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Changes in platelet count as a marker of myocardial iron uptake after administration of ferric carboxymaltose in patients with heart failure

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Iron deficiency (ID) treated with ferric carboxymaltose (FCM) previously showed reduced platelet count; however, no studies have evaluated its biological significance in heart failure. In the current study, we aimed to: (a) assess the changes in platelet count at 7 and 30 days post-FCM, and (b) explore its association with non-invasive surrogates of myocardial iron uptake and left systolic function in patients with ID and heart failure with left ventricular ejection fraction < 50% (HFrEF and HFmrEF). This post-hoc analysis of a randomized, double-blind, FCM vs. placebo clinical trial (Myocardial-IRON Trail) involved 45 outpatients with HFrEF and HFmrEF and ID in which the platelet count value was available. Platelet count, cardiac magnetic resonance T1-mapping and 3D-global longitudinal strain (CMR-GLS) were assessed at baseline, 7, and 30 days. Linear regression models were used to evaluate the between-treatment differences and endpoints. The mean (SD) age was 71 ± 8 years, and 32 (71%) were men. At 30 days, we found a significant reduction in platelet count in those treated with FCM (p-value = 0.027). In those treated with FCM, the greater 30-day decrease in platelets showed lower 30-day changes in T1-mapping ($p = 0.024$) and CMR-GLS ($p = 0.028$). After administration of FCM, we found a significant 30-day reduction in platelet count. The greater platelet count reduction was related to lower myocardial iron repletion and a smaller improvement in left ventricular systolic function.

Keywords Platelet count, Heart failure, Iron deficiency, Myocardial iron repletion, Cardiac magnetic resonance global longitudinal strain

Iron deficiency (ID) is a common comorbidity in heart failure (HF) patients associated with reduced quality of life and increased morbidity and mortality[1]. Intravenous iron supplementation with ferric carboxymaltose (FCM) has shown to improve quality of life, functional capacity, and adverse clinical outcomes in patients with HF and ID. However, to date, a tool for monitoring response to IV iron in HF administration is lacking[1].

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Thrombocytosis is a frequent finding in ID patients, and a reduction in platelet count has been described in patients treated with FCM, which is believed to occur through decreased production or increased destruction of platelets[2].

To date, no studies have evaluated whether reductions in platelet count occurred following FCM administration in the context of HF and whether these changes are related to proxies of myocardial iron repletion. In this post hoc analysis, we aimed to evaluate a) within- and between-treatment changes in platelet count (Δ-platelets) at 7 and 30 days following FCM administration, and b) the association between changes in platelet count and post-treatment cardiac magnetic resonance (CMR) T1-mapping and CMR global three-dimensional left ventricular longitudinal systolic strain (CMR-GLS).

Methods

This study is a post hoc sub-analysis of the Myocardial-IRON trial (Unique identifier: NCT03398681) in which platelet count was available at all study visits. From the original 53 patients included in the trial, 8 were excluded (n = 45). Myocardial-IRON was a double-blind randomized clinical trial to evaluate the effect of intravenous FCM versus placebo on myocardial iron repletion assessed by CMR sequences in patients with HF and stable left ventricular ejection fraction < 50% (HFrEF and HFmrEF) and iron ID[3]. Absolute iron deficiency was defined as serum ferritin < 100 µg/L. Functional iron deficiency was defined as serum ferritin 100–299 µg/L with transferrin saturation (TSAT) < 20%[4]. Study design, patients' eligibility, procedures, ethical issues, and outcomes have been previously published[3,5]. Briefly, the participants were randomly assigned in a 1:1 ratio to receive either FCM or a placebo. FCM (Ferinject, Vifor Pharma, Glattbrugg, Switzerland) was administered intravenously as a 20 mL solution (equivalent to 1000 mg of iron) diluted in sterile saline solution (0.9% NaCl) over at least 15 min. The placebo group received an intravenous saline solution (0.9% NaCl) in a blind form. All participants and/or their legal guardian(s) provided written informed consent prior to enrollment in the study, and all methods were carried out in accordance with relevant guidelines and regulations. The study protocol was approved by the Spanish Agency for Medicines and Medical Devices and the Clinical Research Ethics Committee of the University Clinical Hospital of Valencia. The data supporting the results of this study can be obtained from the corresponding author upon reasonable request.

CMR T1-mapping and CMR-GLS

1.5 Tesla CMR studies (Essenza and Avanto, Siemens, Erlangen, Germany) were performed at baseline, 7 and 30-day after the intervention. Detailed descriptions have been previously reported[6–8]. CMR T1-mapping was measured/calculated using motion-corrected modified Look-Locker recovery (MOLLI) sequences (voxel size: 1.5 × 1.5 × 7 mm) in three short axes (base, middle, and apex). Once the T1 maps were generated, a Region of Interest (ROI) was selected in the mid-septum of the left ventricle in all three short axes, and the average T1 values were computed. Values reported correspond to native T1 mapping (without gadolinium contrast). Myocardial strain analysis using a specific CMR feature tracking software package (CVI42, Circle Cardiovascular Imaging, Canada) was used for 3D-global longitudinal strain. These analyses were performed offline by a single experienced operator blinded to clinical data. For each ventricle, both endocardial and epicardial contours were manually delineated at end-diastole, and the automated tracking algorithm calculated myocardial deformation across the entire myocardial wall (transmural strain), rather than restricting the analysis to the subendocardial layer[9,10].

Exposure: platelet count assessment

Blood tests were performed at baseline, 7, and 30 days. Platelet count was not a prespecified measurement procedure, and data was gathered retrospectively. Platelet count was performed using flow cytometry, identified by the LOINC code 26,515–7, and the results were reported as a concentration in units of 10^9 per liter ($\times 10^9$/L). The endpoints of this sub-study were Δ-platelets after treatment and its relationship with 7- and 30-day T1-mapping and CMR-GLS.

Statistical analysis

Continuous variables were presented as mean and standard deviation (SD) or median and percentile 25 -percentile 75 (p25-p75), as appropriate. Discrete data were expressed as numbers and percentages. Baseline variables across treatment arms were compared using chi^2, T-test, or Mann–Whitney U, as appropriate. Platelet counts at baseline, 7 days, and 30 days, were log-transformed due to deviations from a parametric distribution (log-platelet count). Linear mixed regression models were used to analyze the between-treatment changes (FCM vs placebo) in log-platelet count. These estimates were adjusted for baseline platelet count (log) and study center (as a cluster). Additionally, multivariate linear regression models were applied to evaluate the effect of treatment (FCM vs. placebo) on 30-day changes in platelet counts (Δ-platelets) as predictors of corresponding changes in T1-mapping and CMR-GLS. Estimates were adjusted for baseline T1-mapping or CMR-GLS, baseline platelet count, age, sex, anticoagulant/antiplatelet therapy at baseline, and study center (as a cluster). A p-value < 0.05 was considered significant for all analyses. All analyses were performed using STATA 18.0 (Stata Statistical Software, College Station, TX).

Results

Baseline characteristics

In this analysis, we included 45 patients (20 in the placebo arm and 25 in the FCM arm) of 53 patients (84.9%) from the whole study sample. The mean ± SD age was 71 ± 8 years, and 32 (71%) were men. Ischemic etiology was present in 19 patients (42.2%), and most (95.6%) were in stable New York Heart Association class II. The

median (p25-p75) NT-proBNP was 1728 pg/ml (1010–2828). All patients exhibited ID at baseline, with median (p25- p75) ferritin and TSAT of 63 ng/mL (42–01.1) and 15.7% (11–19.2), respectively. The proportion of patients with absolute and functional ID were 73.3% and 27.7%, respectively. The median (p25-p75) platelet count at baseline was 210×10^9 /L (182–255). The mean ± SD value of T1-mapping at baseline and CMR-GLS were 1088 ± 50 ms and −5.7 ± 4%, respectively. The baseline characteristics of the sample showed no significance across both treatment arms, including the exposure (platelet count) and endpoints (T1-mapping and CMR-GLS), as shown in Table 1.

FCM and changes in platelet count at 7 and 30-day visits

Compared to baseline, raw data showed a significant decrease in median (p25-p75) platelet count in the active arm (within-group comparisons) which was statistically significant at 30 days [214×10^9/L (177 -228) vs. 187×10^9/L (160–209), $p = 0.002$] as shown in Fig. 1. We did not find substantial within-group changes in the placebo arm at the two-time points (Fig. 1). Between-treatment analysis, adjusted for baseline log-transformed platelet counts, confirmed a significantly lower mean log Δ-platelets at 30 days—but not at 7 days—in patients treated with FCM (overall $p = 0.027$; Fig. 2).

Between-treatment changes in log Δ-platelets 30-day were not differentially modified by baseline platelet count and hemoglobin above and below the median (Supplementary Fig. 1 S1). Correlation between 30-

	Placebo n = 20	Iron n = 25	Total n = 45	*p*-value
Age, years	70.2 ± 7.9	71.5 ± 8.2	70.9 ± 8.0	0.612
Male, n (%)	13 (65.0)	19 (76.0)	32 (71.1)	0.419
Previous admission for AHF (12 months), n (%)	11 (55.0)	14 (56.0)	25 (55.6)	0.947
Hypertension, n (%)	13 (65.0)	20 (80.0)	33 (73.3)	0.258
NYHA I-II, n (%)	20 (100.0)	23 (92.0)	43 (95.6)	0.196
Diabetes Mellitus, n (%)	11 (55.0)	14 (56.0)	25 (55.6)	0.947
Dyslipidemia, n (%)	11 (55.0)	17 (68.0)	28 (62.2)	0.371
Ischemic Heart disease, n (%)	8 (40.0)	11 (44.0)	19 (42.2)	0.787
Physical examination at baseline				
Heart rate, bpm	69.3 ± 13.4	74.4 ± 15.6	72.2 ± 14.7	0.254
SBP, mmHg	127.4 ± 24.9	118.9 ± 18.9	122.7 ± 22.0	0.201
DBP, mmHg	68.3 ± 9.5	63.8 ± 8.2	65.8 ± 9.0	0.095
Laboratory values and CMR parameters at baseline				
Hemoglobin, g/dL	12.9 ± 1.5	12.7 ± 1.2	12.8 ± 1.3	0.554
Hematocrit, %	41.1 ± 4.7	40.1 ± 4.0	40.5 ± 4.3	0.447
RDW,%	15.9 ± 2.4	15.1 ± 1.6	15.5 ± 2.0	0.170
Sodium, mEq/L	141.5 ± 2.5	140.4 ± 2.5	140.9 ± 2.5	0.148
NT-proBNP, pg/mL*	1182 (959.5- 2422)	2110 (1220- 2830)	1728 (1010- 2828)	0.876
eGFR, mL/min × 1.73 m^{2*}	67.5 (49.1–79.7)	59.9 (50.4- 71.3)	64.3 (49.7–79.2)	0.935
Leukocytes, × 10^9 /L*	7735 (6640–8960)	6680 (5920–8480)	6950 (6330- 8730)	0.167
Ferritin, ng/mL*	51.7 (24.0- 102.7)	68.5 (56.0- 101.0)	63.0 (42.0–101.0)	0.238
TSAT,%*	16 (10–20)	15.7 (12- 19.2)	15.85 (11–19.6)	0.907
Platelet count, × 10^9/L*	202.5 (186.0–241.0)	214.0 (177.0–228.0)	210.0 (182.0- 255.0)	0.265
LVEF-CMR, %*	37.0 (33.0- 45.5)	42.0 (36.0- 48.0)	39.0 (33.0- 46.0)	0.567
GLS-CMR, %	− 5.7 ± 3.1	− 5.6 ± 4.7	− 5.7 ± 4.0	0.944
T1-mapping, ms	1084.3 ± 47.2	1092.3 ± 52.0	1088.7 ± 49.5	0.597
Treatment				
Anticoagulants	8 (40)	9 (36)	17 (37.8)	0.755
Antiplatelets	5 (41.7)	7 (43.7)	12 (42.9)	0.912
Diuretics	19 (95)	23 (92)	42 (93.3)	0.685
Betablockers	17 (85)	22 (88)	39 (86.7)	0.769
MRAs	12 (60)	12 (48)	24 (53.3)	0.423
RAS Inhibitors	16 (80)	17 (68)	33 (73.3)	0.361

Table 1. Baseline characteristics. AHF: acute heart failure; NYHA: New York heart association class; SBP: systolic blood pressure; DBP: diastolic blood pressure; RDW: red cell distribution width; NT-proBNP: amino-terminal pro-brain natriuretic peptide; eGFR: estimated glomerular filtration rate – MDRD formula; TSAT: transferrin saturation; LVEF: left ventricular ejection fraction; CMR: Cardiac magnetic resonance; GLS: Global longitudinal strain; MRAs: Mineralocorticoid Receptor Antagonists; RAS: Renin-Angiotensin system. Values for continuous variables are expressed as mean ± standard deviation. * Values expressed as the median (p25–p75).

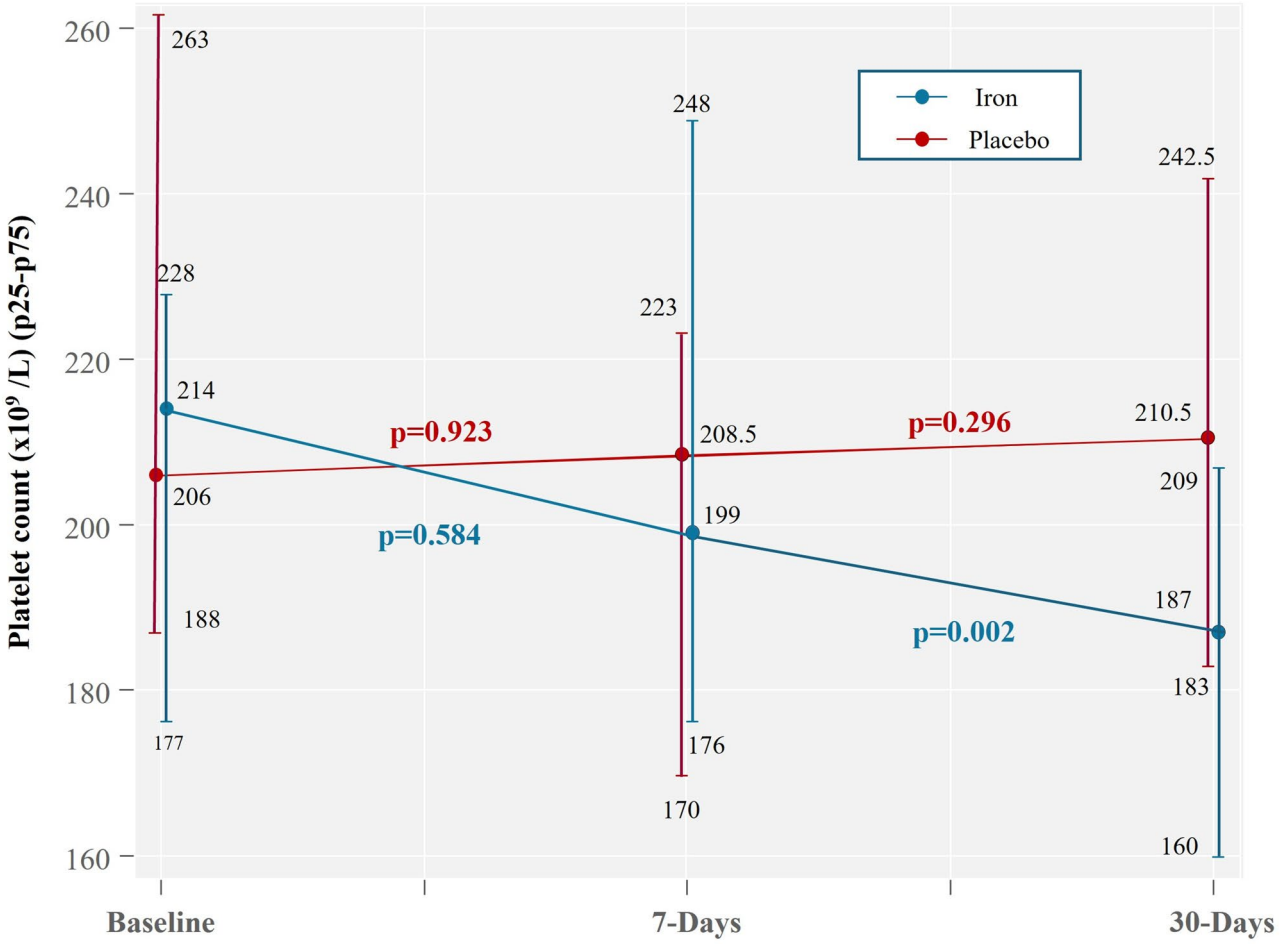

Fig. 1. Platelet count by visits (within-group comparisons). Raw data.

day platelet count changes and other hematological parameters across treatment allocation is defined in Supplementary Table 1 S1.

Changes in platelet count and CMR native T1-mapping at 30 days

In the whole sample, raw data revealed significant changes in T1-mapping in patients receiving FCM (Supplementary Table 2 S2).

At the 30-day visit, changes in platelet count (Δ-platelets) showed a borderline, inverse correlation with changes in native T1-mapping among patients randomized to the FCM arm (Spearman r = –0.331, $p = 0.093$), but not in those receiving placebo (Spearman r = –0.110, $p = 0.565$). In multivariable linear regression adjusting for baseline T1-mapping, baseline platelet count, age, sex, and anticoagulant/antiplatelet therapy, non-association was observed in the placebo group ($p = 0.573$; Fig. 3a), in contrast, a greater reduction in platelet count was independently associated with a smaller change in T1-mapping in the FCM group ($p = 0.023$; Fig. 3b).

Changes in platelet count and CMR-derived left ventricular global longitudinal strain at 30 days

In the overall cohort, observed data showed significant changes in CMR-GLS among patients treated with FCM (Supplementary Table 2 S2).

In the FCM arm, 30-day Δ-platelets were inversely correlated with changes in left ventricular CMR-GLS (Spearman r = –0.383, $p = 0.010$), whereas no significant correlation was found in the placebo arm (Spearman r = –0.143, $p = 0.549$). After multivariate adjustment, no association was evident in the placebo group (Fig. 4a), while a greater reduction in platelet count remained significantly associated with less reduction in CMR-GLS at 30 days in patients treated with FCM ($p = 0.028$; Fig. 4b).

Discussion

In patients with chronic HF and left ventricular ejection fraction below 50% (HFrEF and HFmrEF) and ID, we found a significant reduction in platelet count in the group treated with FCM at 30 days. Interestingly, the greater reduction in platelet count in the FCM group identified patients with CMR proxies, indicating less myocardial iron repletion and smaller improvement in left ventricular systolic function. These findings

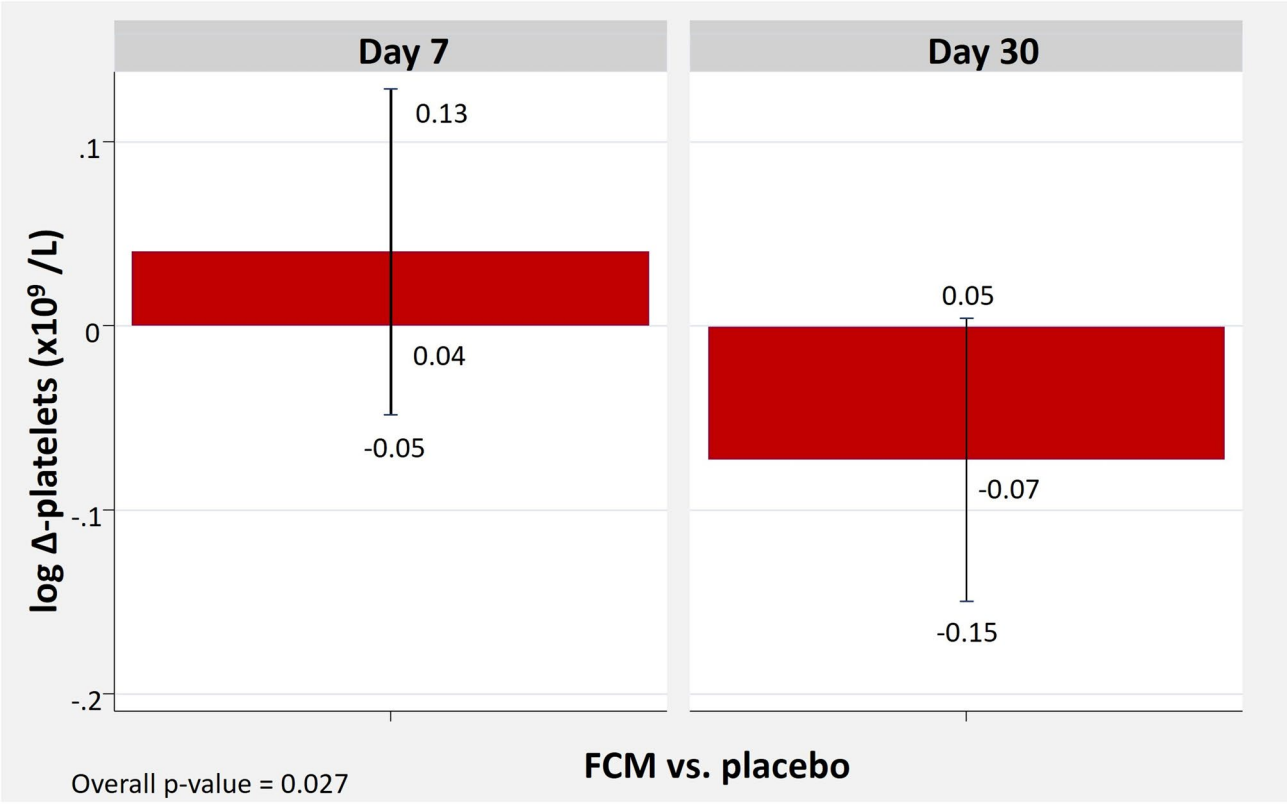

Fig. 2. Between treatment changes in log-platelet count by visits. FCM: Ferric carboxymaltose; log Δ-platelets: changes in log-platelet

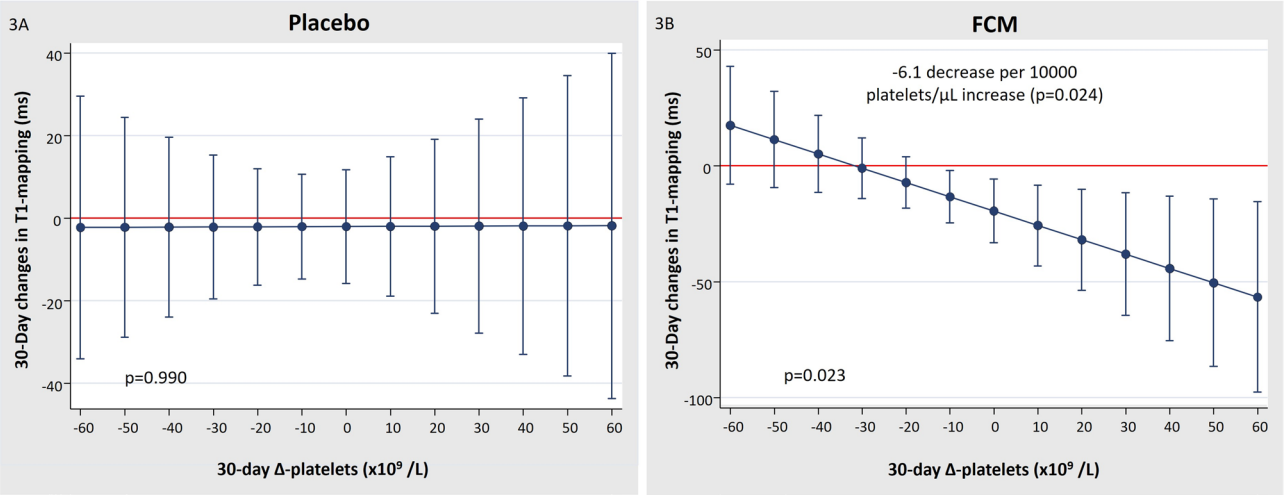

Fig. 3. Changes in 30-day T1 mapping across 30-day changes in platelet count. Estimates adjusted for baseline T1-mapping, baseline platelet count, age, sex, and anticoagulant/antiplatelet treatment. FCM: Ferric carboxymaltose. Δ-platelets: changes in platelet count.

suggest a physiological link between platelet count trajectory and iron tissue distribution after intravenous iron supplementation.

Iron plays a vital role in hematopoiesis, including thrombopoiesis, by influencing the lineage commitment of megakaryocytic/erythroid progenitors[2]. While the role of iron in red and white blood cell formation is well-documented[11], its effects on platelet dynamics remain less explored. It is well known that ID favors the differentiation of hematopoietic stem cells into megakaryocytes rather than erythroid precursors, leading to an

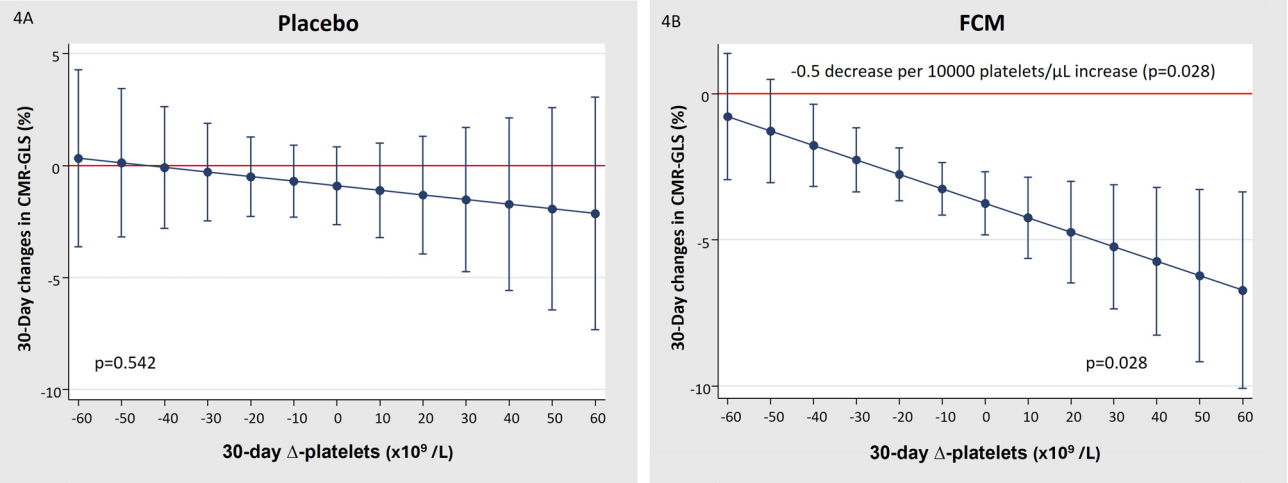

Fig. 4. Changes in 30-day CMR-GLS across 30-day changes in platelet count. Estimates adjusted for baseline T1-mapping, baseline platelet count, age, sex, and anticoagulant/antiplatelet treatment. FCM: Ferric carboxymaltose. CMR-GLS: Cardiac magnetic resonance 3D global longitudinal strain. Δ-platelets: changes in platelet count.

increased platelet count[2]. Iron supplementation reverses this shift, restoring normal erythropoiesis and causing platelet counts to decline to baseline.

Indeed, some studies have shown that iron supplementation reduces platelet count in ID across diverse conditions, such as inflammatory bowel disease[12,13], chronic kidney disease[14,15], and ID anemia[16,17], and within a range of 4 to 8 weeks. The mechanisms behind this pathophysiological phenomenon remain not fully understood. However, we postulate some reasons that may explain platelet reduction after ID supplementation: (a) Increased bone marrow iron availability may shift the balance in hematopoietic stem cells towards erythropoiesis, while reducing thrombopoiesis[18], (b) Erythropoietin shares structural similarities with thrombopoietin and can synergistically enhance platelet production. However, endogenous erythropoietin levels drop during ID correction, potentially reducing megakaryocyte productivity and causing transient thrombocytopenia[2], and (c) Intravenous iron formulations are preferentially sequestered by spleen/liver macrophages[19]. This may enhance the activity of splenic macrophages, leading to increased phagocytosis of blood cells, especially platelets, potentially mimicking what we found in the hypersplenism state. Indeed, reduced platelet count is a common finding in hypersplenism-related diseases[19]. In the FCM-treated group, we found greater decreases in platelet count linked to higher T1-mapping and higher CMR-GLS values interpreted as reduced myocardial iron repletion and less improvement in left ventricular systolic function. According to prior hypotheses, preferential iron uptake by the bone marrow, liver, or spleen over the myocardium may explain these intriguing results. Vera-Aviles et al.[20]. conducted a longitudinal study in patients with ID treated with FCM, showing that myocardial iron increased rapidly and maximally within 3 h and remained elevated for at least 42 days. In contrast, splenic iron rose more gradually, reaching a peak at 14 days before declining at 42 days. These findings suggest distinct temporal kinetics of iron distribution across organs, which may help explain our observation that greater platelet reduction was associated with less myocardial iron repletion and functional recovery. Thus, we postulate that decreased platelet counts may serve as a proxy for heightened splenic activity after iron supplementation. The role of hypersplenism and iron metabolism in platelet reduction parallels other conditions, such as liver cirrhosis, where hypersplenism is a well-documented cause of thrombocytopenia[19]. In these settings, splenectomy or splenic artery embolization has been shown to improve thrombocytopenia[21]. Furthermore, splenectomy in patients with beta-thalassemia major has been associated with increased cardiac iron overload and liver enlargement[21]. These findings underscore a potential interplay between splenic iron handling and systemic iron redistribution, although the exact physiological mechanisms remain unclear. Our findings should be interpreted as hypothesis-generating, and additional research is required to unravel the underlying mechanisms of platelet dynamics in the context of myocardial iron handling.

Further lines of research and limitations

Further research is necessary to validate these findings and to explore the mid-and long-term effects of FCM administration on platelet dynamics and their clinical implications. Specifically, further studies to elucidate the tissue-iron trafficking interactions after iron supplementation are warranted. Additionally, the role of platelet count or other widely available biomarkers for monitoring cardiac response to iron therapy must be more fully addressed.

This study has several limitations: (1) the study's limited sample size (n = 45) restricts the generalizability of the findings and statistical power; (2) as secondary analysis, the study is susceptible to bias and confounding, with no control over the original study design or randomization; (3) 30-day follow-up period may not capture longer-term dynamics in platelet count and myocardial iron metabolism; (4) potential confounders, such as

inflammatory markers, iron trafficking proteins, platelet activation status were not evaluated; (5) the concomitant use or modification of cardiovascular medications that could affect platelet counts during the trial should be acknowledged as a potential limitation, and (6) we did not register imaging proxies of spleen iron uptake.

Conclusions

In this post hoc analysis of the Myocardial-IRON trial on patients with stable HFrEF and HFmrEF and ID, treatment with FCM was associated with a short-term decrease in platelet count (at 30 days). Furthermore, the greater decrease in platelet count was significantly associated with higher T1-mapping and CMR-GLS and borderline significant, suggesting lower myocardial iron uptake.

Data availability

The data supporting the results of this study can be obtained from the corresponding author upon reasonable request.

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Author contributions

Conceptualization, J.N; methodology, I.C, R.L., I.C, MPLL, JV.M, A.M; formal analysis, J.N and A. M.; data curation, A.M, I.C, R.L.; writing original draft preparation, A.M and C.GC; writing review and editing R.E, E.R, A.C, M.P; supervision, S.LL, L.A, A.BG, J. N. All authors have read and agreed to the published version of the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Additional information
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