

The effect of iron deficiency on cardiac resynchronization therapy: results from the RIDE-CRT Study

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Abstract

Aims Cardiac resynchronization therapy (CRT) improves functional status, induces reverse left ventricular remodelling, and reduces hospitalization and mortality in patients with symptomatic heart failure, left ventricular systolic dysfunction, and QRS prolongation. However, the impact of iron deficiency on CRT response remains largely unclear. The purpose of the study was to assess the effect of functional and absolute iron deficiency on reverse cardiac remodelling, clinical response, and outcome after CRT implantation.

Methods and results The relation of iron deficiency and cardiac resynchronization therapy response (RIDE-CRT) study is a prospective observational study. We enrolled 77 consecutive CRT recipients (mean age 71.3 ± 10.2 years) with short-term follow-up of 3.3 ± 1.9 months and long-term follow-up of 13.0 ± 3.2 months. Primary endpoints were reverse cardiac remodelling on echocardiography and clinical CRT response, assessed by change in New York Heart Association classification. Echocardiographic CRT response was defined as relative improvement of left ventricular ejection fraction ≥ 20% or left ventricular global longitudinal strain ≥ 20%. Secondary endpoints were hospitalization for heart failure and all-cause mortality (mean follow-up of 29.0 ± 8.4 months). At multivariate analysis, iron deficiency was identified as independent predictor of echocardiographic (hazard ratio 4.97; 95% confidence interval 1.15–21.51; *P* = 0.03) and clinical non-response to CRT (hazard ratio 4.79; 95% confidence interval 1.30–17.72, *P* = 0.02). We found a significant linear-by-linear association between CRT response and type of iron deficiency (*P* = 0.004 for left ventricular ejection fraction improvement, *P* = 0.02 for left ventricular global longitudinal strain improvement, and *P* = 0.003 for New York Heart Association response). Iron deficiency was also significantly associated with an increase in all-cause mortality (*P* = 0.045) but not with heart failure hospitalization.

Conclusions Iron deficiency is a negative predictor of effective CRT therapy as assessed by reverse cardiac remodelling and clinical response. Assessment of iron substitution might be a relevant treatment target to increase CRT response and outcome in chronic heart failure patients.

Keywords Iron deficiency; Cardiac resynchronization therapy; Heart failure

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Introduction

Cardiac resynchronization therapy (CRT) is a proven and well-established method for the management of

symptomatic heart failure (HF) in patients with reduced left ventricular (LV) systolic function and prolongation of the QRS interval.¹ Numerous large randomized multicenter trials have demonstrated that CRT alleviates electromechanical

dyssynchrony in patients with HF, thereby reducing LV size and mitral regurgitation, improving LV ejection fraction, quality of life, exercise capacity, and functional status [improvements of ≥ 1 New York Heart Association (NYHA) class].^{2–4} In addition, CRT is associated with a significant reduction in hospitalization for HF and all-cause mortality.^{5–7}

However, a variable proportion of system recipients, depending on the definition and criteria applied, do not benefit from CRT.^{8,9} The prevalence of clinical non-responders, defined as patients with no improvement in NYHA functional class, is nearly 30% while that of echocardiographic non-responders, identified by an increase in LV end-systolic volume $< 10\%$, is reported around 45%.¹⁰ However, non-response to CRT is multifactorial and includes pre-implant, peri-implant, and post-implant factors.¹¹ Possible reasons include inadequate selection of candidates, suboptimal lead position, irreversible end-stage disease, extensive scar burden, and inadequate device programming (atrioventricular delay and interventricular delay). Thus, non-response to CRT therapy remains the Achilles' heel of CRT therapy, associated with considerable financial and medical challenges.

Iron deficiency (ID) is known to be a frequent and important co-morbidity in patients with heart failure with reduced ejection fraction with a prevalence of up to 50%.¹² In addition, ID constitutes the most frequent cause of anaemia in these patients. However, even more important, ID occurs in around 45% of non-anaemic patients with systolic HF.¹³ ID can be either absolute, when total body iron is decreased, or functional, when iron content is normal or increased, but does not meet the needs of the target tissue due to maldistribution. ID, with or without concomitant anaemia, has been shown to worsen symptoms and impair exercise capacity and quality of life and increases mortality and hospitalization in patients with HF.^{14–17} Moreover, absolute ID was found to be associated with an increased risk of early readmission after an episode of acute HF.¹⁸

Beside its role in oxygen transport and storage, iron is a key component of diverse enzymes involved in cellular respiration, oxidative phosphorylation, citric acid cycle, and reactive oxygen species (ROS) scavenging enzymes.¹⁹ Numerous studies demonstrated that intravenous iron supplementation improves exercise capacity, functional status, and quality of life in iron deficient patients with chronic HF.^{20–23} However, data on impact of ID on response to CRT therapy are limited.^{24,25} Thus, the aim of the present study was to assess the impact of functional and absolute ID at CRT implantation on reverse cardiac remodelling, clinical response, and outcome of CRT.

Methods

Study design

The relation of iron deficiency and cardiac resynchronization therapy response (RIDE-CRT) study is a prospective observational trial evaluating the impact of functional and absolute ID with and without concomitant anaemia on echocardiographic and clinical CRT response. Primary endpoints were clinical response (defined as improvement in NYHA functional class ≥ 1) and reverse cardiac remodelling [defined as relative improvement of LV ejection fraction $\geq 20\%$ or relative increase of LV global longitudinal strain (LV GLS) $\geq 20\%$] on echocardiography. Secondary endpoints were all-cause mortality and hospitalization for HF. Hospitalization for HF was defined as admission primarily for its treatment. A patient admitted for this reason had to show signs and symptoms of worsening HF and require treatment with intravenous diuretics. Evidence of worsening of HF had to include at least one of the following points: increasing exertional dyspnoea, orthopnoea, pulmonary oedema, increasing peripheral oedema, deterioration in renal function, and radiological signs of acute decompensated HF.

The study protocol was approved by the human ethics committee of the Charité—Universitätsmedizin Berlin (ethic application number: EA2/107/13) and is in accordance with the Declaration of Helsinki. All patients provided written informed consent. The study was registered on German Clinical Trials Register (DRKS00015304).

Study population

Between November 2012 and January 2016, a total of 103 patients were prospectively enrolled in the RIDE-CRT study at our institution (Department of Internal Medicine and Cardiology, University Hospital). All patients received a CRT device in accordance with current guidelines.¹

Eligible subjects for implantation of a biventricular device with or without a defibrillator function were (i) patients who had chronic HF of NYHA Class II, III, or IV, an LV ejection fraction $\leq 35\%$, a prolonged QRS duration (≥ 120 ms), and adequate pharmacotherapy and (ii) pacemaker patients with a right ventricular (RV) pacing-induced cardiomyopathy (defined as $\geq 10\%$ decrease in LVEF, with resultant LVEF $< 50\%$).²⁶ Anaemia was defined according to the definitions of the World Health Organization with haemoglobin levels less than 13 g/dL in men and less than 12 g/dL in women.²⁷ ID was diagnosed as serum ferritin level less than 100 $\mu\text{g/L}$ (absolute ID), or serum ferritin level 100–299 $\mu\text{g/L}$ and transferrin saturation less than 20% (functional ID).^{18,28} Patients who received red blood cell transfusion or iron substitution during the follow-up period and patients with inadequate biventricular pacing were excluded from the analysis.

Patient evaluation and follow-up

Baseline characteristics included age, gender, body mass index, aetiology of HF, type of CRT (CRT-D or CRT-P), electrocardiogram (ECG) analysis, relevant co-morbidities, concomitant medication, and laboratory values. In addition, NYHA functional class, echocardiographic parameters [LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), LV end-systolic diameter, LV end-systolic volume index, LV end-diastolic volume index, LVEF, LV GLS, degree of mitral valve, and tricuspid valve regurgitation], and parameters of iron metabolism (haemoglobin, iron, ferritin, and transferrin saturation) were measured at baseline and at follow-up. Response to CRT was assessed at short-term (3.3 ± 1.9 months) and long-term (13.0 ± 3.2 months) follow-up, always with clinical evaluation and device testing. Follow-up for the secondary endpoint mortality was 29.0 ± 8.4 months.

Left ventricular assessment by echocardiography

Echocardiographic parameters were obtained according to a pre-specified protocol in a central echocardiography laboratory at our institution using a Vivid 7 or E9 (GE Healthcare) ultrasound system. Images were analysed offline with commercially available software (Echo-Pac) by European Association of Cardiovascular Imaging certified observers blinded to the clinical and functional outcome of the patients in the echocardiography core lab (Echo CoreLab, Charité Berlin). Conventional LV measurements were performed as recommended by the European Association of Cardiovascular Imaging.²⁹ LVESV and LVEDV as well as LVEF were analysed using the biplane Simpson's method. LV global longitudinal systolic strain was assessed by 2D speckle tracking, averaging the value of the longitudinal systolic strain peak from all segments of the LV in the apical 4-chamber, 2-chamber, and long-axis views in accordance with the recommendations for LV strain measurements of European Association of Cardiovascular Imaging.³⁰ Only patients with echocardiographic high image quality for LV GLS ($n = 77$) were included in the data analysis. All reported measurements were calculated as the average of three measurements and performed at conditions of respiratory and haemodynamic stability.

Cardiac resynchronization therapy device implantation

Cardiac resynchronization therapy (CRT) devices with or without defibrillator function from Biotronik, Medtronic, Boston Scientific, and St. Jude Medical (now Abbot) were used. Device implantations were carried out in a hybrid

catheter laboratory (room air class 1B) using a monoplane heart catheter system. All patients received an atrial lead, and the LV lead was implanted transvenously in all cases. RV pacing was performed either from the apex or from the mid-septum. The LV lead was placed in a posterolateral or lateral vein. A quadripolar LV lead was implanted in 53.2% of the patients from our study cohort. All CRT devices were programmed to biventricular pacing (no 'LV only' programming).

Definition of cardiac resynchronization therapy response

Echocardiographic CRT response was defined as relative improvement of the LVEF $\geq 20\%$ or LV GLS $\geq 20\%$.³¹ Patients with an LVEF $\geq 50\%$ were classified as super-responder.³² Clinical response was defined as improvement ≥ 1 NYHA functional class.

Statistical analysis

Quantitative measurements are presented as mean values with standard deviation. Ordinal and nominal values are shown as absolute and relative frequencies. Spearman's correlation coefficient was used for bivariate correlation analysis. Differences in metric values between independent binary groups were evaluated with Mann-Whitney *U* test, while for independent ternary groups, Kruskal-Wallis test was used. The Wilcoxon test was used to compare baseline values with follow-up values. Comparison between nominal values was performed with Pearson's chi-square test. Evaluation of linear trends of nominal with ordinal or both ordinal values was performed with Mantel-Haenszel linear-by-linear association. Adjustment for potential confounders and the identification of independent possible predictors for non-response to CRT were performed using binary logistic regression analyses. For this matter, parameters significantly associated with non-response in univariate analysis were taken into consideration, followed by forward and backward selection. Cox regression analysis was used to calculate unadjusted and adjusted hazard ratios. Kaplan-Meier survival analysis and log-rank test expressed the chronological sequence of occurring events (hospitalization and death) in a survival curve and disparity among different groups. Two-sided *P*-values ≤ 0.05 were considered significant, and no Bonferroni correction was performed due to the exploratory character of this study. SPSS Statistics Version 24 (IBM Corporation) was used for each statistical analysis.

Results

Baseline clinical and echocardiographic parameters

Between November 2012 and January 2016, a total of 103 patients were enrolled in the RIDE-CRT study. Echocardiography with high image quality for LV GLS analysis was available in only 77 patients (mean age 71.3 ± 10.2 , 68.8% male). The patients' baseline clinical characteristics are summarized in *Table 1*. Causes of HF were ischaemic cardiomyopathy (54.5%), idiopathic dilated cardiomyopathy (32.5%), RV pacing-induced cardiomyopathy (6.5%), valvular cardiomyopathy (5.2%), and hypertrophic cardiomyopathy (1.3%). In total, 42 patients (54.5%) received a de novo CRT implantation, whereas 35 patients (45.5%) were upgraded to CRT from a pacemaker or an implantable cardioverter defibrillator. Of note, 31.2% of the patients had a history of atrial fibrillation, and among these, 41.7% had paroxysmal and 58.3% persisting/permanent atrial fibrillation. The RV lead was placed in the RV apex in 44 (57.1%) patients, and at the RV septum in 33 (42.9%) patients. LV lead position was posterior/posterolateral mid-ventricular in 53 (68.8%), posterior/posterolateral basal in 16 (20.8%), lateral midventricular in 3 (3.9%), and lateral basal in 5 (6.5%) of the patients. Iron deficient and non-iron deficient patients had similar baseline characteristics with respect to age, gender, NYHA functional class, body mass index and prevalence of diabetes mellitus, and arterial hypertension. However, patients with ID were more likely to have coronary artery disease, chronic renal failure with a glomerular filtration rate < 60 mL/min* 1.73 m² and more often received loop diuretics and antiplatelet therapy, whereas the prevalence of dilated cardiomyopathy and use of aldosterone antagonist was more frequent in patients with no ID. Anaemia according to the definition of the World Health Organization was statistically more frequent in patients with ID than in those with normal iron metabolism. The patient baseline echocardiographic and ECG parameters are shown in *Table 2*. The mean value of LVEF at baseline was $24.0 \pm 9.7\%$ with an LVESV of 122.1 ± 44.8 mL, an LVEDV of 158.3 ± 52.7 mL, an LV end-systolic volume index of 64.2 ± 26.5 mL, and an LV GLS of $6.0 \pm 2.1\%$. No significant differences in the collected baseline echocardiographic and ECG parameters were observed between patients with normal iron metabolism compared with those with ID (*Table 2*).

Iron metabolism of the study population group

Serum parameters of iron metabolism in our study population at baseline are summarized in *Figure 1*. At enrolment,

43 patients (55.8%) were diagnosed with ID (31.2% with absolute ID and 24.7% with functional ID) and 34 patients (44.2%) with anaemia. Twenty-five anaemic patients (73.5% of the anaemic subset) were also iron deficient (functional ID in 11 anaemic patients and absolute ID in 14 anaemic patients) (*Figure 1A*). As depicted in *Figure 1B*, mean corpuscular volume ranged from 74 to 108 fL with a mean of 89.7 ± 6.4 fL. In the majority of anaemic patients, we found a normocytic anaemia ($n = 29$, 87.9% of the anaemic subset), whereas macrocytic anaemia was found in one (3.0%) and microcytic anaemia in three patients (9.1%). Haemoglobin level ranged from 7.8 to 16.5 g/dL with a mean of 12.5 ± 2.0 g/dL. Serum ferritin levels ranged from 21 to 962 mg/L with a mean of 162.3 ± 138.3 mg/L. Transferrin saturation ranged from 3.9% to 58.4% with a mean of $21.0 \pm 9.6\%$. Noteworthy, parameters of iron metabolism did not change in the course of the follow-up period (data not shown).

Response to cardiac resynchronization therapy

In our study cohort, echocardiographic CRT response with regard to LVEF improvement was observed in 64.9% of the overall study population, and improvement of LV GLS $\geq 20\%$ occurred in 67.5% of the patients. Clinical improvement according to a change in NYHA functional class occurred in 62.3% of the patients during the follow-up period (Supporting Information, *Figure S1*). Noteworthy, no significant differences in biventricular pacing rate were found in patients with ID compared with patients with no ID (97.8 ± 3.0 vs. 98.0 ± 3.0 , $P = 0.150$). Echocardiographic parameters and QRS duration at baseline and at follow-up (13.0 \pm 3.3 months) are depicted in Supporting Information, *Table S1*.

Predictors of non-response to cardiac resynchronization therapy

In univariate analysis, ID, right bundle branch block (RBBB), and an LVEF at baseline $\geq 25\%$ significantly correlated with echocardiographic CRT non-response (*Table 3*). Moreover, ID, RBBB, an LVEF at baseline $\geq 25\%$, and a higher LV GLS were significant predictors of a lack of improvement in NYHA functional class on univariate analysis. After multivariate analysis, including co-morbidities with a P -value < 0.05 and known predictors of CRT response, namely, male sex, coronary artery disease and a QRS width < 150 ms, ID, RBBB, and an LVEF $\geq 25\%$ at baseline were identified as independent predictors of an echocardiographic CRT non-response (*Table 3*). In addition, multivariate analysis demonstrated that ID and RBBB are significant predictors of non-improvement of NYHA functional class (*Table 3*). Furthermore, we separately analysed the impact of both absolute and functional ID on CRT response (*Table 3*). Univariate analysis showed that

Table 1 Baseline demographics and clinical characteristics of the study population

Baseline characteristics	Total population (n = 77)	No iron deficiency (n = 34)	Functional iron deficiency (n = 19)	Absolute iron deficiency (n = 24)	Iron deficiency (n = 43)	P ID vs. no ID
Age (years) ± SD	71.3 ± 10.2	68.6 ± 11.8	71.6 ± 10.1	74.8 ± 6.6	73.4 ± 8.4	0.078
Body mass index (kg/m ² ± SD)	28.5 ± 4.9	28.2 ± 4.8	29.4 ± 5.0	28.1 ± 5.1	28.7 ± 5.0	0.735
Male sex	53 (68.8%)	24 (70.6%)	11 (57.9%)	18 (75.0%)	29 (67.4%)	0.767
NYHA functional class						
I	0	0	0	0	0	—
II	14 (18.2%)	7 (20.6%)	5 (26.3%)	2 (8.3%)	7 (16.3%)	0.626
III	55 (71.4%)	25 (73.5%)	11 (57.9%)	19 (79.2%)	30 (69.8%)	0.717
IV	8 (10.4%)	2 (5.9%)	3 (15.8%)	3 (12.5%)	6 (14.0%)	—
Type of implanted device						
CRT-D	69 (89.6%)	31 (94.2%)	17 (89.5%)	21 (87.5%)	38 (88.4%)	0.689
CRT-P	8 (10.4%)	3 (8.8%)	2 (10.5%)	3 (12.5%)	5 (11.6%)	0.689
Co-morbidities						
Ischaemic cardiomyopathy	42 (54.5%)	13 (38.2%)	11 (57.9%)	18 (75.0%)	29 (67.4%)	0.011
Dilated cardiomyopathy	25 (32.5%)	17 (50.0%)	6 (31.6%)	2 (8.3%)	8 (18.6%)	0.003
Valvular cardiomyopathy	4 (5.2%)	1 (2.9%)	2 (10.5%)	1 (4.2%)	3 (7.0%)	—
Hypertrophic cardiomyopathy	1 (1.3%)	1 (2.9%)	0	0	0	—
Pacing-induced cardiomyopathy	5 (6.5%)	2 (5.9%)	0	3 (12.5%)	3 (7.0%)	—
Myocardial infarction within previous 3 months	4 (5.2%)	1 (2.9%)	1 (5.3%)	2 (8.3%)	3 (7.0%)	—
PCI within previous 3 months	7 (9.1%)	3 (8.8%)	2 (10.5%)	2 (8.3%)	4 (9.3%)	—
CABG within previous 3 months	0 (0.0%)	0	0	0	0	—
Atrial fibrillation	24 (31.2%)	9 (26.5%)	5 (26.3%)	10 (41.7%)	15 (34.9%)	0.429
Paroxysmal	10 (13.0%)	2 (5.9%)	3 (15.8%)	5 (20.8%)	8 (18.6%)	—
Persistent/permanent	14 (18.2%)	7 (20.6%)	2 (10.5%)	5 (20.8%)	7 (16.3%)	0.626
AV block						
I	17 (22.1%)	8 (23.5%)	5 (13.9%)	4 (16.7%)	9 (20.9%)	0.785
II	2 (2.6%)	2 (5.9%)	0	0	0	—
III	10 (13.0%)	5 (14.7%)	2 (10.5%)	3 (12.5%)	5 (11.6%)	0.690
AV node ablation						
Before CRT	1 (1.3%)	0	0	1 (4.2%)	1 (2.3%)	—
After CRT	0 (0.0%)	0	0	0	0	—
Anaemia	34 (44.2%)	9 (26.5%)	11 (57.9%)	14 (58.3%)	25 (58.1%)	0.006
Diabetes mellitus type 1 and 2	27 (35.1%)	8 (23.5%)	9 (47.4%)	10 (41.7%)	19 (44.2%)	0.059
Arterial hypertension	59 (76.6%)	25 (73.5%)	14 (73.7%)	20 (83.3%)	34 (79.1%)	0.568
Hyperlipoproteinemia	47 (61.0%)	18 (52.9%)	13 (68.4%)	16 (66.7%)	29 (67.4%)	0.195
Chronic renal failure (GFR < 60 mL/min)	44 (57.1%)	13 (38.2%)	14 (73.7%)	17 (70.8%)	31 (72.1%)	0.003
Chronic obstructive pulmonary disease	15 (19.5%)	5 (14.7%)	3 (15.8%)	7 (29.2%)	10 (23.3%)	0.347
Stroke/TIA	11 (14.3%)	4 (11.8%)	2 (10.5%)	5 (20.8%)	7 (16.3%)	—
Laboratory values						
Haemoglobin (g/dL ± SD)	12.5 ± 2.0	13.1 ± 2.0	12.1 ± 1.7	12.1 ± 2.2	12.1 ± 2.0	0.031
Creatinine (mg/dL ± SD)	1.4 ± 0.5	1.3 ± 0.6	1.5 ± 0.6	1.4 ± 0.4	1.5 ± 0.5	0.024
Glomerular filtration rate (mL/min*1.73m ² ± SD)	54.6 ± 20.5	62.6 ± 21.8	46.9 ± 19.2	49.5 ± 15.5	48.3 ± 17.1	0.002
Medication						
ACE inhibitor or ARB	68 (88.3%)	30 (88.2%)	17 (89.5%)	21 (87.5%)	38 (88.4%)	0.985
Beta-blocker	72 (93.5%)	32 (94.1%)	19 (100.0%)	21 (87.5%)	40 (93.0%)	0.847
Amiodarone	18 (23.4%)	7 (20.6%)	4 (21.0%)	7 (29.2%)	11 (25.6%)	0.607
Digitalis glycoside	8 (10.4%)	3 (8.8%)	2 (10.5%)	3 (12.5%)	5 (11.6%)	—
Loop diuretics	69 (89.6%)	26 (76.5%)	19 (100.0%)	24 (100.0%)	43 (100.0%)	0.001
Aldosterone antagonist	47 (61.0%)	26 (76.5%)	9 (47.4%)	12 (50.0%)	21 (48.8%)	0.014
Anticoagulant therapy	32 (41.6%)	12 (35.3%)	9 (47.4%)	11 (45.8%)	20 (46.5%)	0.321
Antiplatelet therapy	45 (58.4%)	15 (44.1%)	11 (57.9%)	19 (79.2%)	30 (69.8%)	0.023
Lipid lowering therapy	54 (70.1%)	21 (61.8%)	15 (79.0%)	18 (75.0%)	33 (76.7%)	0.154

ABG, coronary artery bypass grafting; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; AV, atrioventricular; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SD, standard deviation. Data are presented as mean ± SD or as n (%).

absolute ID, RBBB, an LVEF at baseline ≥ 25%, and a higher LV GLS were associated with echocardiographic CRT non-response and no improvement of NYHA functional class.

After multivariate analysis, absolute ID, RBBB, and an LVEF-25% remained independent predictors of an echocardiographic CRT non-response, whereas only absolute ID and

Table 2 Baseline electrocardiographic and echocardiographic parameters

Electrocardiographic and echocardiographic parameters at baseline	Total population (n = 77)	No ID (n = 34)	Functional ID (n = 19)	Absolute ID (n = 24)	ID (n = 43)	P (ID vs. no ID)
ECG						
Heart rate (b.p.m. ± SD)	72.5 ± 18.3	72.9 ± 16.7	73.7 ± 23.3	71.1 ± 16.5	72.2 ± 19.6	0.361
PQ interval (ms ± SD)	193.8 ± 64.0	202.43 ± 76.3	185.6 ± 52.8	189.7 ± 57.0	187.8 ± 54.3	0.809
QRS duration (ms ± SD)	162.2 ± 24.4	165.7 ± 20.3	155.2 ± 25.5	162.7 ± 28.6	159.4 ± 27.2	0.088
Left bundle branch block	31 (40.3%)	14 (41.2%)	9 (47.4%)	8 (33.3%)	17 (39.5%)	0.884
Left anterior hemi-block	13 (16.9%)	6 (17.7%)	4 (21.1%)	3 (12.5%)	7 (16.3%)	0.874
Right bundle branch block	10 (13.0%)	4 (11.8%)	4 (21.1%)	2 (8.3%)	6 (14.0%)	—
Intraventricular conduction defect	9 (11.7%)	3 (8.8%)	2 (10.5%)	4 (16.7%)	6 (14.0%)	—
Right ventricular pacing	5 (6.5%)	2 (5.9%)	0	3 (12.5%)	3 (7.0%)	—
Echocardiography						
LVEDV (mL)	158.3 ± 52.7	164.3 ± 52.8	156.7 ± 51.9	151.1 ± 54.5	153.6 ± 52.8	0.397
LVEDVi (mL/m ²)	82.9 ± 31.4	88.2 ± 36.6	80.2 ± 25.2	77.7 ± 27.9	78.8 ± 26.4	0.361
LVESV (mL)	122.1 ± 44.8	126.0 ± 43.9	124.5 ± 43.2	114.8 ± 48.1	119.1 ± 45.7	0.518
LVESVi (mL/m ²)	64.2 ± 26.5	67.9 ± 30.0	63.7 ± 20.5	59.3 ± 25.6	61.2 ± 23.3	0.515
LVEF (%)	24.0 ± 9.7	23.4 ± 8.9	23.2 ± 8.4	25.3 ± 11.7	24.4 ± 10.3	0.711
LV GLS (%)	6.0 ± 2.1	5.7 ± 1.9	6.2 ± 1.8	6.4 ± 2.6	6.3 ± 2.3	0.204
MR grade						
I	40 (52.0%)	18 (53.0%)	12 (63.2%)	10 (41.7%)	22 (51.2%)	0.877
II	9 (11.7%)	4 (9.3%)	1 (5.3%)	4 (16.7%)	5 (11.6%)	—
III	0	0	0	0	0	—
TR grade						
I	39 (50.6%)	20 (58.8%)	9 (47.4%)	10 (41.7%)	19 (44.2%)	0.186
II	14 (18.2%)	5 (14.7%)	4 (21.1%)	5 (20.8%)	9 (20.9%)	0.489
III	7 (9.1%)	2 (5.9%)	0	5 (20.8%)	5 (11.6%)	—

b.p.m., beats per minute; ID, iron deficiency; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESVi, left ventricular end-systolic volume index; LV GLS, left ventricular global longitudinal strain; MR, mitral regurgitation; SD, standard deviation; TR, tricuspid regurgitation. Data are presented as mean ± SD or as n (%).

RBBB were independent predictors of non-improvement of NYHA functional class. In contrast, chronic renal failure (glomerular filtration rate < 60 mL/min) was no independent predictor of echocardiographic or clinical CRT response. LV lead positions in our study population had also no effect on reverse cardiac remodelling and clinical CRT response (data not shown).

Secondary endpoints

The secondary outcome, death from any cause during a mean follow-up of 29.0 ± 8.4 months, occurred in 12 patients (15.6% of the study population) in the iron deficient group died, as compared with three patients (3.9%) in the group without ID ($P = 0.045$, Supporting Information, *Figure S2A*). Analysis of functional and absolute ID as subgroups revealed a significant increase in all-cause mortality in patients with absolute ID ($P = 0.022$) but not in patients with functional ID (Supporting Information, *Figure S2B*). Overall, 25 patients (32.5% of the study population) were hospitalized for worsening of HF at least once during the follow-up period (72.0% with ID vs. 28.0% without ID). In contrast to all-cause mortality, the hospitalization rate for worsening of HF was not significantly different between patients with ID (functional and/or absolute) and normal iron status (Supporting Information, *Figures S2C and S2D*). The results

of the univariate analysis and multivariate analysis are depicted in Supporting Information, *Table S2*. Supporting Information, *Figure S3* illustrates the cumulative all-cause mortality of patients with ID and no ID (Supporting Information, *Figure S3A*) and no ID vs. functional and absolute ID (Supporting Information, *Figure S3B*). The cumulative freedom from HF admission with regard to the iron status is shown in Supporting Information, *Figures S3C and S3D*.

Short-term and long-term cardiac remodelling

Cardiac reverse remodelling at short-term follow-up (3.3 ± 1.9 months) and long-term follow-up (13.0 ± 3.2 months) after CRT implantation is depicted in *Figure 2*. Relative LVEF and LV GLS improvement at short-term follow-up was similar in patients with and without ID. However, cardiac reverse remodelling in the period between short-term follow-up and long-term follow-up was more pronounced in patients with no ID compared with patients with absolute ID. Corresponding differences in LV GLS improvement were statistically significant ($P = 0.026$), whereas statistical significance was narrowly missed with regard to differences in LVEF improvement ($P = 0.054$).

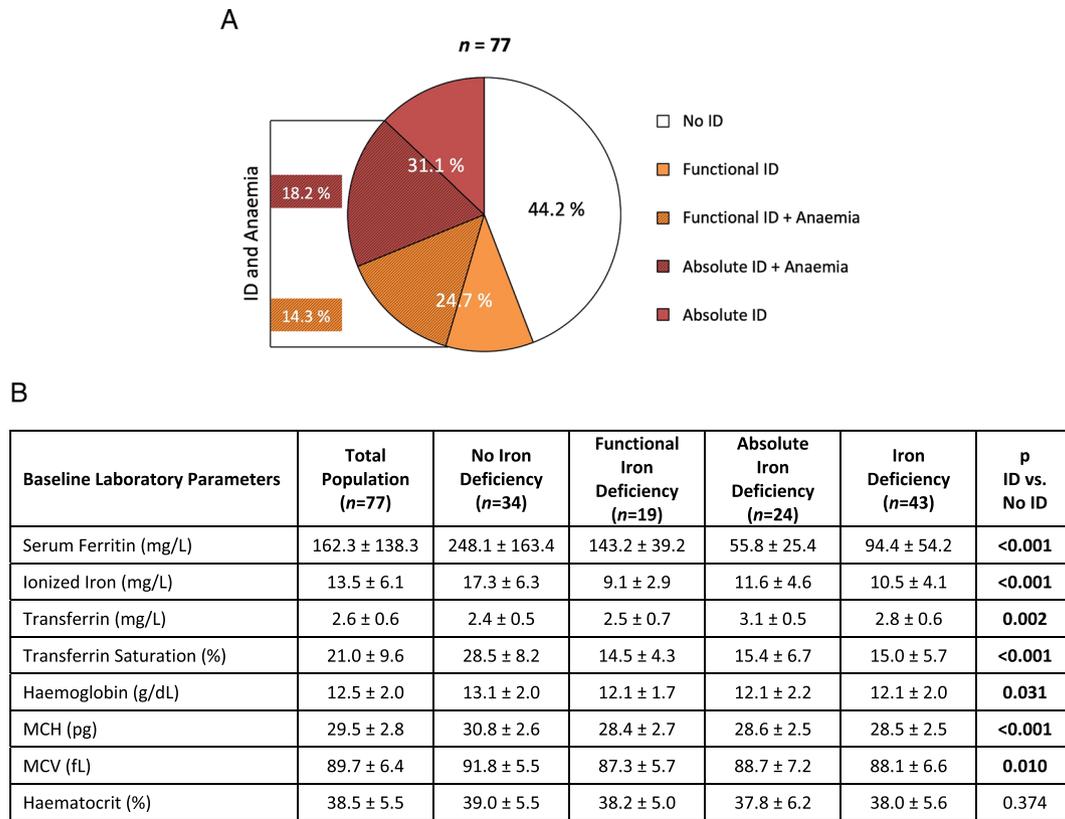


Figure 1 Iron metabolism of the study population group. (A) Percentage distribution of patients with no iron deficiency, functional iron deficiency, and absolute iron deficiency. Absolute iron deficiency is defined as serum ferritin < 100 µg/L and functional iron deficiency as ferritin 100–300 µg/L, if transferrin saturation is <20%. (B) Serum parameters of iron metabolism. ID, iron deficiency; MCH, mean corpuscular haemoglobin; MCV, mean corpuscular volume.

Type of iron deficiency and cardiac resynchronization therapy response

Echocardiographic CRT response depending on iron status is shown in Supporting Information, *Figure S4*. Allocating patients with ID according to the type of ID, linear-by-linear association test showed a significant linear-by-linear association between the type of ID and response to CRT. Thus, a linear-by-linear association was found between the type of ID and CRT response according to LVEF improvement ($P = 0.004$) and CRT response according to LV GLS improvement ($P = 0.02$). In addition, linear-by-linear analysis also revealed a strong association between clinical CRT response and type of ID ($P = 0.003$). The strength of the relationship (measured by Kendall's-tau τ values) was 0.35 for NYHA response, 0.34 for LVEF response, and 0.27 for LV GLS response.

'Super-responder' to cardiac resynchronization therapy

In this study, we defined super-response to CRT as LVEF-50% at follow-up. Using this definition, super-response was

observed in total in 10 patients (13.0%). In the super-responder group, five patients (50%) had a normal iron status, four patients (40%) had a functional, and one patient (10%) had an absolute ID. However, due to the low number of super-responders, a statistical analysis with regard to predictors of CRT super-response is not useful.

Adverse cardiovascular events during patient follow-up

During the follow-up period of 13.0 ± 3.3 months, a total of 27 serious adverse events occurred (*Table 4*). These events were documented in 29.4% of the patients with normal serum parameters of iron metabolism, in 31.6% of the patients with functional ID and in 45.8% of the patients with absolute ID (no statistically significant difference). A total of 22 cardiovascular events, defined as HF hospitalization, and atrial or ventricular arrhythmias leading to hospitalization, occurred in seven patients (20.6%) with no ID, in six patients (31.6%) with functional ID, and in 11 patients (45.8%) with absolute ID. A total of five serious adverse events related to the device or implantation occurred. Atrial lead dislodgement occurred

Table 3 Clinical Predictors of Non-Response to Cardiac Resynchronization Therapy (A) Univariate and multivariate determinants of CRT non-response comparing patients with iron deficiency with patients without iron deficiency. (B) Univariate and multivariate determinants of CRT non-response comparing patients with functional iron deficiency and absolute iron deficiency with patients without iron deficiency

A				
Variable	Univariate analysis	Binomial logistic regression analysis		
	P-value	OR	95% CI	P-value
Relative change of LVEF < 20%				
Iron deficiency	0.018	6.16	1.23–30.72	0.027
RBBB	0.013	7.91	1.13–55.11	0.037
LVEF ≥ 25% at baseline	<0.001	8.92	1.65–48.33	0.011
LV GLS at baseline	<0.001	1.41	0.93–2.14	0.103
Male sex	0.078	3.79	0.77–18.77	0.103
ICM	0.116	1.79	0.41–7.75	0.436
QRS < 150 ms	0.114	0.86	0.19–3.81	0.843
Anaemia	0.970	0.91	0.22–3.81	0.900
Antiplatelet therapy	0.554	0.45	0.10–2.05	0.304
Relative change of LV Strain < 20%				
Iron deficiency	0.014	4.55	0.94–21.96	0.041
RBBB	<0.001	41.98	3.67–480.47	0.003
LVEF ≥ 25% at baseline	<0.001	9.39	1.41–62.66	0.021
LV GLS at baseline	0.003	1.33	0.88–2.02	0.173
Male sex	0.142	2.72	0.54–13.72	0.227
ICM	0.248	0.73	0.16–3.22	0.675
QRS < 150 ms	0.013	2.35	0.55–10.01	0.250
Anaemia	0.99	1.05	0.23–4.76	0.952
Antiplatelet therapy	0.09	2.23	0.49–10.13	0.301
No change of NYHA class				
Iron deficiency	0.006	5.17	1.31–20.46	0.019
RBBB	0.024	6.05	1.09–33.56	0.039
LVEF ≥ 25% at baseline	0.023	2.65	0.70–10.01	0.152
LV GLS at baseline	0.007	1.33	0.95–1.86	0.102
Male sex	0.984	0.72	0.20–2.59	0.615
ICM	0.133	1.85	0.54–6.31	0.102
QRS < 150 ms	0.230	0.66	0.19–2.32	0.512
Anaemia	0.703	0.65	0.19–2.16	0.478
Antiplatelet therapy	0.145	1.27	0.36–4.46	0.709
B				
Variable	Univariate analysis	Binomial logistic regression		
	P-value	OR	95% CI	P-value
Relative change of LVEF < 20%				
Functional ID	0.372	2.07	0.28–15.33	0.477
Absolute ID	0.003	14.48	2.03–103.59	0.008
RBBB	0.013	11.48	1.51–87.50	0.018
LVEF ≥ 25% at baseline	<0.001	9.76	1.68–56.62	0.011
LV GLS at baseline	<0.001	1.47	0.91–2.35	0.112
Male sex	0.078	3.15	0.62–16.06	0.167
ICM	0.116	1.85	0.38–9.02	0.448
QRS < 150 ms	0.114	1.18	0.23–6.22	0.843
Anaemia	0.970	1.05	0.23–4.87	0.955
Antiplatelet therapy	0.554	0.37	0.07–1.97	0.245
Relative change of LV strain < 20%				
Functional ID	0.053	3.43	0.47–25.01	0.225
Absolute ID	0.020	5.21	0.97–27.95	0.043
RBBB	<0.001	44.91	3.88–519.37	0.002
LVEF ≥ 25% at baseline	<0.001	9.34	1.40–62.32	0.021
LV GLS at baseline	0.003	1.33	0.88–2.02	0.179
Male sex	0.142	2.53	0.49–12.97	0.267
ICM	0.248	0.72	0.16–3.22	0.666
QRS < 150 ms	0.013	2.55	0.57–11.46	0.221
Anaemia	0.985	1.10	0.24–5.10	0.900
Antiplatelet therapy	0.094	2.24	0.49–10.29	0.300
No change of NYHA class				
Functional ID	0.095	3.12	0.62–15.79	0.170
Absolute ID	0.003	7.46	1.62–34.48	0.010

(Continues)

Table 3 (continued)

Variable	Univariate analysis		Binomial logistic regression		
	P-value	OR	95% CI	P-value	
RBBB	0.024	7.23	1.25–41.71	0.027	
LVEF \geq 25% at baseline	0.023	2.49	0.65–9.56	0.185	
LV GLS at baseline	0.007	1.31	0.92–1.87	0.133	
Male sex	0.984	0.66	0.18–2.44	0.530	
ICM	0.133	1.68	0.45–6.24	0.439	
QRS $<$ 150 ms	0.230	0.76	0.21–2.77	0.677	
Anaemia	0.703	0.66	0.19–2.24	0.504	
Antiplatelet therapy	0.145	1.18	0.32–4.32	0.806	

CI, confidence interval; ICM, ischaemic cardiomyopathy; LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; OR, odds ratio; RBBB, right bundle branch block.

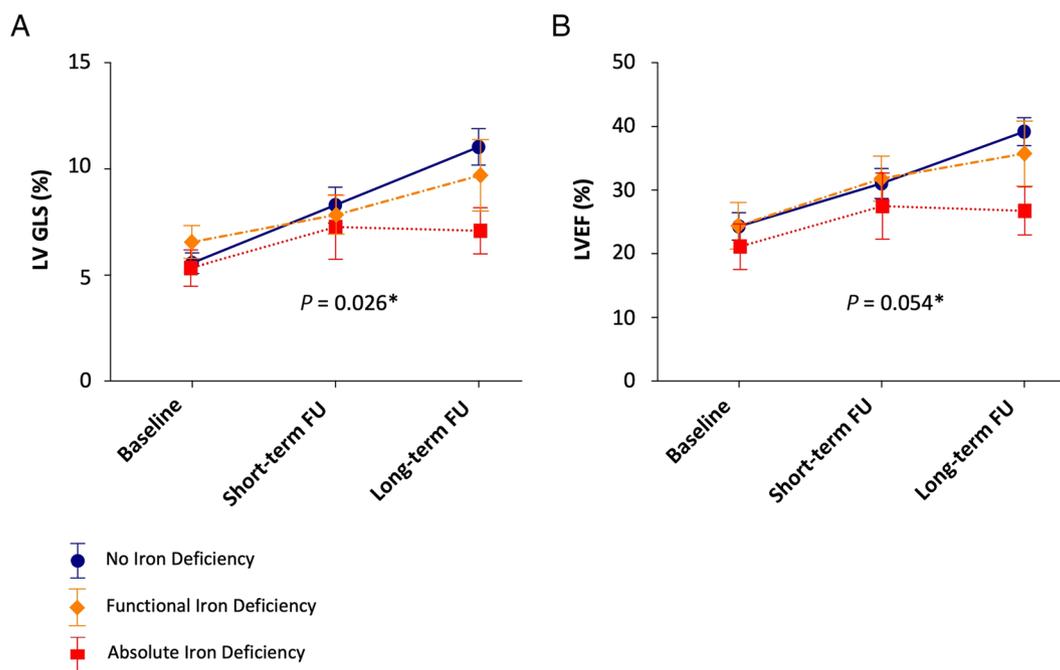


Figure 2 Time course of cardiac reverse remodelling. (A) Improvement in global left ventricular strain including baseline, short-term follow-up (3.3 ± 1.9 months) and long-term follow-up (13.0 ± 3.2 months) analysis. (B) Improvement in left ventricular ejection fraction including baseline, short-term follow-up (3.3 ± 1.9 months) and long-term follow-up (13.0 ± 3.2 months) analysis. FU, follow-up; LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain. The *P*-values are from comparison between no iron deficiency and absolute iron deficiency at long-term follow-up.

in total in two patients. Device pocket haematoma were observed in three patients and required clearing out the haematoma in one case.

Discussion

The main findings of this study are that (i) ID is a predictor of echocardiographic CRT non-response, (ii) ID is a predictor of

lack of improvement in NYHA functional class, and (iii) ID is associated with a significant increase in all-cause mortality in CRT patients.

Iron deficiency (ID) is known to be an important co-morbidity and strong and independent predictor of outcome in heart failure with reduced ejection fraction, with a prevalence ranging from 16% to 57% depending on the study population and criteria used.^{12,33} The high prevalence of ID in our study cohort (55.8%) is comparable with previously published studies.¹² According to previous studies, our

Table 4 Serious adverse events

	No ID (n = 34)	Functional ID (n = 19)	Absolute ID (n = 24)	P-value functional ID vs. no ID	P-value absolute ID vs. no ID
All events	10 (29.4%)	6 (31.6%)	11 (45.8%)	0.971	0.236
Cardiovascular events					
Heart failure hospitalization	5 (50.0%)	5 (83.3%)	8 (72.7%)	0.300	0.094
Atrial arrhythmia	0	1 (16.7%)	0	0.177	—
Ventricular arrhythmia	2 (20.0%)	0	1 (9.1%)	0.281	0.771
CRT system related					
ICD lead	0	0	0	—	—
LV lead	0	0	0	—	—
Atrial lead	1 (10.0%)	0	1 (9.1%)	0.450	0.801
Implantation related					
Haematoma	2 (20.0%)	0	1 (9.1%)	0.281	0.771
Pocket infection	0	0	0	—	—
Pneumothorax	0	0	0	—	—

CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; ID, iron deficiency; LV, left ventricular. Adverse events after CRT implantation during a follow-up of 13.0 ± 3.3 months. Data are presented as *n* (%).

data show that ID is often present even in the absence of anaemia.³⁴

CRT is a proven and well-established method that reduces morbidity and mortality in patients with symptomatic HF, reduced LVEF, and broadened QRS complex. However, up to one third of the CRT recipients do not benefit from biventricular stimulation, although the proportions of non-responder vary depending on the definitions and criteria applied.^{9,11} However, it must be considered that certain patients would deteriorate further in the absence of CRT.³⁵ Remarkably, despite 20 years of CRT, a consensus definition of response and non-response to CRT has not been reached. In our study population, CRT response included evaluation of reverse cardiac remodelling by echocardiography, change in NYHA functional class, and clinical outcome. At multivariate analysis, ID, RBBB, and an LVEF $\geq 25\%$ were identified as independent predictors of echocardiographic non-response to CRT. In addition, ID appeared as independent predictor of non-improvement of NYHA functional class. This is important, as from a patient perspective, clinical improvement (NYHA functional class) is of higher relevance than echocardiographic improvement. Importantly, previous studies have shown that clinical response does not necessarily correlate with reverse cardiac remodelling.³⁶ However, in our study population, the majority of echocardiographic CRT responders (82.0% and 82.7% in terms of LVEF and LV GLS improvement, respectively) also exhibited an improvement in NYHA functional class. Although functional ID was not an independent predictor of an echocardiographic CRT non-response at multivariate logistic regression analysis, linear-by-linear association revealed a strong association between type of ID (functional and absolute ID) and response to CRT. Our study demonstrates that ID was related to an increased all-cause mortality (3.82 times higher in patients with ID compared with patients without ID). However, in contrast to a previous study by Martens *et al.*²⁴ we did not observe a significant difference in HF hospitalization associated with ID.

Martens *et al.*²⁴ and Bojarczuk *et al.*²⁵ retrospectively evaluated CRT response only at 6 months of follow-up. In contrast, we examined cardiac reverse remodelling at short-term follow-up (3.3 ± 1.9 months) and at long-term follow-up (13.0 ± 3.2 months) after CRT implantation. Interestingly, ID mainly affected the long-term cardiac reverse remodelling, indicating an impact on factors other than restoring ventricular synchrony. The current concept of CRT is that it exerts its beneficial effects by improving ventricular synchrony. In addition, recent studies suggest that improving LV filling by shortening atrioventricular delay is an important mechanism through which CRT improves cardiac function.³⁷ However, previous studies suggest that CRT also potently alters cellular energy metabolism in the mitochondria by specifically altering proteins that control the redox state and oxidative phosphorylation pathways within the mitochondria.^{38,39}

Data on a possible link between iron status and favourable cardiac reverse remodelling after CRT implantation are limited.^{24,25} Following reasons for reduced reverse remodelling and clinical response in iron deficient CRT recipients in our study population are conceivable. First, ID might reflect a more advanced disease state with reduced ability to reverse remodelling. Second, ID itself might be responsible for the impaired reverse remodelling and clinical response to CRT. Our data do not prove a pathophysiological link of ID to CRT non-response. However, we believe that the pathophysiological reason observed might be the role of iron as obligate component of diverse enzymes involved in cellular respiration, oxidative phosphorylation, citric acid cycle, and ROS production.¹⁹ Thus, especially metabolic active cells such as cardiomyocytes depend on iron for their function.⁴⁰ Previously published animal data show that ID by itself impairs oxidative metabolism and cellular energetics that result in mitochondrial and LV dysfunction.⁴¹ In addition, Melenovsky *et al.*⁴² found in patient samples that reduced LV iron correlated with a lower activity of citric acid cycle enzymes, a reduced expression of ROS scavenging enzymes, and reduced

mitochondrial oxygen consumption. Thus, myocardial ID in patients with HF may promote glucose rather than fatty acid utilization and may, in concert with impaired protection against ROS, contribute to diminished remodelling and clinical response to CRT.

Several randomized controlled trials reported an effect of intravenous iron administration on exercise capacity, NYHA class, and quality of life in patients with HF.^{20–22} In addition, a recent meta-analysis by Anker *et al.*⁴³ found that intravenous iron supplementation is associated with lower rates of mortality and cardiovascular hospitalizations. Thus, it is tempting to speculate that an intravenous iron replacement therapy could reduce the rate of CRT non-responders.

Study limitations

The present study has several limitations. First, the study is a prospective observational study in a single centre with a relatively small number of patients. Thus, the incidence of HF hospitalization and death from any cause was low, which limits to analyse the secondary endpoints. Second, while our findings indicate that ID is a predictor of echocardiographic and clinical CRT non-response, we did not analyse whether iron supplementation improves CRT response in non-responder. Third, our study reports associations and correlations and does not prove a pathophysiological link of ID to CRT non-response.

Conclusions

Our results show that the presence of ID predicts the lack of therapeutic efficacy of CRT therapy in both clinical terms (lack of NYHA improvement) and functional terms (lack of echocardiographic remodelling). We suggest that screening for ID at the time of CRT implantation is a relevant diagnostic step prior to CRT implantation. Further studies are necessary to evaluate whether iron supplementation improves CRT response in patients with ID.

Acknowledgement

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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.

Figure S1. Response to cardiac resynchronization therapy. CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; NYHA, New York Heart Association.

Figure S2. Outcome analysis. (A) All-cause mortality of patients with no iron deficiency vs. patients with iron deficiency. (B) All-cause mortality of patients without iron deficiency in comparison with patients with functional and absolute iron deficiency. (C) Hospitalization due to worsening of heart failure comparing patients without iron deficiency and with iron deficiency. (D) Hospitalization due to worsening of heart failure in patients without iron deficiency, functional iron deficiency and absolute iron deficiency patients. ID, iron deficiency. HR, hazard ratio; ID, iron deficiency.

Figure S3. Kaplan-Meier curve for cumulative survival and hospitalization. (A) Kaplan-Meier curves for death from any cause in patients with iron deficiency compared to patients with no iron deficiency and (B) patients with iron deficiency compared to patients with functional or absolute iron deficiency. (C) Kaplan-Meier curves for hospitalization due to worsening of heart failure in patients with iron deficiency compared to patients with no iron deficiency and (D) patients with iron deficiency compared to patients with functional or absolute iron deficiency. ID, iron deficiency. The *p* values are from comparison between no iron deficiency and iron deficiency / absolute iron deficiency.

Figure S4. Response to cardiac resynchronization therapy depending on the iron status. ID, iron deficiency.

Table S1. Echocardiographic parameters at baseline and at follow-up. Data are presented as mean \pm SD or as n (%). LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LVESV, left ventricular end-systolic volume; LVESVi, left ventricular end-systolic volume index; LV GLS, left ventricular global longitudinal strain; MR, mitral regurgitation; TR, tricuspid regurgitation.

Table S2. Univariate and multivariate analysis for all-cause mortality and hospitalization due to worsening of heart failure. CI, confidence interval; HR, hazard ratio; ID, iron deficiency.

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