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# Impact of iron replacement therapy on six minutes walking test (functional state) in patients with heart failure with reduced ejection fraction and iron deficiency

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## Abstract

**Background and objective:** Iron deficiency may impair aerobic performance. This study aimed to assess whether intravenous iron (ferric carboxymaltose) will improve symptoms in patients with heart failure with reduced left ventricular ejection fraction and iron deficiency or not, depending on serum ferritin or transferrin saturation with or without anemia.

**Methods:** We enrolled 100 patients with heart failure with reduced ejection fraction (less than 40%) and iron deficiency (serum ferritin less than 100 ng/ml, or between 100-299 ng/ml but transferrin saturation less than 20%). The patient received an intravenous iron supplement of ferric carboxymaltose (1000-2500mg) until the correction of their iron status. We checked the 6-minute walking test, New York Heart Association functional class, and ejection fraction for each patient at baseline, 12 weeks, and 24 weeks after intervention.

**Results:** Our study showed a significant improvement in the patient's functional status. The 6-minute walking test, New York Heart Association functional class, improved significantly in patients at 12 weeks and continues to improve beyond 24 weeks with or without anemia. The left ventricular ejection fraction in our study was not improved significantly.

**Conclusion:** Treatment with intravenous iron supplement (ferric carboxymaltose) in patients with chronic stable heart failure and iron deficiency, with or without anemia, improves symptoms, functional capacity, and quality of life.

**Keywords**: Iron replacement therapy; Six minute walking test; Heart failure; Ejection fraction; Iron deficiency.

## Introduction

One-third of the world's population suffers from iron deficiency, one of the world's most common nutritional deficiencies.[1] Heart failure has become an epidemic issue with significant medical, social, and financial implications as the prevalence and magnitude of the disease continue to expand.[2]

Recent advances in treating chronic heart failure in patients with a reduced left ventricular ejection fraction have altered the condition's typical history and improved patient outcomes.[2] However, many patients with heart failure continue to be limited in their everyday activities; they complain of exhaustion and shortness of breath which negatively affects their quality of life and contributes to high morbidity.[3,4] Iron is implicated in erythropoiesis, oxygen consumption, transport, storage, and oxidative metabolism in skeletal muscle.[5,6] Iron deficiency has historically been thought to have clinical effects only when anemia is present. On the other hand, a lower hemoglobin level can be seen as the final result of a process that started with iron stores' gradual depletion.[6,7]

Iron deficiency in patients with or without anemia reduces aerobic capacity and is associated with fatigue and exercise intolerance. Iron replacement increases

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emotional, symptomatic, and exercise function in iron deficiency patients but not heart failure.[8-10]

Recently, it has been noted that patients with heart failure are more likely to experience iron deficiency due to reduced production of iron recycled in the reticuloendothelial system and loss of iron reserves or defective iron absorption.[11,12] Iron deficiency is becoming more widely known as severe comorbidity in patients with heart failure, with up to 35 percent to 50 percent of heart failure patients suffering from it.[13-17] In both the presence and absence of anemia, its occurrence is related to the disease's seriousness and is a good and independent predictor of outcome. In both healthy volunteers and patients with chronic heart failure, iron deficiency reduces exercise ability. Iron is involved in oxygen transport not only through hematopoiesis but also through cardiac and skeletal muscle metabolism. All of these factors contribute to heart failure patients' decreased exercise capability.[16,18-20] Absolute iron deficiency is described as a decrease in total body iron stores (primarily in macrophages and hepatocytes) that may or may not progress to iron deficiency anemia. Absolute iron deficiency may occur when there is an increase in demand, a decrease in consumption, a reduction in or malabsorption of nutrients, or chronic blood loss.[21]

The terms ‘functional' or ‘relative' iron deficiency (and subsequent iron deficiency anemia) define two key scenarios. In the first scenario, in patients with chronic kidney disease, chronic heart failure, inflammatory bowel disease, chronic pulmonary disorders, cancer, obesity, other autoimmune diseases, and chronic infections, iron is hardly mobilized from stores to circulation and erythropoietic tissue due to chronic inflammation and elevated hepcidin levels. Because of decreased iron absorption signaled by high hepcidin levels, absolute iron deficiency can manifest later.[22,23] The second scenario is situations in which increased erythropoiesis is caused by endogenous erythropoietin responses to anemia or therapy with erythropoiesis-stimulating agents (ESA), resulting in an iron demand/ supply mismatch.[21,22,24]

This study aimed to investigate those patients with stable chronic heart failure with reduced ejection fraction and iron deficiency, depending on serum ferritin and transferrin saturation, then replacing iron deficiency with intravenous iron, and find the impact of intravenous iron on the functional status of the patient.

## Methods

An observational study was carried out in the cardiac center and cardiovascular unit of Erbil Teaching Hospital and Rizgary Teaching Hospital. The study period ranged from June 2019 to January 2021. Informed consent was obtained from each patient. The research ethics committee of the Kurdistan Board of Medical Specialties approved the study.

The study group included patients with ambulatory chronic stable heart failure attending the hospital for follow-up and rearranging the treatment. Patients with reduced ejection fraction (less than 40%) with an iron deficiency (serum ferritin less than 100ng\ml or serum ferritin between 100 and 299 ng/ml but transferrin saturation less than 20%) were included in the study. Written informed consent was obtained from the patients willing to participate in the study.

The exclusion criteria included all those with acute or acute decompensation of chronic heart failure, nonambulatory patients, patients without reduced ejection fraction, hemoglobin more than 15 gm/dl, and patients with uncontrolled hypertension, infection, malignancy, significant liver, and end-stage renal failure.

One hundred patients were enrolled in the study; at the baseline visit, complete clinical history and physical examination were made for each patient and assessed

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6 minutes walking test (6MWTs), NYHA classification, serum ferritin, transferrin saturation, and ejection fraction. Intravenous iron was given as ferrous carboxymaltose (Ferinject); each vial contained 500 mg of iron diluted at 100cc normal saline and given intravenously. One dose of Ferinject was given every two weeks for three doses. Then, we reinvestigated the enrolled patients at 12 weeks of baseline investigation. Complete clinical history, physical examination, NYHA assessment, 6MWTs, ejection fraction, and serum ferritin with transferrin saturation were made for all patients. If any patient still has iron deficiency, another one or two doses of Ferinject were given two weeks apart. At 24 weeks of baseline assessment, the patient is reinvestigating in the same manner as the 12-week assessment; then, we calculate the different distances in 6MWTs and the NYHA of an enrolled patient. Subjects were instructed to eat only a light meal and not to exercise vigorously within two hours of the exam. The 6MWTs are supposed to happen immediately after breakfast (in the early morning) or immediately after lunch (i.e., early afternoon). All tests were conducted on a smooth, straight, hard-surfaced corridor at least 25 meters long, with two chairs marked turnaround points at either end of the measured track. NYHA classification is used as follows: Class one: no limitation on physical activity, class two: slight limitation on physical activity, class three: marked limitations on physical activity, and class four: unable to carry on any physical activity without discomfort.[31] According to the WHO definition of anemia, a patient with hemoglobin less than 13 gm/dl in males and 12 gm/dl in females is anemic.[32] Body Mass Index (BMI) was used according to WHO classification as follows: BMI <18.6 was regarded as underweight, BMI between 18.6-24.9 was regarded as normal weight, BMI between 25 and 29.9 was regarded as overweight, and BMI ≥30 was regarded as obese.[33]

### Statistical analysis

Data on demography and clinical features of patients was expressed as means ± SD and/or frequencies and percentages. The data were checked for normal distribution by the Shapiro-Wilk test. A repeated-measures ANOVA to estimate the intervention with intravenous iron in SIXMWT in time points (baseline, after 12 and 24 weeks) was used. A *P* value of ≤0.05 was considered the significance level for all analyses. The statistical package for the social sciences software, version 22, was used for data analysis.

## Results

In this study that enrolled 100 cases, 59% were male while 41% were female, with a male:female ratio of 1.43:1. The mean ± standard deviation (SD) of the BMI of the cases was 27.35 ± 3.61. Most of the cases during the admission were diagnosed to have diabetes mellitus (61%), hypertension (77%), ischemic heart diseases (82%), and smoking (62%), while the minimum of them was alcoholic (3%), as shown in Table 1.

The maximum serum ferritin for an enrolled patient was 190 mg/l, and the minimum was 56 mg/l. The maximum transferrin saturation was 19%, and the minimum was 11%. The ejection fraction mean was 32%, with a maximum of 39% and a minimum of 12%. The hemoglobin of the patients ranged between 9 gm/dl and 14.9 gm/dl, blood urea ranged between 17 mg/dl and 86mg/dl, and serum creatinine ranged from 0.4 mg/dl and 1.9 mg/dl, as shown in Table 2.

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**Table 1** Characteristics of patients (N=100)

| Characteristics | | No. | (%) |
|---|---|---|---|
| **Gender** | Male | 59 | (59.0) |
| | Female | 41 | (41.0) |
| **Body mass index** | Normal weight | 24 | (24.0) |
| | Overweight | 52 | (52.0) |
| | Obese | 24 | (24.0) |
| **Diabetes mellitus** | Yes | 62 | (62.0) |
| | No | 38 | (38.0) |
| **Hypertension** | Yes | 77 | (77.0) |
| | No | 23 | (23.0) |
| **Ischemic heart diseases** | Yes | 82 | (82.0) |
| | No | 18 | (18.0) |
| **Smoking** | Yes | 62 | (62.0) |
| | No | 37 | (37.0) |
| | Ex-smoker | 1 | (1.0) |
| **Alcohol** | Yes | 3 | (3.0) |
| | No | 97 | (97.0) |

**Table 2** Characteristics of baseline blood tests (N=100)

| Baseline measures | Minimum | Maximum | Mean | ±SD |
|---|---|---|---|---|
| Serum ferritin (mg/l) | 56 | 190 | 112 | (±41) |
| Transferrin saturation (%) | 11 | 19 | 14 | (±2) |
| Ejection fraction (%) | 12 | 39 | 32 | (±6) |
| Hemoglobin (gm/dl) | 9.0 | 14.9 | 11.9 | (±1.3) |
| Blood urea (mg/dl) | 17 | 86 | 45 | (±17) |
| Creatinine (mg/dl) | 0.4 | 1.9 | 1.2 | (±0.4) |

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A repeated-measures ANOVA with a Greenhouse-Geisser correction determined that mean SIXMWT differed significantly between time points (baseline, after 12 weeks and after 24 weeks) (F (1.407, 139.323)=9.074, *P* <0.001). Post hoc tests using the Bonferroni correction revealed that intervention with intravenous iron elicited a slight increase in SIXMWT from baseline after 12 weeks of intervention (285.060 ± 57.019 vs. 287.750 ± 26.937, respectively), which was not statistically significant (*P* = 1.00). However, SIXMWT had been increased to 303.770 ± 30.168 after 24 weeks, which was significantly different from baseline (*P* = 0.003) and 12 weeks of intervention (*P* <0.001). Therefore, we can conclude that intervention with intravenous iron (6 months) elicits a statistically significant increase in SIXMWT, but not after only 12 weeks of intervention (Table 3).

A repeated-measures ANOVA with a Greenhouse-Geisser correction determined that the mean ejection fraction did not differ significantly between ejection fraction at baseline, after 12, and 24 weeks of intervention (F (1.72, 171.2)=1.138, *P* = 0.317). Post hoc tests using the Bonferroni correction revealed that intervention with intravenous iron elicited a slight increase in ejection fraction from baseline after 12 and 24 weeks of intervention (31.674± 5.878 vs. 32.160± 5.89251, respectively), which was not statistically significant (*P* = 0.597). However, the ejection fraction had increased to 32.030± 5.93816 after 24 weeks, which was not significantly different from baseline (*P* = 0.944) and 12 weeks of intervention (*P* = 1.00). Therefore, we can conclude that intervention with intravenous iron (6 months) elicits a statistically non-significant increase in ejection fraction after 12 and 24 weeks of intervention, as shown in Table 4.

Figure 1 showed that NYHA class at 24 weeks compared to the 12 weeks and the baseline significantly improved (*P* <0.001 for all comparisons). NYHA classification of patients was slightly improved from baseline vs. after 12 weeks of iron intervention (mild restriction was 40 in baseline vs. 52 after 12 weeks), and moderate restriction was 60 at baseline vs. 48 after 12 weeks) these improvements were statistically significant, *P* = 0.020). Meanwhile, mild and moderate restrictions were significantly improved after 24 weeks of intervention compared to the changes in the baseline and after 12 weeks of intervention (*P* <0.001).

Post hoc tests using the Bonferroni correction revealed that intervention with intravenous iron produced a large increase in serum ferritin from baseline and after 12 weeks of intervention (112.33±40.581 vs. 190±27.70, respectively), which was statistically significant (*P* <0.001). However, serum ferritin had been increased to 213.33±12.076 after 24 weeks, which was statistically significantly different from baseline (*P* <0.001) and 12 weeks of intervention (*P* <0.001). Therefore, we can conclude that intervention with intravenous iron (6 months) elicits a statistically significant increase in serum ferritin after 12 and 24 weeks of intervention, as shown in Table 5.

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**Table 3** Estimates of intervention with intravenous iron in SIXMWT in baseline, after 12 and 24 weeks

| SIXMWT | Mean | ±SD | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| Baseline | 285.060 | (±57.019) | 273.746 | 296.374 |
| After 12 weeks | 287.750 | (±26.937) | 282.405 | 293.095 |
| After 24 weeks | 303.770 | (±30.168) | 297.784 | 309.756 |

**Table 4** Estimates of intervention with intravenous iron in ejection fraction in baseline, after 12 and 24 weeks

| Ejection Fraction | Mean | ±SD | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| Baseline | 31.674 | (±5.878) | 30.508 | 32.840 |
| After 12 weeks | 32.160 | (±5.892) | 30.991 | 33.329 |
| After 24 weeks | 32.030 | (±5.938) | 30.852 | 33.208 |

**Table 5** Estimates of intravenous with iron in serum ferritin status at baseline, after 12 and 24 weeks of intervention

| Serum ferritin status | Mean | (±SD) | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| Baseline | 112.33 | (±40.581) | 104.278 | 120.382 |
| After 12 weeks | 190.00 | (±27.702) | 184.503 | 195.497 |
| After 24 weeks | 213.33 | (±12.076) | 210.934 | 215.726 |

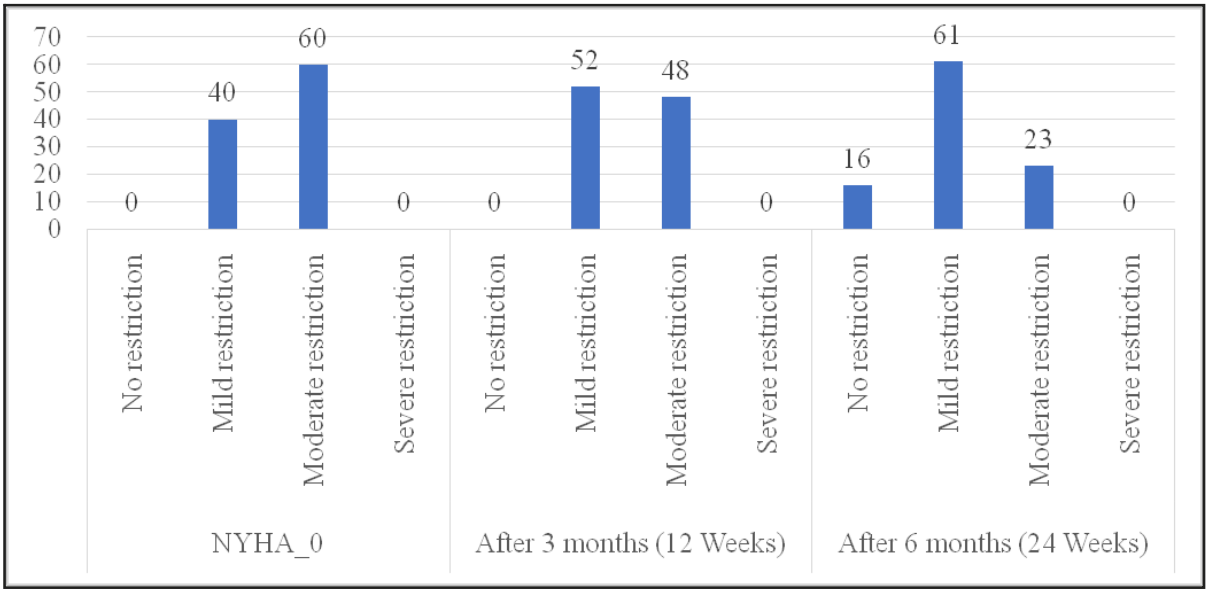


**Figure 1** Estimates of intervention with intravenous iron in NYHA in baseline, after 12 and 24 weeks

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Regarding males with and without anemia, a repeated-measures ANOVA with a Greenhouse-Geisser correction determined that mean SIXMWT has differed significantly between time points among anemic males ($F$ (1.253, 71.401) = 4.346, $P$ = 0.032). Post hoc tests using the Bonferroni correction revealed that iron intervention elicited a slight increase in the mean score of SIXMWT among anemic males from baseline to 12 weeks of iron intervention (272.69 ± 12.906 vs. 288.96 ± 24.765, respectively), which was not statistically significant ($P$ = 1.00). Also, 24 weeks of intervention had increased to 311.207 ± 30.491, which was not significantly different from the baseline ($P$ = 0.132) but significantly different from the 12 weeks of intervention ($P$ <0.001). Therefore, we can conclude that a long-term iron intervention (6 months) elicited a statistically significant increase in SIXMWT among anemic males. Regarding non-anemic patients, one-way ANOVA showed that their mean±SD was significantly different from the anemic patients in the baseline only ($P$ = 0.038). Their difference after 12 weeks and after 24 weeks was not statistically significant ($P$ = 0.223 and $P$ = 0.614, respectively), as shown in Table 6.

**Table 6** Effect of intravenous iron on six-minute walking test in anemic and non-anemic heart failure male patient with iron deficiency at baseline, after 12 and 24 weeks of intervention

| Male Anemia | SIXMWT | Mean | Std. Deviation | 95% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound |
| **Anemia** | Baseline | 272.690 | 12.906 | 246.866 | 298.514 |
| | After 12 weeks | 288.966 | 24.765 | 278.386 | 299.545 |
| | After 24 weeks | 311.207 | 30.491 | 300.863 | 321.551 |
| **No anemia** | Baseline | 311.100 | 96.534 | 285.710 | 336.490 |
| | After 12 weeks | 298.100 | 31.606 | 287.698 | 308.502 |
| | After 24 weeks | 307.533 | 24.964 | 297.363 | 317.703 |

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Regarding females with and without anemia, a repeated-measures ANOVA with a Greenhouse-Geisser correction determined that mean SIXMWT did not differ significantly between time points among anemic females ($F(1.66, 64.7) = 0.48$, $P = 0.58$). Post hoc tests using the Bonferroni correction revealed that iron intervention elicited a slight increase in the mean score of SIXMWT among anemic females from baseline to 12 weeks of iron intervention (267.44± 16.096 vs. 276.67±17.700, respectively), which was not statistically significant ($P = 0.46$). Also, 24 weeks of intervention had increased to 291.38± 39.795, which was significantly different from the baseline ($P < 0.001$) and the 12 weeks of intervention ($P = 0.003$). Therefore, we can conclude that a long-term iron intervention (6 months) elicited a statistically significant increase in SIXMWT among anemic females. Regarding non-anemic patients, one-way ANOVA showed that their mean ± SD was significantly different from the anemic patients in the baseline only ($P = 0.048$). Their difference after 12 weeks and after 24 weeks is not statistically significant ($P = 0.504$ and $P = 0.449$, respectively), as shown in Table 7.

**Table 7** Effect of intravenous iron on six-minute walking test in anemic and non-anemic heart failure female patient with iron deficiency at baseline, after 12 and 24 weeks of intervention

| Female Anemia | SIXMWT | Mean | Std. Deviation | 95% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound |
| **Anemia (n=18)** | Baseline | 267.44 | 16.096 | 259.44 | 275.45 |
| | After 12 weeks | 276.67 | 17.700 | 267.86 | 285.47 |
| | After 24 weeks | 291.38 | 39.795 | 271.59 | 311.17 |
| **No anemia (n=23)** | Baseline | 280.48 | 23.067 | 270.50 | 290.45 |
| | After 12 weeks | 281.39 | 25.199 | 270.49 | 292.29 |
| | After 24 weeks | 299.17 | 25.048 | 288.34 | 310.00 |

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## Discussion

This study aimed to find the impact of intravenous iron on 6MWT, NYHA, and ejection fraction in patients with heart failure with a reduced ejection fraction and iron deficiency depending on serum ferritin and transferrin saturation. In total, 100 cases were enrolled in our study; 41% were females and 59% were males, 52% were overweight, 24% were obese, and 24% were average weight. Around 62% had diabetes, 77% had hypertension, 82% had ischemic heart disease, 62% were smokers, and 3% were alcoholics. Compared with the FAIR-HF trial, which enrolled 459 patients, in which 52.3% were females, the body mass index ratio was 28±4.8, 30.6% had diabetes, 79.9% were hypertensive, and 80.6% had a history of ischemic heart disease as a cause of heart failure.[6]

In our study, iron deficiency depends on serum ferritin and transferrin saturation, either serum ferritin less than 100ng/ml or between 100-299 ng/ml but the transferrin saturation less than 20%, which agrees with FAIR-HF trial and CONFIRM-HF trial.[6,29]

The average serum ferritin in our study was 112 ng/ml, transferrin saturation was 14%, hemoglobin was 12.6 gm/dl, ejection fraction was 32%, blood urea was 45 mg/dl, and serum creatinine was 1.2 mg/dl. Compared with the FAIR-HF trial, serum ferritin of their included patients was 52.5±54.5 µg/liter, transferrin saturation was 17.7±12.6%, hemoglobin was 11.9±1.3 gm/dl, serum creatinine was 1.2±0.6, and ejection fraction was 31.9±5.5.[6]

Our study found that ferric carboxymaltose (FCM) therapy significantly improves patients' functional capacity. The positive benefits of FCM could be noticed as early as week 12; however, it was not significant at that week and reached statistical significance by week 24. The amount of FCM's treatment effect on the 6MWT distance is robust and clinically relevant, exceeding 30 m in the last 6-month research period. However, as is seen in other studies like the FAIR-HF trial,[6] CONFIRM-HF trials,[29] and the EFFECT-HF trial.[27] There was a significant improvement in 6MWT after intravenous iron replacement. The 6MWT is a well-established, reliable measure for assessing functional capacity sensitive to changes in self-reported symptoms and has been used in multiple heart failure studies to examine the effects of various treatments.[25,26]

Our study found that ejection fraction does not increase statistically significantly at weeks 12 and 24 after intravenous iron supplement. In contrast, another study by Zhou et al. revealed that iron replacement increases ejection fraction significantly as these studies have many limitations, including the methodological quality of the included studies was subpar. Thus, there was no way to rule out the possibility of bias. Due to the lack of information, we did not consider the impact of iron dose, administration technique, or heart function on therapeutic effects. Third, the sample size and duration of follow-up in these trials varied significantly, potentially reducing statistical power.[30]

In our study, most patients had stable heart failure with NYHA II or III. The improvement of NYHA functional class is statistically significant at week 24; nevertheless, improvement was noted at week 12, similar to another study like the FAIR-HF trial.[6]

The 2017 update of the American Heart Association and American College of Cardiology states that “intravenous iron replacement might be reasonable to improve functional status and quality of life in patients with NYHA functional class II and III heart failure and iron deficiency (ferritin 100 mg/l or 100 to 300 mg/l if TSAT is 20 percent)," giving this recommendation a IIb level of evidence.[28]

Our study revealed that iron replacement in anemic and non-anemic patients has the same result of improved functional status as 6MWT and NYHA functional

classification and has no statistically significant difference between these two groups. In the FAIR-HF trial, intravenous iron was shown to improve symptoms, quality of life parameters, and a 6-minute walking distance test after 24 weeks in patients with and without anemia.[6]

## Conclusion

In conclusion, treatment with ferric carboxymaltose over 24 weeks improves symptoms and physical performance as detected by improvement of 6MWT, NYHA functional classification in symptomatic, ambulatory patients with chronic heart failure with reduced left ventricular ejection fraction and iron deficiency. The advantage was shown in both anemia and non-anemia patients.

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## Competing interests

The authors declare that they have no competing interests.

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