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ORIGINAL ARTICLE

Impact of intravenous ferric carboxymaltose on heart failure with preserved and reduced ejection fraction

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Abstract

Aims Heart failure (HF) is a proinflammatory disease often associated with the onset of iron deficiency (ID). ID alters mitochondrial function, reducing the generation of cellular energy in skeletal muscle and cardiomyocytes. This study aimed to analyse the response of patients with HF to intravenous iron administration according to the type of HF: preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF).

Methods and results We conducted a retrospective, single-centre study of 565 consecutive outpatients diagnosed with HF, recruited over 5 years, who were given intravenous ferric carboxymaltose (FCM) for the treatment of ID [defined as ferritin $<$ 100 μg/L or ferritin 100–300 μg/L with transferrin saturation (TSAT) $<$ 20%]. Clinical, laboratory, and echocardiographic parameters were analysed before and after administration. After FCM administration, overall ferritin, TSAT, and haemoglobin levels increased up to 5-fold, 1.6-fold, and 1.1-fold, respectively, relative to baseline values in HF patients with reduced and preserved ejection fraction ($P < 0.0001$), with a greater increase in ferritin and TSAT in HFpEF patients. The left ventricular ejection fraction of the overall series improved by 8 percentage points in both types of HF (from 40% to 48%, $P < 0.0001$). The percentage of patients with normalization of right ventricular function increased by 6.9 points (from 74.1% to 81%) in HFpEF patients and by 6.4 points (from 53% to 59.4%) in the HFrEF subgroup ($P < 0.0001$). New York Heart Association functional status slightly improved, from a median of 2.4 (interquartile range, IQR: 2–2.7) to 1.9 (IQR: 1.5–2.5; $P < 0.0001$) after FCM in both types of HF. No changes were noted in plasma levels of liver enzymes, creatinine, or natriuretic peptide ($P > 0.05$).

Conclusions Intravenous iron administration appeared to improve ejection fraction and cardiac functional status in outpatients with ID and HF with both preserved and reduced ejection fraction.

Keywords Ferric carboxymaltose; Iron deficiency; Heart failure; Preserved ejection fraction; Reduced ejection fraction; Ferritin

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Introduction

Heart failure (HF) is a very prevalent disease associated with high morbidity and mortality,[1] prompting research into new therapeutic avenues to improve prognosis and quality of life (QoL) for patients with this condition. Existing evidence points to iron deficiency (ID) as one of the most common co-morbidities in HF.[2–6] Reduced iron stores in the body have been linked to major pathophysiological problems, because iron is an essential micronutrient in mitochondrial function and energy production in cells and tissues. Basic research studies have confirmed that ID has adverse effects on the contractile function of cardiomyocytes and that this effect can be reversed by replenishing iron stores.[7]

The 2012 European Society of Cardiology (ESC) guidelines for HF were based on the results of a clinical trial that examined the effect of administering iron in patients with HF and ID[8,9] and suggested that intravenous (i.v.) iron may be considered for the treatment of ID. In the light the scientific evidence available to date, subsequent editions of the guidelines (2021) finally established the recommendation for the routine use of i.v. iron [ferric carboxymaltose (FCM)] for the treatment of HF and improvement of QoL and functional status (FS) in patients with ID.[10] Since then, this treatment option has been included in the routine pharmacopoeia for outpatient treatment of symptomatic patients with HF and reduced left ventricular ejection fraction (LVEF). Additionally, magnetic resonance imaging (MRI) techniques (T2-weighted scans) have shown that the iron administered is taken up by the myocardium[11] and can improve LVEF 30 days after administration.[12]

The administration of FCM in patients with decompensated HF has been effective in reducing long-term hospitalizations.[13] However, most studies have included patients with HF and reduced ejection fraction (EF) (HFrEF) and mid-range LVEF (40–50%), but no trials have been conducted to date on patients with HF and preserved LVEF (HFpEF).

This retrospective study evaluated the real-world effectiveness of outpatient administration of FCM in repleting the body's iron stores, and its effect on the patient's FS and echocardiographic parameters of ventricular function. All results were analysed in terms of functional class, ventricular systolic function, type of heart disease (HFrEF vs. HFpEF), reversal of ID as assessed by restoration of iron status parameters and haemoglobin levels, and the effects of FCM treatment on kidney and liver function.

Methods

Study and patient cohort

A retrospective study was conducted in 565 consecutive patients referred from cardiology outpatient clinics to the day hospital for outpatient administration of i.v. FCM between January 2016 and December 2020. During selection of the study population, admissions due to decompensation, death during the observation time (within 3 months of treatment administration), and patients undergoing major medical or surgical procedures during that period were excluded. In total, 484 patients were finally included, of whom 288 had HFrEF and 196 HFpEF (*Figure 1*). Clinical, laboratory, and echocardiographic variables were compared prior to administration (baseline) and 3 months after administration of FCM.

Heart failure with preserved ejection fraction was described according to European Guidelines for the diagnosis and treatment of acute and chronic HF.[10] Patients were diagnosed with HFpEF if they had symptoms and signs of HF with normal or near-normal LVEF (LVEF $\geq$ 50%), elevated levels of natriuretic peptides [BNP $>$ 35 pg/mL or N-terminal pro-brain natriuretic peptide (NT-proBNP) $>$ 125 pg/mL], and at least one additional criterion (either relevant structural heart disease or diastolic dysfunction).

The diagnosis of ID was based on the standard criteria defined in the consensus document of the Spanish Society of Cardiology and the Spanish Society of Internal Medicine on the diagnosis and treatment of ID in HF[14] [laboratory diagnosis of ID: ferritin $<$ 100 μg/L or ferritin 100–300 μg/L with transferrin saturation (TSAT) $<$ 20%]. Exclusion criteria for the administration of FCM were as follows:

- iron allergy;
- uncontrolled hypertension (HT) (blood pressure $>$ 160/100 mmHg) at the time of FCM administration;
- infection, inflammatory disease, or active neoplastic disease;
- severe liver dysfunction (transaminases $\geq$3 times the upper limit of normal); and
- polycythaemia (haemoglobin $>$ 16 g/dL).

The FCM dose[15] administered was 1000 mg diluted in 250 cc of 9% saline infused over 30 min or the same dose diluted in 100 cc infused over 15 min. For patients weighing $<$50 kg, 500 mg were administered in the same diluent and over the same time. For patients with haemoglobin $>$ 14 g/dL, the dose administered was 500 mg. Among HT patients, only those who achieved normal controlled blood pressure values after anti-hypertensive treatment were treated with FCM.

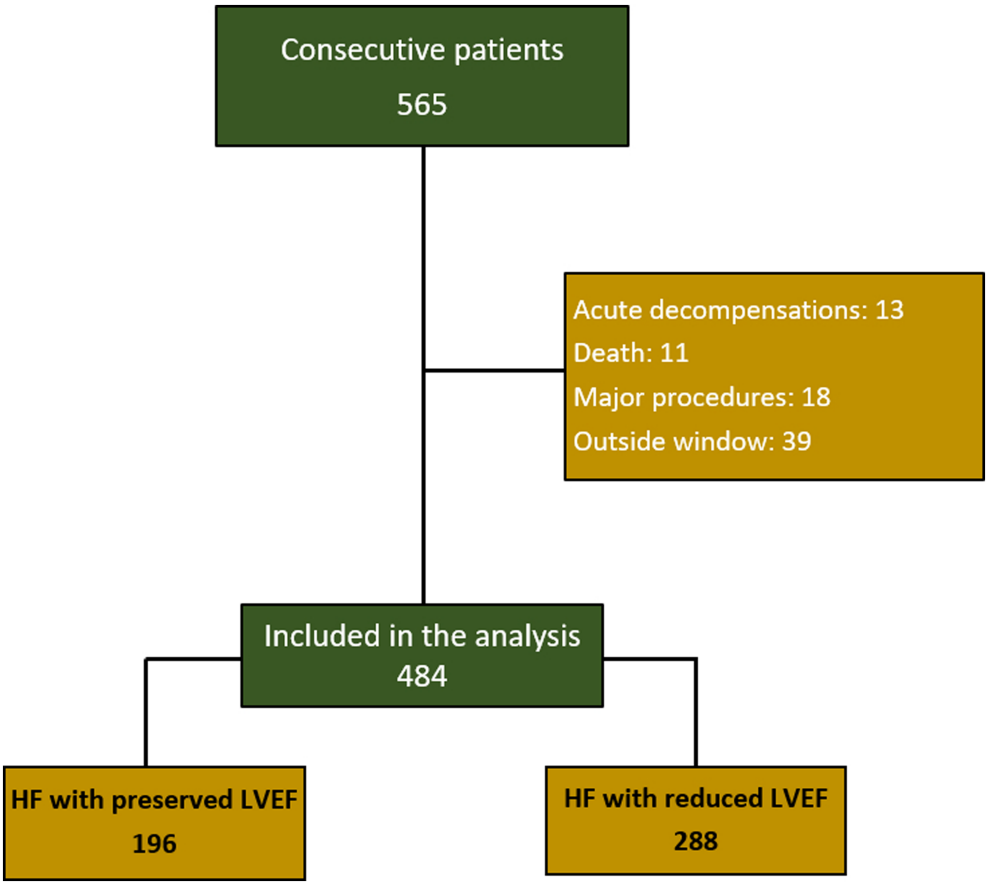
Evaluation of the patients' FS was based on the New York Heart Association (NYHA) functional classification,[16] which was slightly adapted, establishing a set of criteria included in a questionnaire designed by nursing staff specialized in HF (Supporting Information, *Appendix S1*). Assessment of left ventricular function was quantitative; assessment of right ventricular (RV) function was qualitative and was performed by echocardiogram. Renal failure was defined as the presence of an at least moderately decreased glomerular filtration rate (GFR) calculated using the abbreviated MDRD equation (GFR $\leq$ 59 mL/min/1.73 m^2).[17,18]

Systolic function and iron metabolism parameters were assessed by echocardiography and blood tests, respectively, in all patients before and after FCM administration (3 months after treatment initiation). FS was also assessed at each visit.

All follow-up assessments were performed 2 months after iron administration (range 1 to 3 months).

This study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Hospital Universitario y Politécnico La Fe, Valencia (Spain).

Figure 1 Flow chart of study patient selection. HF, heart failure; LVEF, left ventricular ejection fraction.



Statistical analysis

Qualitative variables were expressed as percentages and quantitative variables as means and standard deviation or as medians and interquartile ranges (IQRs; 25–75%) in case of $P < 0.05$ after confirming normality with the Kolmogorov–Smirnov (Z) test. The association between quantitative variables with normal distribution was analysed using the Student's t-test, while we used the χ^2 test or Wilcoxon rank test for two related samples for the remaining variables. A P-value of <0.05 was taken as significant. Statistical analysis was performed using SPSS Statistics software Version 27® and Stata Statistics/Data analysis 16.1 serial number 501606323439.

Results

Baseline clinical characteristics

The baseline characteristics of the study population are shown in *Table 1*. The mean number of patients treated per year was 96.8. Mean age in the study series was 68 years, with a higher percentage of men (59%). The most common aetiologies in patients were ischaemic heart disease, idiopathic cardiomyopathy, and valvular heart disease. Other aetiologies present in the study population were mainly hypertensive heart disease and hypertrophic and restrictive cardiomyopathy in the HFpEF group, and chemotherapy-induced cardiomyopathy and arrhythmogenic RV dysplasia in the HFrEF group. In the overall patient series, there was a higher prevalence of HFrEF (60%). This patient subgroup had a lower mean age (65 vs. 71 years on average in patients with HFpEF) and a higher frequency of ischaemic heart disease and dilated cardiomyopathy compared with valvular heart disease.

There were differences in history and concomitant treatments between both groups of patients with HF. A history of HT and atrial fibrillation (AF) was more frequent among patients with HFpEF, while alcoholism and chronic obstructive pulmonary disease (COPD) reached a significantly higher percentage among patients with HFrEF. In terms of treatment, anticoagulant therapy was more prevalent among patients with HFpEF, which may be explained by the higher prevalence of valvular heart disease and AF in this patient profile,

Table 1 Baseline characteristics of study patients

	HF according to LVEF *N* (%)		Statistical significance		Total patients *N* (%)
	HFpEF 196 (40%)	HFrEF 288 (60%)	*P*-value	*P*-value	All patients 484 (100%)
Men, *n* (%)	82 (42)	204 (71)		<0.0001	286 (59)
Age (years), mean ± SD	71 ± 14	65 ± 13		<0.0001	68 ± 14
FS (NYHA), *n* (%)				0.39	
I	0 (0)	0 (0)	0.655		0 (0)
I–II	54 (28)	60 (21)	0.087		114 (24)
II	58 (30)	99 (34)	0.270		157 (32)
II–III	49 (25)	62 (22)	0.372		111 (23)
III	29 (14)	61 (20)	0.076		90 (18)
III–IV	4 (2)	4 (2)	0.850		8 (2)
IV	2 (1)	2 (1)	0.902		4 (1)
Baseline heart disease, *n* (%)				<0.0001	
IHD	51 (26)	122 (42)	0.0001		173 (36)
DCM	19 (10)	96 (33)	0.0001		115 (14)
VHD	88 (45)	32 (12)	0.0001		120 (25)
CHD	13 (7)	8 (3)	0.041		21 (4)
Other	25 (12)	30 (10)	0.426		55 (11)
History (*n*, %)					
CVS	39 (20)	63 (22)	0.6		102 (21)
HT	159 (81)	210 (73)	0.04		369 (76)
Dyslipidaemia	100 (51)	150 (52)	0.8		250 (52)
DM	84 (43)	135 (47)	0.4		219 (45)
Smoking	88 (45)	144 (50)	0.3		232 (48)
Alcoholism	6 (3)	26 (9)	0.01		32 (7)
COPD	18 (9)	81 (28)	0.0001		99 (20)
Obesity (BMI > 30)	31 (16)	35 (12)	0.2		66 (14)
Renal failure[a]	49 (25)	72 (25)	1		121 (25)
Hypothyroidism	14 (7)	34 (12)	0.09		48 (10)
AF	139 (71)	138 (48)	0.0001		277 (57)
Treatment (*n*, %)					
ACE/ARA-II inhibitors	123 (37)	199 (69)	0.1		322 (67)
ARNI	2 (1)	46 (16)	0.0001		48 (10)
Beta-blockers	123 (63)	187 (65)	0.6		310 (64)
MRA	49 (25)	112 (39)	0.001		161 (33)
Ivabradine	25 (13)	49 (17)	0.2		74 (15)
Loop diuretics	145 (74)	198 (69)	0.2		343 (71)
Thiazides	33 (17)	35 (12)	0.1		68 (14)
Tolvaptan	4 (2)	12 (4)	0.2		16 (3)
Antiplatelet agents	57 (29)	124 (43)	0.002		181 (37)
Anticoagulants	96 (49)	101 (35)	0.002		197 (41)
Nitrates	14 (7)	32 (11)	0.1		46 (10)
Digoxin	8 (4)	6 (2)	0.2		14 (3)
OAD	55 (28)	84 (29)	0.8		139 (29)
SGLT2i	10 (5)	55 (19)	0.0001		65 (13)

ACE/ARA-II inhibitors, angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists; AF, atrial fibrillation; ARNI, angiotensin receptor-neprilysin inhibitors; BMI, body mass index; CHD, congenital heart disease; COPD, chronic obstructive pulmonary disease; CVS, cardiovascular surgery; DCM, dilated cardiomyopathy; DM, diabetes mellitus; FS, functional status; HF, heart failure; HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; HT, hypertension; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association functional classification of the HF; OAD, oral antidiabetics; SD, standard deviation; SGLT2i, sodium-glucose co-transporter inhibitors type 2; VHD, valvular heart disease.
[a]Renal failure was defined as the presence of a glomerular filtration rate ≤ 59 mL/min/1.73 m^2.

while in the subgroup with HFrEF, combined neprilysin and renin-angiotensin-aldosterone system inhibitors (such as angiotensin receptor-neprilysin inhibitors, ARNI), mineralocorticoid receptor agonists (MRA), antiplatelet agents, and sodium-glucose co-transporter 2 inhibitors (SGLT2i) were the most widely used therapeutic agents due to their proven efficacy in this patient profile.[16,19]

Effectiveness and toxicity of ferric carboxymaltose

Laboratory tests for ferritin and TSAT levels post-FCM administration showed an up to 5-fold increase in ferritin and 1.6-fold increase in TSAT relative to baseline values, both statistically significant (*Table 2*). Furthermore, this result was

Table 2 Effectiveness and toxicity parameters in the total population and according to type of heart failure (with preserved or reduced left ventricular ejection fraction)

	Total study population		
Parameters	Baseline	Follow-up	*P*-value
Fer[a] (μg/L)	55 (27–99)	278 (131–418)	<0.0001
TSAT[a] (%)	15 (10–19)	24 (18–32)	<0.0001
Hb[b] (g/L)	12.8 ± 2.1	13.6 ± 2.1	<0.0001
AST[a] (U/L)	19 (16–25)	20 (18–26)	0.07
ALT[a] (U/L)	16 (12–22)	17 (12–24)	0.06
Cr[a] (mg/dL)	1.1 (0.9–1.4)	1.1 (0.9–1.4)	0.68

	HF with preserved EF			HF with reduced EF		
Parameters	Baseline	Follow-up	*P*-value	Baseline	Follow-up	*P*-value
Fer[a] (μg/L)	38 (17–36)	217 (95–401)	0.0001	67 (35–131)	293 (169–424)	<0.0001
TSAT[a] (%)	12 (8–19)	23 (17–30)	0.0001	16 (11–21)	25 (19–33)	<0.0001
Hb[b] (g/L)	12.2 ± 2.2	12.9 ± 2.2	0.0001	13.3 ± 1.9	14.0 ± 2.0	<0.0001
AST[a] (U/L)	19 (16–23)	20 (16–27)	0.09	19.5 (16–26)	20 (17–26)	0.25
ALT[a] (U/L)	15 (11–20)	16 (11–23)	0.07	17 (13–23)	18 (13–26)	0.06
Cr[a] (mg/dL)	1.0 (0.8–1.4)	1.0 (0.8–1.4)	0.8	1.2 (0.9–1.5)	1.2 (0.9–1.5)	0.6

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; EF, ejection fraction; Fer, ferritin; Hb, haemoglobin; HF, heart failure; TSAT, transferrin saturation.
[a]Median and interquartile range 25–75%.
[b]Mean ± standard deviation.

confirmed in both patient subgroups (HFpEF and HFrEF), although the changes were of a different magnitude. Larger increases were found in ferritin and TSAT levels in patients with preserved LVEF (6-fold and 2-fold, respectively) compared with patients with reduced LVEF (4.4-fold and 1.6-fold, respectively) (*Table 2* and *Figure 2*).

After administration, no significant differences were found in levels of markers for liver necrosis and kidney dysfunction. Liver parameters showed a non-statistically significant increase, with no clinical relevance (the increase was only one point above baseline values). These results were similar for both types of HF (*Table 2* and *Figure 3*).

Effects of the administration of ferric carboxymaltose on systolic function and functional status

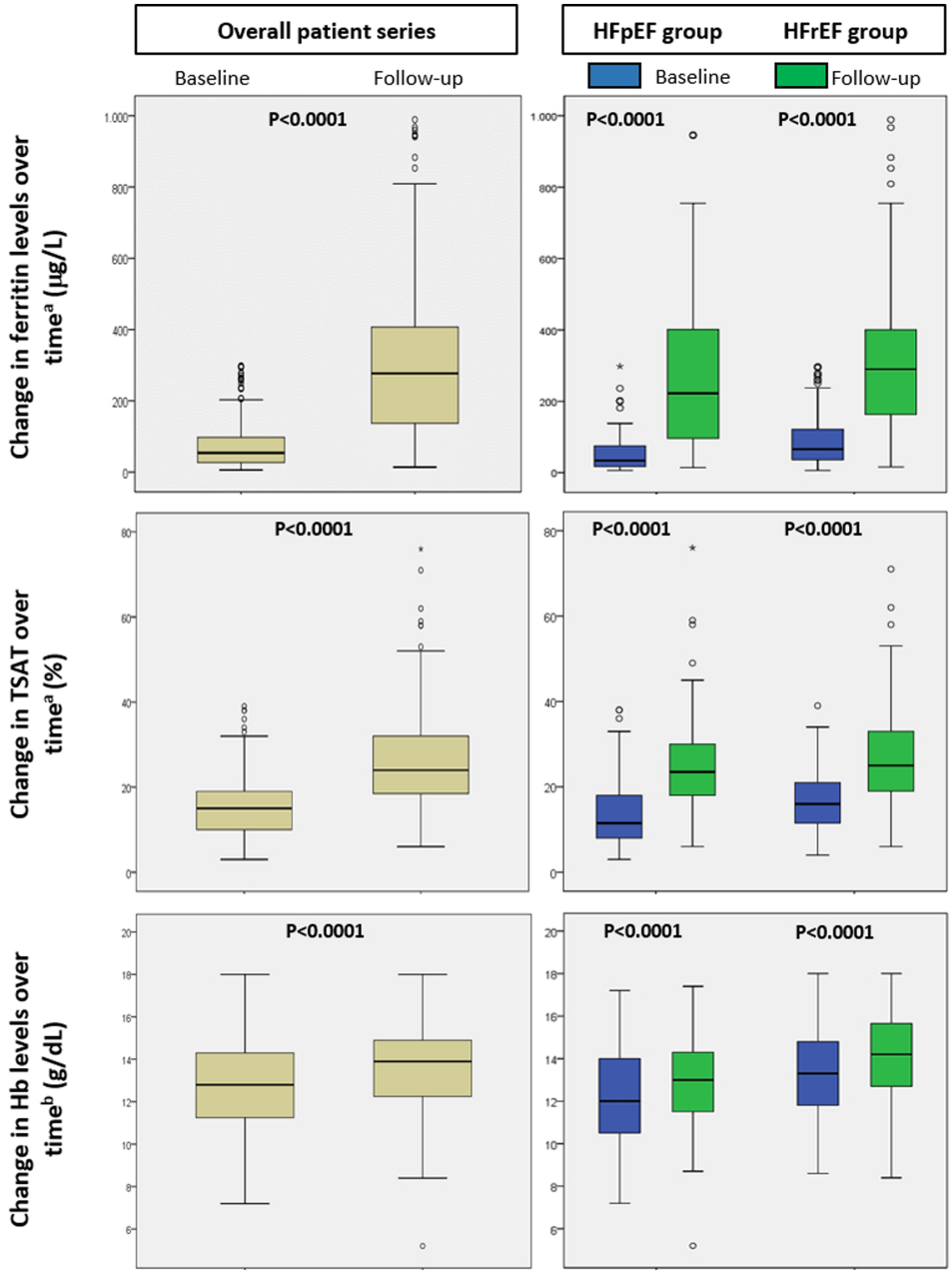
A significant increase in LVEF of 8 percentage points was confirmed in the overall patient series (baseline LVEF vs. follow-up LVEF) (*Table 3*). RV contractility was qualitatively assessed and classified as normal RV contractility, or mildly, moderately, or severely depressed RV function. Follow-up showed an increase of almost 5 percentage points in the number of patients with normal RV contractility, mainly due to the number of patients with previous moderately depressed function who achieved normal contractility. These changes were significant for patients with both HFpEF and HFrEF (*Table 3* and *Figure 4*). The effect of treatment on cardiac stress was assessed by measurement of the injury marker NT-proBNP. No differences were found in the levels of this marker after iron administration, either in the overall study population or according to the type of HF (*Table 3* and *Figure 4*).

Comparison of FS between the patient groups was established with the aid of the modified NYHA functional scale (Supporting Information, *Annex S1*), so that each functional class was awarded its own numerical value. The FS of patients according to the modified NYHA classification showed a slight improvement that was significant both in the overall patient series and in the HFpEF and HFrEF subgroups during follow-up (*Table 3*). Notably, the majority of patients in the subgroup with HFpEF improved their FS from class III to II–III, while in the subpopulation of patients with HFrEF, FS improved mostly from class III to class II (*Figure 5*).

Discussion

This retrospective study analysed the effectiveness of i.v. administration of FCM in outpatients with HF in relation to the functional and structural status of patients with reduced and preserved LVEF. Although the efficacy of FCM has been demonstrated in several clinical trials, there are hardly any studies on its real-world effectiveness that assess the benefits of its administration, harmful effects, and potential improvement of functional and myocardial status in a large number of patients. Our results confirmed that iron metabolism parameters were considerably restored 3 months after administration of FCM, with no increase in markers of kidney and liver dysfunction; our results also suggest different degrees of improvement in ventricular function parameters and FS.

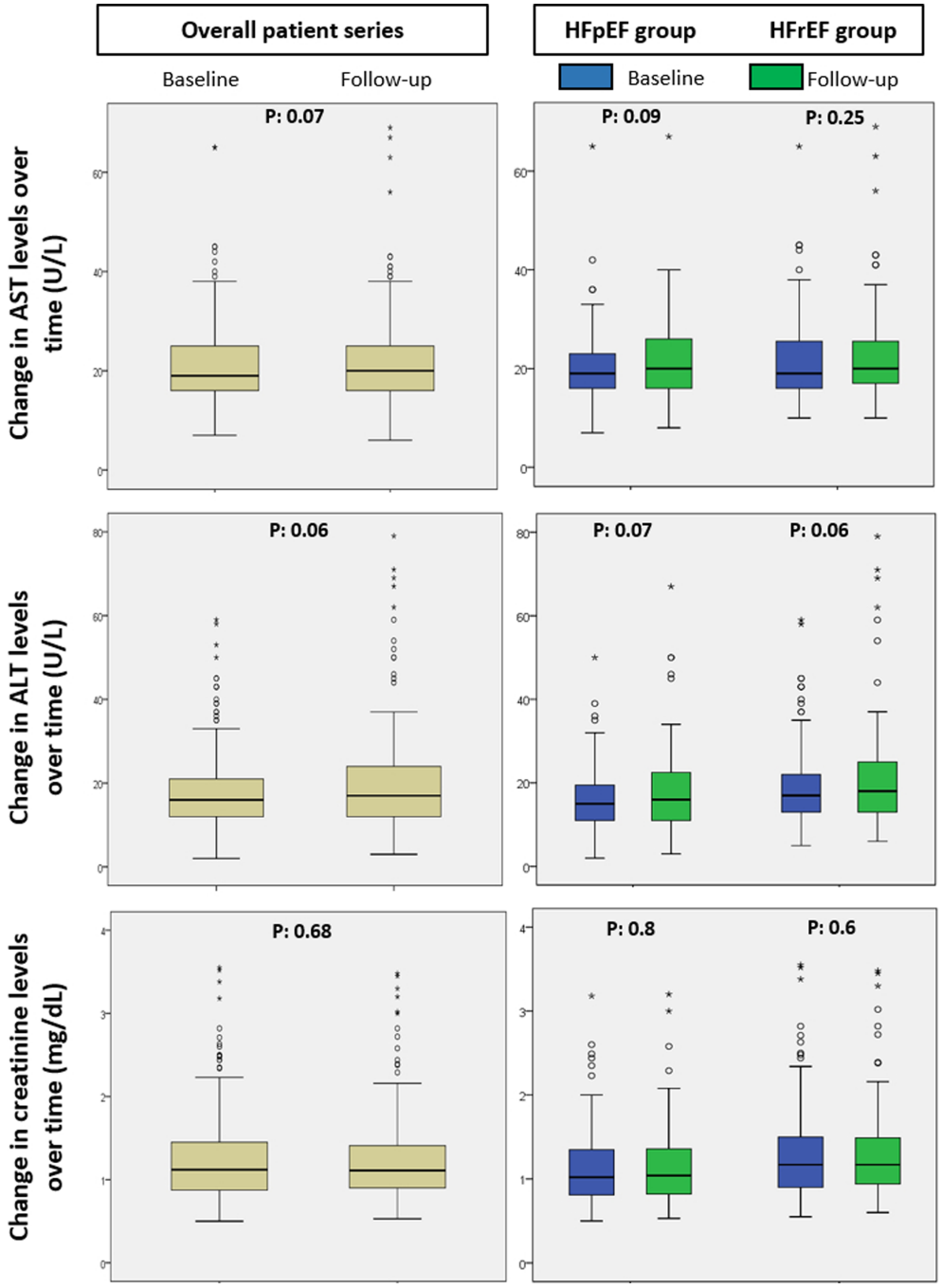
Figure 2 Effectiveness of treatment with ferric carboxymaltose in iron repletion. Hb, haemoglobin; HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; TSAT, transferrin saturation. [a]Median and interquartile range 25–75%. [b]Mean ± standard deviation.



Furthermore, these findings were found to be independent of the type of HF, preserved or reduced.

Most pharmacological studies in patients with HF include patients with reduced LVEF and generally have a larger proportion of men and a higher prevalence of ischaemic heart disease. Similarly, the relationship between HFrEF and COPD or alcohol consumption is well known[20] (the latter due to the toxic effect of alcohol on the myocardium).[21] The aetiological characteristics of our patient population coincide with the published evidence in this regard. ID is highly prevalent in HF patients with both reduced and preserved EF, which impacts negatively on their clinical status.[4–6] The presence of HF with preserved LVEF is as common as HFrEF.[22,23] In our overall patient population, the HFpEF subgroup was older and had a higher proportion of women, a lower probability of presenting coronary artery disease, and a higher prevalence of a history of underlying HT, which is consistent with that described in other studies.[24,25] Although several

Figure 3 Impact of treatment with ferric carboxymaltose at the hepatic or renal level. All values correspond to median and interquartile range 25–75%. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction.



studies have attempted to identify different HFpEF phenotypes,[26,27] some authors have argued that HFpEF lacks a unifying pathophysiology and is a heterogeneous disease whose treatment needs to be tailored specifically to the different underlying aetiologies, pathophysiological factors, and comorbidities.[28] To date, there is still a lack of robust evidence from clinical trials supporting the efficacy of iron repletion treatments in HFpEF patients. As a result, treatment of this patient population in real-world clinical practice has been largely empiric and based on the efficacy and safety of i.v. iron administration in HFrEF in clinical trials. In this context, evidence from real-world studies based on clinical prac-

Table 3 Functional and ventricular function parameters in the total population and according to type of heart failure (with preserved or reduced left ventricular ejection fraction)

Parameters	Total study population		
	Baseline	Follow-up	*P*-value
NYHA-HF score[a]	2.4 (2–2.7)	1.9 (1.5–2.5)	<0.0001
LVEF (%)[a]	40 (29–53)	48 (30–57)	<0.0001
RVEF (%)			<0.0001
Normal	61.9	66.7	
Mildly depressed	12.5	11.8	
Moderately depressed	13.2	8.1	
Severely depressed	12.5	13.4	
NT-proBNP[a] (pg/mL)	1532 (591–3021)	1442 (593–3409)	0.29

Parameters	HF with preserved EF			HF with reduced EF		
	Baseline	Follow-up	*P*-value	Baseline	Follow-up	*P*-value
NYHA-HF score[a]	2.2 (1.5–2.5)	2.0 (1.4–2.4)	<0.0001	2.4 (2.0–2.5)	2.0 (1.5–2.5)	<0.0001
LVEF (%)[a]	54 (52–56)	57 (55–61)	<0.0001	30 (25–39)	35 (26–40)	<0.0001
RVEF (%)			<0.0001			<0.0001
Normal	74.1	81		53	59.4	
Mildly depressed	9.9	8.9		13.9	12.5	
Moderately depressed	5.4	2.5		16.6	9.4	
Severely depressed	10.6	7.6		16.6	18.8	
NT-proBNP[a] (pg/mL)	982 (412–1917)	955 (350–1882)	0.3	1771 (777–3172)	1546 (682–4060)	0.239

EF, ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association classification; RVEF, right ventricular ejection fraction.
[a]Median value and interquartile range 25–75% of heart failure score based on modified NYHA classification.

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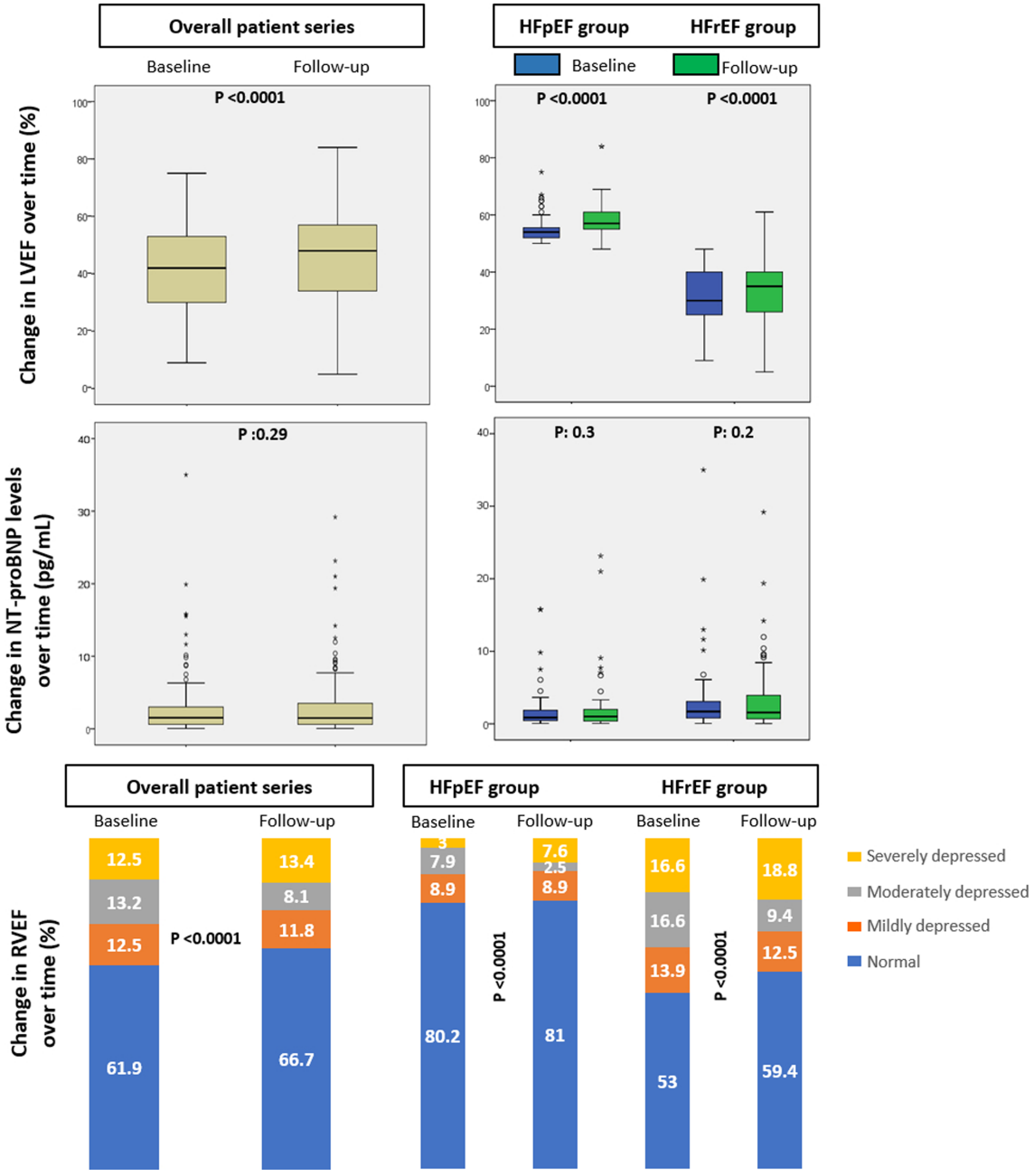
Figure 4 Impact of treatment with ferric carboxymaltose on ventricular function parameters. The values for NT-proBNP levels correspond to median and interquartile range 25–75%. HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; RVEF, right ventricular ejection fraction.

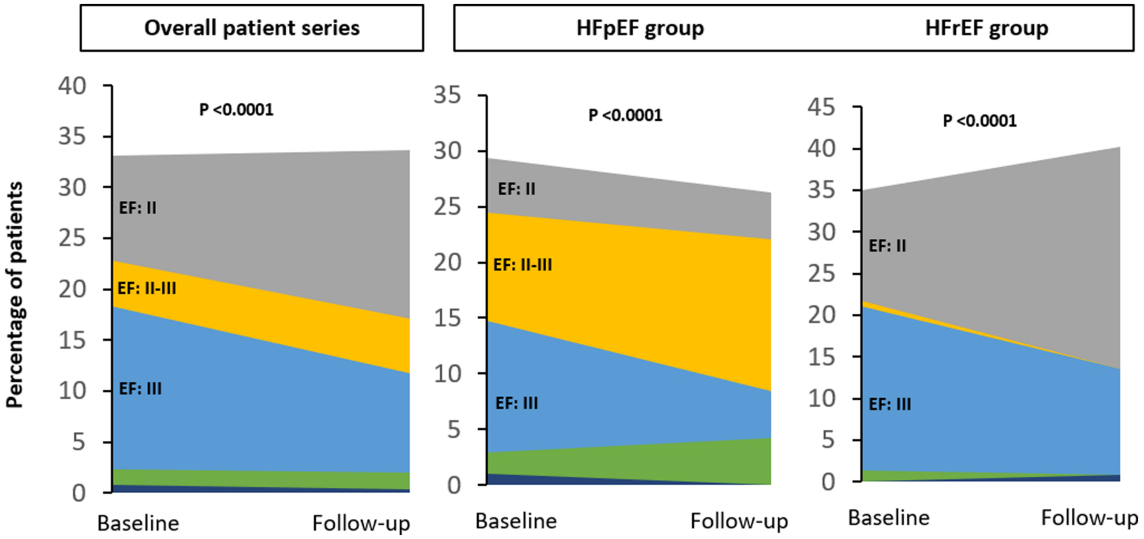


tice may help to better understand how to manage ID in different types of HF.

The good safety profile of FCM at the cardiovascular, respiratory, renal, and nervous system level offered the possibility of administering higher doses of iron with a shorter infusion time and fewer adverse reactions than other i.v. compounds, making it the most widely used therapeutic agent for replenishing iron stores in HF.[29,30] Pharmacokinetic studies have shown that FCM is safely and gradually absorbed by the liver and is effectively distributed for the synthesis of haem in new red blood cells.[31]

The results of our analyses have confirmed the absence of clinically relevant negative effects at renal or hepatic level, as demonstrated by the lack of significant changes observed in the expression of biomarkers of hepatic necrosis or creatinine.

Figure 5 Functional class of the overall patient series and patient subgroups with preserved and reduced left ventricular ejection fraction at baseline and after follow-up. EF, ejection fraction; FS, functional status; HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction.



Intracellular iron restoration may reverse the negative effects of ID on the cardiomyocytes and their contractility,[7,32] which would explain the significant improvement in left ventricular function observed in our overall patient series. Some studies have suggested that iron therapy may be related to reverse cardiac remodelling and improved LVEF on echocardiogram.[33–35] The Myocardial-IRON clinical trial found no improvement in LVEF with FCM therapy in patients with HF, although myocardial iron repletion was observed by cardiac MRI.[11]

The myocardial iron load is known to be reduced in the RV in patients with advanced HF.[36] However, there is very limited information at present on the effect of iron therapy on the RV, and the mechanisms underlying the improvement in RV function after i.v. iron administration are not fully known. In a recent substudy of the Myocardial-IRON trial with patients with left ventricular and RV systolic dysfunction, FCM treatment was associated with a significant improvement in LVEF at 30 days and with a significant and early improvement in RV function.[12] These findings are consistent with our results, which confirmed an increase in the number of patients with normal RV contractility in both the HFpEF and HFrEF subgroups. In our study, the most striking percentage increase occurred in patients with moderately depressed right ventricular ejection fraction (RVEF), which improved to normal function, especially in patients with left ventricular dysfunction; thus, ventricular interdependence may be involved to some extent.

Contrary to what we expected, we found no significant differences in the levels of the myocardial stress marker (NT-proBNP) after iron administration, either in the overall patient series or in the analysis of the two subgroups of patients with HF. There are few studies on the effect of iron repletion on NT-proBNP levels. Although we might expect in theory to see a reduction due to improved systolic function in patients, we did not observe any changes, perhaps because the levels of the stress marker were not excessively high and the number of patients with advanced FS was rather low. As far as we know, only one study has reported a reduction in NT-proBNP levels after i.v. iron therapy, although in this case, patients with HF, anaemia, and chronic renal failure were analysed.[37]

Finally, a particularly interesting finding in our study was a slight but significant improvement in the FS of patients according to the NYHA scale, both in the case of HFpEF and HFrEF. As previously discussed, although the iron repletion facilitated by FCM theoretically occurs in both types of HF, studies on the effects on HFpEF are still very scarce. The CONFIRM-HF clinical trial showed that the treatment of ID with FCM was associated with an improvement in the FS of patients with HF and LVEF $\leq$ 45%.[38] In our analysis, we found that this symptomatic improvement was also achieved in patients with HFpEF, although to a lesser degree. This is particularly interesting, because there is no evidence in the literature regarding changes in FS produced after the correction of ID in an entity as complex as HFpEF.

Study limitations

This study has certain limitations, including its retrospective nature and the absence of prior randomization of patients, which would have allowed us to balance the baseline characteristics between the two patient subgroups. Moreover,

assessment of the degree of cardiac function from some parameters such as RV function was not based on more precise measurements but on visual and qualitative measurements more frequently used in routine clinical practice. However, in the aforementioned setting, ventricular function is usually assessed by echocardiography and imaging studies.[39] In this respect, it is important to highlight that all echocardiograms were performed by the same cardiac imaging specialist team using uniform criteria, thereby avoiding the potential bias inherent to multicentre studies, in which loss of homogeneity in procedures between centres may affect the integrity of collected data and thus interfere with achieving significant results. The 12 week duration of follow-up was decided based on current guidelines that recommend the re-assessment of iron status after 12 weeks of FCM treatment. A longer follow-up of HF patients with ID might have led to changes in patients' clinical parameters, and modifications in drug and dose schedules might potentially affect some outcomes. Finally, the presence of decompensation and therapeutic changes in patients (other than iron administration) were not recorded, so our findings must be interpreted with caution.

Even so, this study brings many new developments. In the first place, the protocol for administration of FCM, based on a protocol previously established at a single centre, was strictly standardized and adhered to during the 5 year study period, ensuring homogeneity in treatment administration. In view of the lack of real-world studies on effectiveness, particularly in patients with HFpEF, this study provides real clinical practice data in a large number of HFpEF patients, yielding statistical significance in several of the parameters analysed.

Conclusions

The results of i.v. iron administration suggest an improvement in the EF and NYHA FS in outpatients with ID and HF, with whether preserved or reduced EF.

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Conflict of interest

None declared.

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Supporting information

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

Data S1. Supporting information

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