TSAT are routinely used to check all HF patients for anaemia and iron deficiency. If anaemia and/or iron deficiency are detected, it should prompt appropriate investigations to determine their underlying causes [26]. The guideline also states that intravenous iron supplementation with FCM should be taken into consideration in symptomatic patients with left ventricular ejection fraction less than 45% and iron deficiency, to reduce HF symptoms, enhance exercise capacity, and enhance quality of life [26]. In the current study, IV FCM was administered to the HF patients for the iron-deficient state and there was a serial and significant improvement in the haematological parameters (serum ferritin, TIBC and TSAT) throughout the study duration. The present study shows that IV FCM is an effective and tolerable therapy in chronic HF patients. However, our study has a few limitations. Firstly, this was a single arm study, hence, the comparative efficacy of IV FCM could not be evaluated with other available IV preparations. Secondly, a longer follow-up period or greater exposure dose would have resulted in a more notable improvement in iron reserves and boosted exercise capacity.

Conclusion

This is a first multicentre study evaluating the clinical utility of IV FCM in Indian HF patients. In conclusion, our study states that the correction of ID in chronic HF with IV FCM results in significant improvement in disease symptoms and haematological parameters. This could lead to a reduction in hospitalisations which may occur due to worsening of HF. The findings of this study provide valuable insights into the benefits of iron deficiency correction in heart failure which adds to the existing body of evidence that emphasizes the potential of IV FCM as a promising therapeutic intervention in HF. Early detection of ID and timely correction with IV FCM can improve heart failure outcomes.

Conflict of Interest

The author reports no conflicts of interest with anyone with regards to this study. Dr. Nanette Suares, Dr. Dhammdeep Dabhade, Dr. Rishikesh Shewale and Dr. Sachin Suryawanshi are full time employees of Emcure Pharmaceuticals Ltd. which actively markets IV Ferric Carboxymaltose.

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