communications medicine

A Nature Portfolio journal

Article

https://doi.org/10.1038/s43856-026-01619-1

Role of dyssynchrony in short-term left ventricular systolic function after iron repletion in patients with heart failure

Irene del Canto[1,2,3,20], Gema Miñana[1,2,20], Ingrid Cardells[4,20], Raquel López[5], Luis Almenar[5], Pau Llácer[6], Maria Pilar López-Lereu[7], José Vicente Monmeneu[7], Vicent Bodí[1,2], Juan Sanchis[1,2], Alicia Maceira[7], Carlos G. Santos-Gallego[8], Pieter Martens[9,10] & Julio Núñez[1,2] ✉ On behalf of Myocardial-IRON Investigators*

Abstract

Background The mechanisms underlying the clinical benefit of intravenous iron in patients with heart failure (HF), left ventricular ejection fraction (LVEF) < 50%, and iron deficiency (ID) remain incompletely defined. Clinical evidence suggests that iron repletion may improve ventricular synchrony and augment the response to cardiac resynchronization therapy (CRT). The longitudinal systolic dyssynchrony index (L-SDI), derived from cardiac magnetic resonance feature tracking (CMR-FT), provides a non-invasive measure of mechanical dyssynchrony. This subanalysis of the Myocardial-IRON trial evaluated the short-term effects of ferric carboxymaltose (FCM) on L-SDI and explored its relationship with global left ventricular longitudinal strain (GLS).

Methods In this post hoc analysis of the randomized, double-blind, placebo-controlled Myocardial-IRON trial (NCT03398681), 51 of 53 ambulatory patients (96.2%) with stable HF, LVEF < 50%, and ID underwent CMR-FT at baseline, and at 7-day, and 30-days post-FCM. Linear mixed-effects models assessed the effect of FCM versus placebo on L-SDI, including subgroup analyses by baseline QRS duration, and evaluated associations between changes in L-SDI and changes in GLS, T2*, and T1-mapping.

Results Data are presented as mean ± SD or median (IQR), as appropriate. The participants have a mean age of 70.4 ± 9.6 years, with a median CMR-derived LVEF of 38.5% (IQR 33–45); the mean global longitudinal strain is −7.5 ± 3.6%. FCM leads to a greater reduction in L-SDI over time versus placebo (omnibus $p = 0.015$), with significance at 30 days (Δ=–3.8; 95% CI –6.9 to –0.7; $p = 0.011$). The benefit is most pronounced in patients with baseline electrical dyssynchrony (interaction $p < 0.001$). Improvements in L-SDI are strongly associated with GLS gains ($p < 0.001$) and myocardial iron uptake [T2*changes ($p = 0.045$) and T1-mapping changes ($p = 0.011$)].

Conclusions In HF with LVEF < 50% and ID, FCM improves short-term LV mechanical synchrony, particularly in those with electrical dyssynchrony, and this is linked to enhanced systolic function and greater myocardial iron repletion.

Plain language summary

Iron deficiency is common in patients with heart failure and makes their condition worse. Although giving iron through an intravenous infusion is known to improve how patients feel and function, we do not fully understand how it benefits the heart itself. In this study, we used a type of heart imaging, cardiac magnetic resonance scans, to determine whether iron treatment improves heart pump coordination and synchronization. We found that patients who received an iron infusion showed clearer improvement in how well their heart muscle worked within 30 days compared with those who received a placebo. The benefit was especially noticeable in patients who already had abnormal heart electrical patterns. These findings suggest that iron treatment helps the heart muscle contract more uniformly, making the heart pump more efficiently and helping to explain why this therapy improves the health of people with heart failure.

[1]Department of Cardiology, Hospital Clínico Universitario de Valencia, Universitat de València, INCLIVA, Valencia, Spain. [2]CIBER Cardiovascular, Valencia, Spain. [3]Department of Electronic Engineering, Universitat de València, Valencia, Spain. [4]Department of Cardiology, Hospital de Manises, Valencia, Spain. [5]Department of Cardiology, Hospital Universitario La Fe de Valencia, Valencia, Spain. [6]Department of Cardiology, Hospital Universitario Ramón y Cajal, Madrid, Spain. [7]Cardiovascular Imaging Unit, Ascires Biomedical Group, Valencia, Spain. [8]Atherothrombosis Research Unit and Fuster Heart Hospital, Mount Sinai Hospital, Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [9]Department of Cardiology, Ziekenhuis Oost Limburg, Belgium, Genk, Belgium. [10]Hasselt University, Hasselt, Belgium. [20]These authors contributed equally: Irene del Canto, Gema Miñana, Ingrid Cardells. *A list of authors and their affiliations appears at the end of the paper. ✉e-mail: juenuvi@uv.es; yulnunez@gmail.com

In patients with heart failure and reduced ejection fraction (HFrEF), intravenous ferric carboxymaltose (FCM) improves symptoms, functional capacity, quality of life, and reduces heart failure (HF) hospitalization[1–6]. Despite these established benefits, the mechanisms underlying clinical improvement and the patient profiles most likely to respond remain incompletely understood. The Myocardial-IRON trial showed significant short-term changes in cardiac magnetic resonance (CMR) sequences T2* and T1-mapping, indicative of myocardial iron repletion following administration of FCM[7]. Moreover, two subanalyses of this trial reported improvements in biventricular and left atrial function assessed by CMR feature tracking (CMR-FT) derived parameters[8,9].

Left ventricular mechanical dyssynchrony is a frequent feature in patients with HF, and has been associated with worse outcomes[10–12]. In optimally treated HFrEF patients with iron deficiency (ID) and who received a cardiac resynchronization therapy (CRT) in the last 6 months, the IRON-CRT trial found that iron repletion with FCM enhanced CRT response, improving LVEF and reducing LV volumes when compared to CRT alone[13]. These findings support the notion that iron supplementation may improve electromechanical coupling, thereby potentially ameliorating electrical and mechanical dyssynchrony. In the current study, we postulate that iron repletion with FCM may improve LV dyssynchrony, and LV systolic function recovery could be partly mediated by these changes. Systolic dyssynchrony index (SDI) is a parameter that allows the assessment of LV dyssynchrony using CMR-FT[14–16]. Therefore, in this subanalysis of the Myocardial-IRON trial, we aim to evaluate: (a) the effect of FCM on short-term longitudinal SDI (L-SDI), (b) the between-treatment effect on L-SDI and global longitudinal strain (GLS) across baseline electrical dyssynchrony, (c) how changes in L-SDI were related to changes in GLS, T2*, and T1-mapping. In this population, we show that intravenous FCM leads to a short-term reduction in LV mechanical dyssynchrony. The improvement in mechanical synchrony is most pronounced in patients with baseline electrical dyssynchrony and is closely associated with concurrent gains in global longitudinal strain and markers of myocardial iron repletion.

Methods

Study sample and trial intervention

This is a posthoc analysis of an investigator-initiated, multicentre, randomized, double-blind, placebo-controlled clinical trial designed to evaluate the effect of intravenous FCM versus placebo (1:1) on myocardial iron repletion estimated by T2* and T1 mapping CMR sequences, in patients with stable chronic HF (New York Heart Association class II and III), with systolic dysfunction (LVEF < 50%), and ID (serum ferritin <100 μg/L or 100–299 μg/L with transferrin saturation <20%). Inclusion and exclusion criteria are reported elsewhere[17]. The trial (NCT03398681, NCT registration date: November 21, 2017) was conducted in five academic centers in Spain from May 2017 to June 2018. The patients provided signed informed consent before being randomized 1:1 to receive either FCM or placebo. The study protocol was approved by Agencia Española del Medicamento y Productos sanitarios (AEMPS) and by Comité Ético de Investigación Clínica (CEIC) del Hospital Clínico Universitario de Valencia. FCM (Ferinject®, Vifor Pharma, Glattbrugg, Switzerland) was given intravenously as a perfusion of 20 mL solution (equivalent to 1000 mg of iron) diluted in a sterile saline solution (0.9% NaCl) administered over at least 15 min. In the placebo group, an intravenous saline solution (0.9% weight/volume NaCl) was administered over the same time. The study design and main results were previously published[17]. In this specific subanalysis, we assessed a total of 51 patients in which L-SDI was measured (96.2% ot the total sample, 25 on placebo and 26 on FCM). By design, patients with an implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) were excluded from the trial.

Electrocardiographic assessment

At baseline, a standard 12-lead electrocardiogram (ECG) was acquired, and QRS duration was measured in milliseconds using automated digital calipers, with manual verification when needed. QRS width was subsequently dichotomized using a 120 ms threshold to classify patients into narrow (<120-ms, no electrical dyssynchrony) and wide (≥120 ms or electrical dyssynchrony).

Cardiac magnetic resonance

CMR studies were performed by two experienced operators on a 1.5 Tesla MR scanner (Essenza and Avanto, Siemens, Erlangen, Germany) using the spine and phased array 6-channel surface coils at 3 time points (baseline, 1-week and 1-month). All images were obtained with electrocardiographic gating and breath-holding. Cine sequences in the 2-chamber, 3-chamber and 4-chamber views were obtained. Also, contiguous short-axis cine from the atrioventricular plane to the apex was acquired at rest every 1 cm with steady-state free precession (SSFP) imaging sequences. The technical specifications of the CMR sequences were described elsewhere[8]. Cine images were analyzed offline by two experienced observers blinded to all patient data using customized software (QMASS-MR 6.1.5, Medis, Leiden, Netherlands). LVEF was quantified by semiautomatic planimetry of endocardial and epicardial borders in short-axis-view cine images by the Simpson method. For T2* quantification, a region of interest (ROI) was placed in the mid-septum of the left ventricle. Mean signal intensities across images acquired at progressively longer echo times were used to construct an exponential decay curve. T2* values were then derived by fitting a monoexponential decay model using a nonlinear curve-fitting algorithm. T1 mapping was performed with a Modified Look-Locker Inversion Recovery (MOLLI) sequence incorporating motion correction (voxel size 1.5 × 1.5 × 7 mm) at three short-axis levels (basal, mid, and apical). ROIs were drawn in the mid-septum at each level, and mean T1 values were calculated by averaging across the three slices. For CMR-FT-based longitudinal strain analysis, three-dimensional (3D) strain was evaluated using cine SSFP images and specialized software (CVI42, Circle Cardiovascular Imaging, Calgary, Canada), as described previously[8]. Segmental strain was assessed using the American Heart Association 17-segment model (excluding the apex)[18]. Longitudinal strain-time curves were generated for each of the 16 segments, and time-to-peak strain was used to calculate a longitudinal SDI (L-SDI). The L-SDI was defined as the standard deviation (SD) of time-to-peak strain across segments, normalized to the duration of the cardiac cycle. L-SDI was measured at baseline, 7 days, and 30 days after randomization. Analyses were performed by two experienced operators, both with European Association of Cardiovascular Imaging-CMR level 3.

Endpoints

The endpoints of this subanalysis were: (a) changes in L-SDI in the whole population, (b) changes in L-SDI and GLS across baseline electrical dyssynchrony, (c) the relationship between changes in L-SDI and changes in GLS, and (d) the relationship between changes in L-SDI and changes in CMR proxies of myocardial iron repletion (T2* and T1-mapping).

Statistical analysis

Baseline correlations among L-SDI, QRS duration, and GLS were evaluated using Spearman's correlation coefficient. Linear mixed-effects models were used to assess the association between treatment allocation and 7 and 30-day changes in the following endpoints: (a) L-SDI; (b) L-SDI stratified by QRS duration; (c) GLS across QRS duration; and (d) L-SDI changes in relation to changes in GLS, T2*, and T1-mapping. Models were adjusted for age, sex, hospital (as a clustering variable), treatment group, visit (7- and 30-day), the interaction term (treatment × visit), and the baseline value of the dependent variable. Multiple testing correction was applied using the Sidak procedure. Results from the mixed models are presented as least square means with corresponding 95% CIs and p-values. Mediation analysis was performed using regression-with-residuals (rwrmed package, Stata 18.1) to decompose the overall effect of FCM on GLS into direct and indirect components via changes in L-SDI. All statistical procedures were executed using STATA 18.1. A two-sided p-value < 0.05 was considered statistically significant.

Table 1 | Baseline characteristics by treatment arm

	Placebo (*N* = 25)	Iron (*N* = 26)	Total (*N* = 51)	*p*-value
Demographics				
Age, years	69.9 ± 11.4	70.9 ± 7.8	70.4 ± 9.6	0.705
Women	7 (28.0)	6 (23.1)	13 (25.5)	0.687
Medical history				
Hypertension	18 (72.0)	21 (80.8)	39 (76.5)	0.460
Diabetes mellitus	13 (52.0)	15 (57.7)	28 (54.9)	0.683
Dyslipidemia	15 (60.0)	18 (69.2)	33 (64.7)	0.490
Former/current smoker	4 (16.0)	3 (11.5)	7 (13.7)	0.643
Ischemic heart disease	9 (36.0)	13 (50.0)	22 (43.1)	0.313
COPD	6 (24.0)	6 (23.1)	12 (23.5)	0.938
NYHA functional class				0.080
II	25 (100.0)	23 (88.5)	48 (94.1)	
III	0 (0.0)	3 (11.5)	3 (5.9)	
Vital signs				
Heart rate, bpm	71.5 ± 11.2	68.9 ± 12.2	70.2 ± 11.7	0.428
SBP, mmHg	129.1 ± 23.8	120.2 ± 19.5	124.6 ± 21.9	0.148
DBP, mmHg	68.5 ± 9.6	63.5 ± 8.2	66.0 ± 9.2	0.052
ECG				
Atrial fibrillation/Flutter	13 (52.0)	10 (38.5)	23 (45.1)	0.331
Bundle branch block	8 (32.0)	10 (38.5)	18 (35.3)	0.629
LBBB	6 (24.0)	5 (19.2)	11 (21.6)	0.679
RBBB	2 (8.0)	5 (19.2)	7 (13.7)	0.244
CMR parameters				
LVEF, %	37 (32-43)	40 (33-45)	38.5 (33-45)	0.637
GLS, %	−6.4 ± 3.2	−8.5 ± 3.7	−7.5 ± 3.6	0.036
L-SDI, %	13.5 ± 4.8	14.0 ± 5.3	13.8 ± 5.0	0.694
T1-mapping, ms	1076.3 ± 49.7	1091.5 ± 49.7	1084.1 ± 49.8	0.279
T2*, ms	38.7 ± 12.2	41.1 ± 9.5	39.9 ± 10.8	0.429
Laboratory parameters				
Hemoglobin, g/dL	13.2 ± 1.5	12.8 ± 1.2	13.0 ± 1.4	0.249
Ferritin, ng/mL	49 (25-114)	75 (58-126)	65 (41-126)	0.072
TSAT, %	16 (9.6-20)	15.9 (12-19.6)	16 (10-20)	0.812
eGFR, mL/min/1.73 m^2	65.0 ± 19.4	63.3 ± 19.2	64.1 ± 19.1	0.763
NT-proBNP, pg/mL	1180 (1010-2527)	2050 (1220-2830)	1690 (1010-2828)	0.301
Heart failure therapies				
Diuretics	23 (92.0%)	24 (92.3%)	47 (92.2%)	0.967
Beta-blockers	20 (80.0%)	23 (88.5%)	43 (84.3%)	0.406
RAAS inhibitors	18 (72.0%)	21 (80.8%)	39 (76.5%)	0.460
MRA	16 (64.0%)	12 (46.2%)	28 (54.9%)	0.200

Values are given as mean ± standard deviation and median (percentile 25%–percentile 75%). Categorical variables are presented as *n* (%).
COPD chronic pulmonary obstructive disease, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *GLS* global longitudinal strain, *L-SDI* longitudinal systolic dyssynchrony index, *LBBB* left bundle branch block, *LVEDV* left ventricular end-diastolic volume, *LVEF* left ventricular ejection fraction, *LVESV* left ventricular end-systolic volume, *MRA* mineralocorticoid receptor antagonist, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *NYHA* New York Heart Association, *RAAS* renin-angiotensin-aldosterone system, *RBBB* right bundle branch block, *SBP* systolic blood pressure, *TSAT* transferrin saturation.

Results

The mean ± SD age of the study sample was 70.4 ± 9.6 years. 38 (74.5%) were men, 48 (94.1%) showed stable NYHA class II–III, 23 (43.1%) had a history of ischemic heart disease, and the median (p25% to p75%) of CMR-derived LVEF and NTproBNP were 38.5% (IQR 33–45) and 1690 pg/mL (1010-2828), respectively. The mean GLS was −7.5 ± 3.6%. The mean ± SD of QRS width was 113 ± 27 mseg, and 18 (34%) patients showed QRS > 120 mseg [12 (22.6%) and 6 (11.3%) left and right bundle branch block, respectively]. The mean ± SD of L-SDI was 13.8 ± 5.0%. Baseline characteristics, including CMR-derived left ventricular systolic function and L-SDI, were comparable between the two treatment arms, except for a lower GLS observed in the FCM arm (Table 1). At baseline, L-SDI showed no significant correlation with GLS ($r = 0.24$, $p = 0.085$).

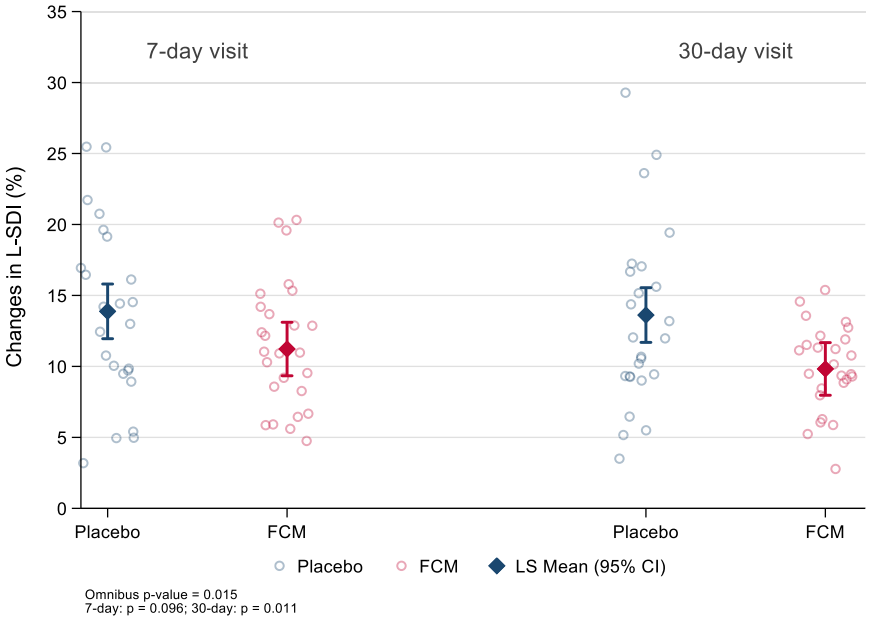

Fig. 1 | Changes in left ventricular (LV) longitudinal systolic dyssynchrony index (L-SDI) measured by cardiac magnetic resonance feature tracking (CMR-FT) at 7 and 30 days after randomization to ferric carboxymaltose (FCM) or placebo. Values represent least-squares means estimated from linear mixed-effects models, adjusted for recruitment center (cluster variable), treatment-by-visit interaction (7 and 30 days), age, sex, and baseline L-SDI. Overall, FCM was associated with a greater reduction in L-SDI over time (omnibus $p = 0.015$), with a statistically significant difference at 30 days ($\Delta = -3.8$; 95% CI −6.9 to −0.7; $p = 0.011$) and a non-significant trend at 7 days ($p = 0.096$). Individual points were added (99 observations from 51 patients; placebo: $n = 25$; FCM: $n = 26$). CMR-FT cardiac magnetic resonance feature tracking, FCM ferric carboxymaltose, L-SDI longitudinal systolic dyssynchrony index, LV left ventricle.

Intravenous iron supplementation with FCM and L-SDI

Inferential analyses revealed a significant improvement in L-SDI among patients treated with FCM compared to placebo (omnibus $p = 0.015$; Fig. 1). At day 7, the reduction in L-SDI with FCM was borderline significant (between-group difference: −2.6; 95% CI: −5.7 to 0.4; $p = 0.096$), while by day 30, the difference reached statistical significance (between-group difference: −3.8; 95% CI: −6.9 to −0.7; $p = 0.011$). Also, in the current sample, we confirmed a significant improvement in GLS after FCM (Supplementary Fig. 1). Changes in L-SDI and GLS did not significantly differ across atrial fibrillation status (Supplementary Figs. 2 and 3).

Baseline electrical dyssynchrony and treatment response

The impact of intravenous iron on L-SDI was modified by baseline QRS duration (p-value for interaction = 0.003). Patients with longer QRS experienced the greatest reductions in L-SDI following FCM treatment (Fig. 2a). A similar interaction was observed when stratifying patients by a QRS threshold of ≥120 ms vs. <120 ms (interaction $p < 0.001$), with those in the ≥120 ms group showing notably greater improvements in dyssynchrony, particularly at 30 days post-treatment (Fig. 2b).

Effect of FCM on GLS and relation to QRS duration

The effect of FCM on GLS was also significantly modulated by baseline QRS duration (p-value for interaction <0.001). Patients with wider QRS complexes exhibited greater improvements in GLS following FCM administration, particularly evident at 30 days (Fig. 3a). Additionally, patients with a QRS duration greater than 120 ms showed a more pronounced improvement in strain compared to those with narrower QRS complexes (Fig. 3b).

Relationship between changes in L-SDI and changes in GLS

Following FCM, the improvement in GLS following FCM was linear and positively related to improvement in L-SDI (p-value for interaction = 0.001). Thus, the greater decrease in L-SDI corresponded to a greater reduction of GLS, being most evident at 30 days (Fig. 4). A mediation analysis revealed that an improvement in L-SDI mediated 19.5% of the GLS improvement.

Relationship between changes in L-SDI and changes in myocardial iron repletion

Greater myocardial iron repletion, reflected by larger reductions in T1-mapping and increases in T2*, was associated with greater improvements in L-SDI (Fig. 5). Specifically, after FCM, a decrease in T1-mapping was related to improvement in L-SDI at 30-days (Fig. 5a). Likewise, a decrease in T2* was associated with improvement in L-SDI after FCM at 7 and 30 days (Fig. 5b).

Discussion

To the best of our knowledge, this study is the first to show that intravenous iron repletion with FCM leads to a short-term reduction in LV mechanical dyssynchrony, as measured by CMR-FT-derived L-SDI, in patients with HF, LVEF < 50%, and ID. Improvements in L-SDI were strongly associated with enhanced LV systolic function and were most pronounced in patients with baseline electrical dyssynchrony. Interestingly, the greater improvement in myocardial synchrony was associated with greater improvement in LV myocardial iron uptake and systolic function. Interestingly, the improvement in mechanical synchrony following iron infusion mediated part of the beneficial effect of iron repletion on left ventricular systolic function, suggesting that enhanced synchrony may partially account for the myocardial functional benefits observed with iron therapy in patients with HFrEF. Similarly, the present findings indicate that patients with baseline electrical dyssynchrony experience a greater short-term improvement in left ventricular systolic function.

LV dyssynchrony, characterized by asynchronous myocardial contraction, is a key contributor to systolic dysfunction, impaired diastolic filling, and adverse remodeling in HF, especially in HFrEF[19,20]. It refers to the temporal dispersion of myocardial contraction across different ventricular segments, leading to inefficient systolic function, impaired ventricular filling, and adverse remodeling[21,22]. Mechanical dyssynchrony is detectable by imaging, whereas electrical dyssynchrony, typically assessed by QRS duration and morphology on a 12-lead ECG, remains the most widely used surrogate in clinical practice. A QRS ≥ 120 ms, particularly with left bundle branch block (LBBB) morphology, is strongly predictive of poor outcomes and constitutes a major indication for CRT[23]. Prior trials have consistently shown that CRT yields the greatest benefit in patients with marked electrical dyssynchrony[24]. Molecular studies have indicated that mechanical dyssynchrony leads to numerous adverse cellular effects, including a disrupted metabolism with decreased reliance on free fatty acid oxidation and increased anaerobic breakdown of glucose, depressed calcium cycling and decreased calcium sensitivity of myofilaments, altered ion channel functioning and mitochondrial dysfunction[25].

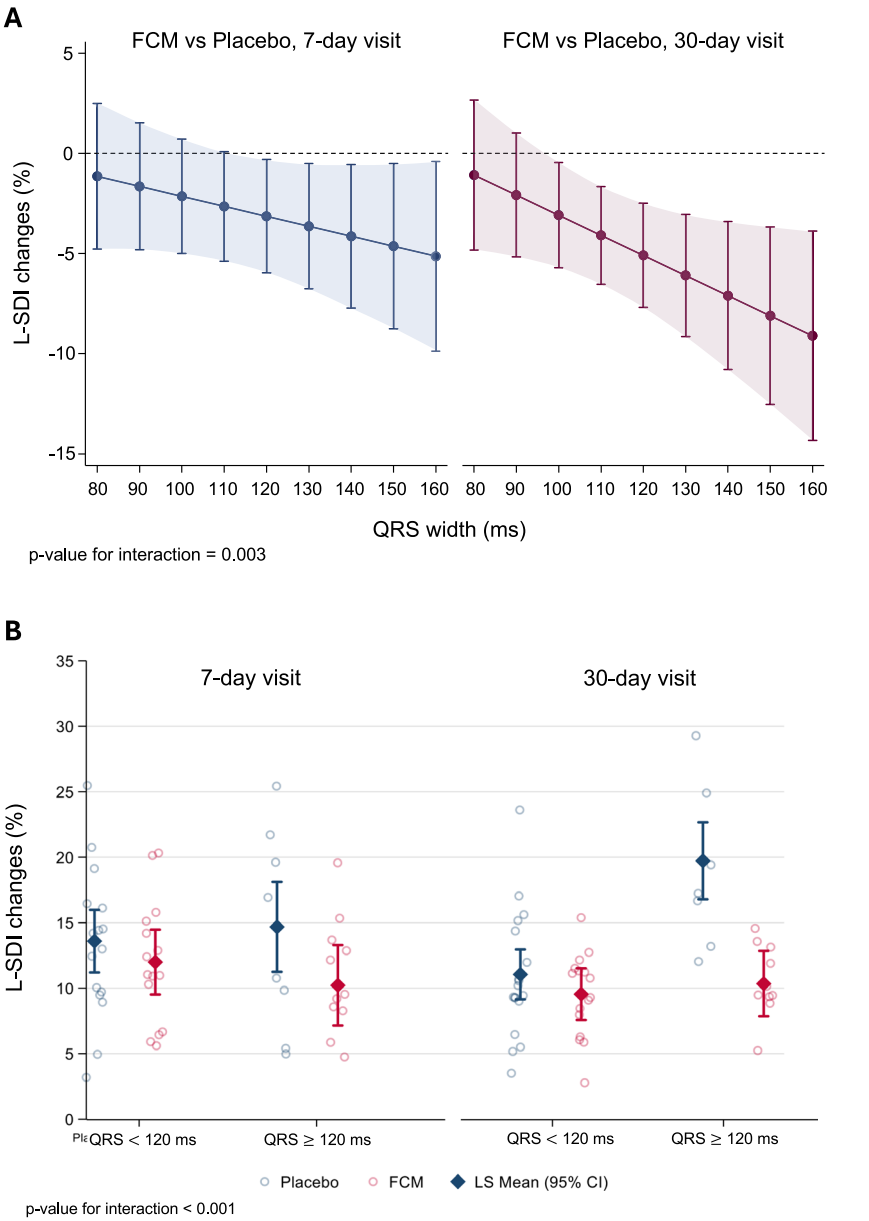

Fig. 2 | Effect of ferric carboxymaltose (FCM) on changes in left ventricular (LV) longitudinal systolic dyssynchrony index (L-SDI) according to baseline QRS duration. A Relationship between baseline QRS duration and changes in L-SDI at 7 and 30 days after treatment. Values represent least-squares means (95% CIs) from linear regression models, adjusted for recruitment center (cluster variable), treatment-by-visit interaction, age, sex, and baseline L-SDI. A significant interaction was found between treatment effect and QRS duration ($p = 0.003$). **B** Changes in L-SDI in subgroups defined by the presence (QRS ≥ 120 ms) or absence (QRS < 120 ms) of bundle branch block at baseline. Values are least-squares means from linear mixed-effects models with the same covariate adjustments as above. Individual points were added (99 observations from 51 patients; placebo: $n = 25$; FCM: $n = 26$). The interaction between treatment effect and baseline QRS category was highly significant ($p < 0.001$). FCM ferric carboxymaltose, L-SDI longitudinal systolic dyssynchrony index, LV left ventricle.

Although ID is prevalent in HFrEF and its correction improves symptoms and functional capacity, direct evidence linking ID to cardiac conduction abnormalities or mechanical dyssynchrony remains scarce. Preclinical studies have shown that myocardial ID disrupts mitochondrial metabolism and calcium handling, potentially contributing to electrical instability[26]. Clinically, some observational data suggest indirect ECG alterations, such as prolonged T wave peak-to-end (Tp-e) intervals and increased Tp-e/QT ratio, in iron-deficient HF patients, with partial normalization following FCM therapy[27]. However, these findings are exploratory, and no studies to date have directly investigated the effects of iron repletion on electrical conduction or ventricular dyssynchrony.

The observed reduction in L-SDI after FCM treatment may reflect the restoration of intracellular iron, which enhances mitochondrial oxidative phosphorylation and ATP production[25,28]. In fact, the increase in myocardial iron content with SGLT2 inhibitors directly correlates with improvements in LVEF and exercise capacity[29]. This metabolic improvement likely facilitates more coordinated myocardial contraction, particularly relevant in iron-deficient HF. These mechanistic insights highlight the potential of FCM therapy to not only improve global LV function but also reduce intraventricular dyssynchrony, a key contributor to adverse outcomes in HF[10–12,30]. The finding that FCM therapy appears to yield greater benefit in patients with mechanical dyssynchrony is intriguing and may be mechanistically explained. Iron deficiency aggravates the molecular derangements already induced by dyssynchrony, particularly impaired phosphocreatine/ATP balance, myofilament contraction, and calcium cycling. Thus, both iron deficiency and dyssynchrony converge on a state of profound myocardial energy deprivation, mutually amplifying each other's effects and ultimately manifesting at the ventricular level as impaired contractile performance (e.g., reduced LVEF, GLS, or L-SDI)[31].

Our findings, together with IRON-CRT results, suggest that iron therapy could enhance mechanical synchrony and systolic performance, with the largest benefits in patients with electrical dyssynchrony. Indeed, in the current study, FCM treatment led to a significant reduction in L-SDI, paralleled by a meaningful improvement in GLS. These results could open a line of investigation focused on identifying patients with intraventricular conduction abnormalities as potential preferential responders to iron repletion in HFrEF and potentially other dyssynchrony-associated conditions.

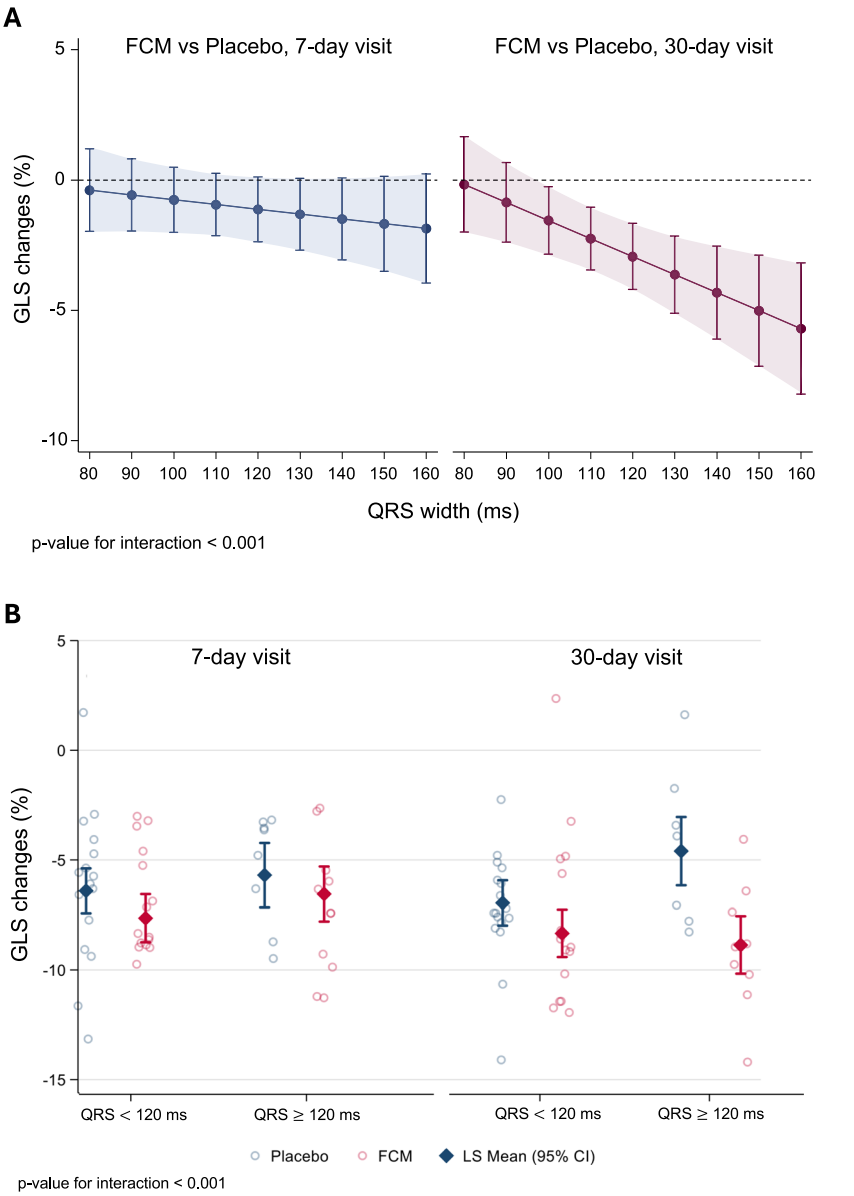

Fig. 3 | Effect of ferric carboxymaltose (FCM) on changes in left ventricular (LV) global longitudinal strain (GLS) according to baseline QRS duration. A Relationship between baseline QRS duration and changes in GLS at 7 and 30 days post-treatment. Values represent least-squares means (95% CIs) from linear regression models, adjusted for recruitment center (cluster variable), treatment-by-visit interaction, age, sex, and baseline GLS. The interaction between treatment effect and QRS duration was highly significant ($p < 0.001$). **B** Changes in GLS in subgroups defined by the presence (QRS ≥ 120 ms) or absence (QRS < 120 ms) of bundle branch block at baseline. Values are least-squares means from linear mixed-effects models with the same covariate adjustments as above. Individual points were added (97 observations from 51 patients; placebo: $n = 25$; FCM: $n = 26$). The interaction between treatment effect and baseline QRS category was also highly significant ($p < 0.001$). FCM ferric carboxymaltose, GLS global longitudinal strain, LV left ventricle.

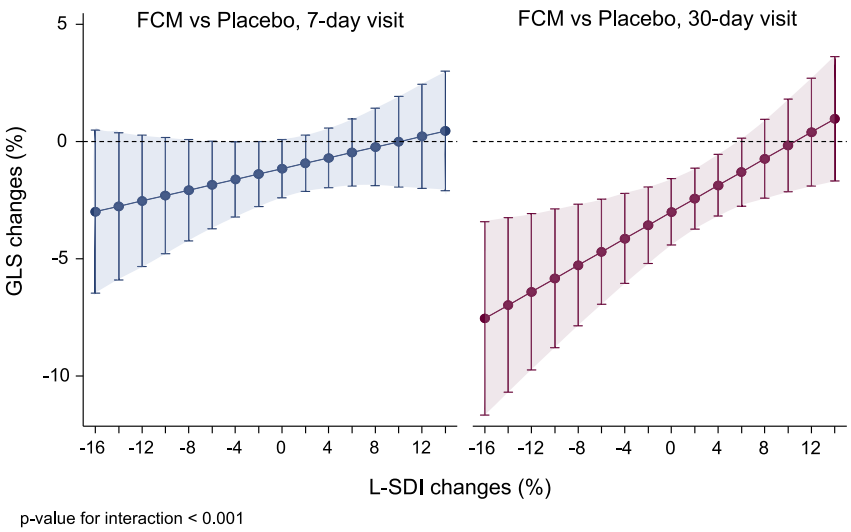

Fig. 4 | Association between changes in left ventricular (LV) global longitudinal strain (GLS) and changes in longitudinal systolic dyssynchrony index (L-SDI) at 7 and 30 days after ferric carboxymaltose (FCM) or placebo administration in the Myocardial-IRON trial. Values represent least-squares means (95% CIs) from linear regression models adjusted for recruitment center (cluster variable), treatment-by-visit interaction, age, sex, and baseline values of the dependent variable. A significant interaction between changes in GLS and L-SDI was observed ($p < 0.001$), indicating that greater reductions in dyssynchrony were associated with larger improvements in GLS. This analysis comprised 96 observations from 50 individuals (placebo: $n = 24$; FCM: $n = 26$). FCM ferric carboxymaltose, GLS global longitudinal strain, L-SDI longitudinal systolic dyssynchrony index, LV left ventricle.

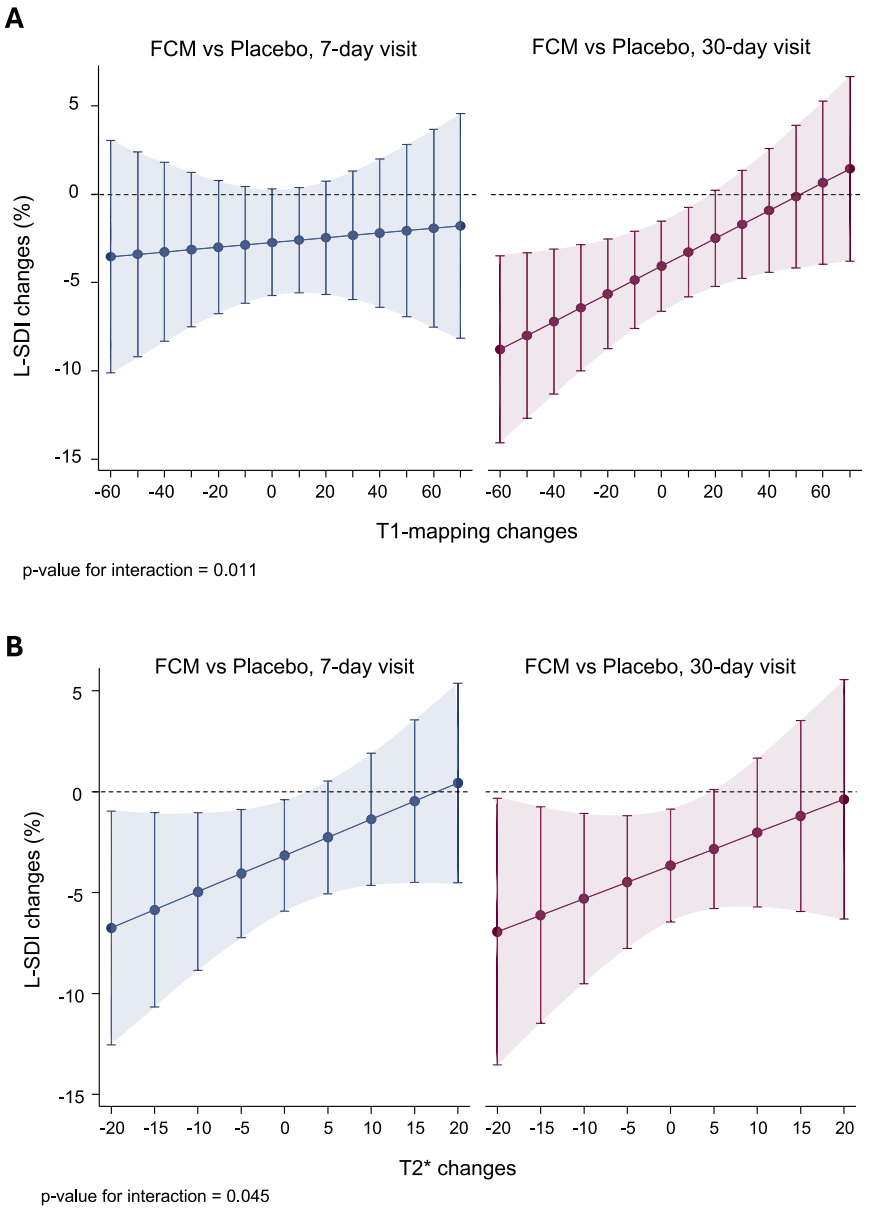

Fig. 5 | Association between changes in left ventricular (LV) longitudinal systolic dyssynchrony index (L-SDI) and changes in CMR proxies of myocardial iron repletion (T1-mapping and T2*) at 7 and 30 days after randomization to ferric carboxymaltose (FCM) or placebo. A Relationship between changes in L-SDI and changes in T1-mapping at 7 and 30 days post-treatment. Values represent least-squares means (95% CIs) from linear regression models adjusted for recruitment center (cluster variable), treatment-by-visit interaction, age, sex, and baseline values of the dependent variable. A significant interaction between changes in L-SDI and T1-mapping was observed ($p = 0.011$), indicating that greater reductions in T1-mapping were associated with larger improvements in dyssynchrony. **B** Relationship between changes in L-SDI and changes in T2* at 7 and 30 days post-treatment. Values represent least-squares means (95% CIs) from linear regression models adjusted for recruitment center (cluster variable), treatment-by-visit interaction, age, sex, and baseline values of the dependent variable. A significant interaction between changes in L-SDI and T2* was observed ($p = 0.045$), indicating that greater reductions in T2* were associated with larger improvements in dyssynchrony. This analysis comprised 96 observations from 50 individuals (placebo: $n = 24$; FCM: $n = 26$). FCM ferric carboxymaltose, L-SDI longitudinal systolic dyssynchrony index, LV left ventricle.

This study has several limitations. First, it represents a post hoc subgroup analysis, and the findings should be interpreted as hypothesis-generating. Confirmation through prospective, well-controlled studies is needed. Second, the results are limited to a selected population of patients with stable heart failure, LVEF < 50%, and iron deficiency as defined by current ESC guidelines. Third, the study was conducted in 2017, and optimal medical treatments have improved since then, so the treatment rates for ARNI and SGLT2i were low. Fourth, the current findings cannot assess the mid or long-term effects of FCM on dyssynchrony and LV systolic function. Fifth, the underlying biological mechanisms driving the observed improvements in dyssynchrony remain unexplored. Finally, we did not assess post-treatment changes in QRS duration, limiting electrophysiological interpretation.

In conclusion, in patients with HF, LVEF < 50%, and ID, intravenous FCM improved short-term LV mechanical synchrony and systolic function, with greater effects in those with baseline electrical dyssynchrony. These findings identify a potentially responsive subgroup and support further investigation into iron supplementation as a strategy to improve LV synchrony in HF.

Data availability

The source data underlying all main figures are provided as Supplementary Data 1.

Received: 4 September 2025; Accepted: 16 April 2026;
Published online: 14 May 2026

References

1. Rocha, B. M. L., Cunha, G. J. L. & Menezes Falcao, L. F. The burden of iron deficiency in heart failure: therapeutic approach. *J. Am. Coll. Cardiol.* **71**, 782–793 (2018).
2. Núñez, J. et al. Iron deficiency and risk of early readmission following a hospitalization for acute heart failure. *Eur. J. Heart Fail.* **18**, 798–802 (2016).
3. Ponikowski, P. et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart

Failure Association (HFA) of the ESC. *Eur. J. Heart Fail.* **18**, 891–975 (2016).
4. Anker, S. D. et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N. Engl. J. Med.* **361**, 2436–2448 (2009).
5. Ponikowski, P. et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur. Heart J.* **36**, 657–668 (2015).
6. Anker, S. D. et al. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. *Eur. J. Heart Fail.* **20**, 125–133 (2018).
7. Nuñez, J. et al. Non-invasive imaging estimation of myocardial iron repletion following administration of intravenous iron: the Myocardial-IRON trial. *J. Am. Heart Assoc.* **9**, e014254 (2020).
8. Del Canto, I. et al. Short-term changes in left and right ventricular cardiac magnetic resonance feature tracking strain following ferric carboxymaltose in patients with heart failure: a substudy of the Myocardial-Iron trial. *J. Am. Heart Assoc.* **1**, e022214 (2022).
9. Santas, E. et al. Improvement in left atrial strain following ferric carboxymaltose in heart failure: an analysis of the Myocardial-IRON trial. *ESC Heart Fail.* **11**, 1258–1262 (2024).
10. Gorcsan, J. et al. Association of persistent or worsened echocardiographic dyssynchrony with unfavourable clinical outcomes in heart failure patients with narrow QRS width: a subgroup analysis of the EchoCRT trial. *Eur. Heart J.* **37**, 49–59 (2016).
11. Biering-Sørensen, T. et al. Prognostic importance of left ventricular mechanical dyssynchrony in heart failure with preserved ejection fraction. *Eur. J. Heart Fail.* **19**, 1043–1052 (2017).
12. Bleeker, G. B., Bax, J. J., Steendijk, P., Schalij, M. J. & van der Wall, E. E. Left ventricular dyssynchrony in patients with heart failure: pathophysiology, diagnosis and treatment. *Nat. Clin. Pract. Cardiovasc. Med.* **3**, 213–219 (2006).
13. Martens, P. et al. The effect of intravenous ferric carboxymaltose on cardiac reverse remodelling following cardiac resynchronization therapy-the IRON-CRT trial. *Eur. Heart J.* **42**, 4905–4914 (2021).
14. Steinmetz, M. et al. Left ventricular synchrony, torsion, and recoil mechanics in Ebstein's anomaly: insights from cardiovascular magnetic resonance. *J. Cardiovasc. Magn. Reson.* **19**, 101 (2017).
15. Jackson, T. et al. The interaction of QRS duration with cardiac magnetic resonance derived scar and mechanical dyssynchrony in systolic heart failure: implications for cardiac resynchronization therapy. *Int. J. Cardiol. Heart Vasc.* **18**, 81–85 (2017).
16. Kowallick, J. T. et al. Quantitative assessment of left ventricular mechanical dyssynchrony using cine cardiovascular magnetic resonance imaging: Inter-study reproducibility. *JRSM Cardiovasc. Dis.* **6**, 2048004017710142 (2017).
17. Miñana, G. et al. Changes in myocardial iron content following administration of intravenous iron (Myocardial-IRON): study design. *Clin. Cardiol.* **41**, 729–735 (2018).
18. Cerqueira, M. D. et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* **105**, 539–542 (2002).
19. Shin, S. H. et al. Mechanical dyssynchrony after myocardial infarction in patients with left ventricular dysfunction, heart failure, or both. *Circulation* **121**, 1096–1103 (2010).
20. Doi, T., Nakata, T., Yuda, S. & Hashimoto, A. Synergistic prognostic implications of left ventricular mechanical dyssynchrony and impaired cardiac sympathetic nerve activity in heart failure patients with reduced left ventricular ejection fraction. *Eur. Heart J. Cardiovasc. Imaging* **19**, 74–83 (2018).
21. Zhang, Q. & Yu, C. M. Clinical implication of mechanical dyssynchrony in heart failure. *J Cardiovasc. Ultrasound* **20**, 117–123 (2012).
22. Mashali, M. A. et al. Mechanical Dyssynchrony of Isolated Left and Right Ventricular Human Myocardium in End-Stage Heart Failure. *Circ. Heart Fail.* **16**, e009871 (2023).
23. Glikson, M. et al. ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur. Heart J.* **42**, 3427–3520 (2021).
24. Gerra, L. et al. Cardiac resynchronization therapy (CRT) nonresponders in the contemporary era: a state-of-the-art review. *Heart Rhythm* **22**, 159–169 (2025).
25. Kirk, J. A. & Kass, D. A. Electromechanical dyssynchrony and resynchronization of the failing heart. *Circ. Res.* **113**, 765–776 (2013).
26. Chung, Y. J. et al. Iron-deficiency anemia reduces cardiac contraction by downregulating RyR2 channels and suppressing SERCA pump activity. *JCI Insight* **4**, e125618 (2019).
27. Yesil, E. et al. The effect of ferric carboxymaltose treatment on the Tp-e interval and the Tp-e/QT and Tp-e/QTc ratios in heart failure patients with iron deficiency. *Kardiologiia* **62**, 42–48 (2022).
28. Sabbah, H. N. Targeting the mitochondria in heart failure: a translational perspective. *JACC Basic Transl. Sci.* **5**, 88–106 (2020).
29. Angermann, C. E. et al. Empagliflozin effects on iron metabolism as a possible mechanism for improved clinical outcomes in non-diabetic patients with systolic heart failure. *Nat. Cardiovasc. Res.* **2**, 1032–1043 (2023).
30. Pouleur, A. C. et al. Relationship between improvement in left ventricular dyssynchrony and contractile function and clinical outcome with cardiac resynchronization therapy: the MADIT-CRT trial. *Eur. Heart J.* **32**, 1720–1729 (2011).
31. Papalia, F. et al. Cardiac energetics in patients with chronic heart failure and iron deficiency: an in-vivo ^{31} P magnetic resonance spectroscopy study. *Eur. J. Heart Fail.* **24**, 716–723 (2022).

Acknowledgements

This work was supported in part by an unrestricted grant from Vifor Pharma, CIBER Cardiovascular [grant numbers 16/11/00420 and 16/11/00403], Unidad de Investigación Clínica y Ensayos Clínicos INCLIVA Health Research Institute, Spanish Clinical Research Network (SCReN; PT13/0002/0031 and PT17/0017/0003), cofounded by Fondo Europeo de Desarrollo Regional-Instituto de Salud Carlos III, and Proyectos de Investigación de la Sección de Insuficiencia Cardiaca 2017 from Sociedad Española de Cardiología.

Author contributions

Conceptualization: J.N., C.G.S.G., P.M.; methodology: I.D.C., G.M., R.L., I.C., M.P.L.L., J.V.M., A.M.; formal analysis: J.N. and I.D.C.; data curation: J.N., I.D.C., G.M., I.C., M.P.L.L., J.V.M., A.M., V.B., J.S.; writing original draft preparation: all authors; writing review and editing: all authors; supervision: G.M., L.A., P.L., V.B., A.M., V.B., J.S., C.G.S.G., P.M. All authors have read and agreed to the published version of the manuscript.

Competing interests

J. Núñez received board speaker fees and travel expenses from Novartis, Roche Diagnostics, Abbott, Rovi, Vifor Pharma, Daiichi Sankyo, Novonordisk, Boehringer Ingelheim, and AstraZeneca (modest). Carlos Santos-Gallego is partially supported by American Heart Association (AHA 25TPA1481207) and by the Robert Winn Career Development Award; has received research funding from Merck and Lexicon (Investigator-Initiated Studies); and received speaker fees and travel expenses from Novo-Nordisk and Merck (modest). The remaining authors have no disclosures to report.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s43856-026-01619-1.

Correspondence and requests for materials should be addressed to Julio Núñez.

Peer review information *Communications Medicine* thanks Luca Monzo, Karl-Philipp Rommel and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. A peer review file is available.

On behalf of Myocardial-IRON Investigators

Julio Núñez[5], Enrique Santas[5], Gema Miñana[11], Patricia Palau[11], Jessika González[11], Ernesto Valero[11], Sergio García-Blas[11], Vicent Bodi[11], Rafael de la Espriella-Juan[11], Jorge Navarro[11], Juan Sanchis[11], Francisco J. Chorro[11], Meritxell Soler[11], Amparo Villaescusa[11], Jose Civera[11], Anna Mollar[11], Martina Amiguet[11], Pau Llácer[11], Maria del Carmen Moreno[12], Ingrid Cardells[13], Luis Almenar[5], Raquel López-Vilella[14], Alicia Serrano[15], Alicia Maceira[16], Maria Pilar López-Lereu[16], Jose Vicente Monmeneu[16], Lorenzo Fácila[17], Vicente Montagud[17], Veronica Vida[17], Antoni Bayés-Genís[18,19] & Josep Lupón[18,19]

[11]Department of Cardiology, Hospital Clínico Universitario de Valencia, Universitat de Valencia, INCLIVA, Valencia, Spain. [12]Department of Cardiology, Hospital General de Castellón, Universitat Jaume I, Castellón, Spain. [13]Department of Internal Medicine, Hospital Ramon y Cajal, Madrid, Spain. [14]Department of Internal Medicine, Hospital de Manises, Manises, Spain. [15]Department of Cardiology, Hospital de Manises, Manises, Spain. [16]Unidad de Imagen Cardiaca (Ascires), Valencia, Spain. [17]Department of Cardiology, Hospital General Universitario de Valencia, Valencia, Spain. [18]Cardiology Department and Heart Failure Unit, Hospital Universitari Germans Trias i Pujol, Badalona, Spain. [19]Universitat Autònoma de Barcelona, Barcelona, Spain.