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Effects of 6-months of oral ferrous and ferric supplement therapy in patients who were hospitalized for decompensated chronic heart failure

Snezana Ciric Zdravkovic[1,2], Svetlana Petrovic Nagorni[2], Irena Cojbasic[1,3], Vesna Mitic[2], Predrag Cvetkovic[2], Ivan Nagorni[1], Nenad Govedarovic[1,3], Ivana Davinic[1] and Dragana Stanojevic[2]

Abstract

Objective: Anemia is common in patients with chronic heart failure (CHF). This study aimed to examine the frequency of iron deficiency anemia in patients with CHF. We investigated the effects of oral ferrous or ferric supplementation on prognosis of CHF and quality of life.

Methods: A total of 201 patients with chronic decompensated heart failure were enrolled in a 6-month prospective study. Patients were randomly assigned to two groups. Patients in group I (n = 100) received ferrous fumarate and those in group II (n = 101) received ferric hydroxide polymaltose complex. Quality of life was measured by the 6-minute walking test (6MWT).

Results: A total of 49% of the patients had iron-dependent anemia in group I and 53.3% were anemic in group II. In group I, the number of anemic patients was significantly lower at 6 months after admission compared with at initial admission (49% versus 45%). Significant improvements were observed in hemoglobin values, the 6MWT distance, and New York Heart Association class after 6 months in both groups.

[1]Medical Faculty, University of Nis, Nis, Serbia
[2]Clinic for Cardiovascular Diseases, Clinical Center Nis, Nis, Serbia
[3]Clinic for Hematology, Clinical Center Nis, Nis, Serbia

Corresponding author:
Dragana Stanojevic, Clinic for Cardiovascular Diseases, Clinical Center Nis, Bulevar Zorana Djindjica 48, 18000 Nis, Serbia.
Email: draganastanojevic1@gmail.com

Conclusions: Iron deficiency is a significant comorbidity in CHF, even without anemia. Iron should be replaced orally or intravenously because it significantly improves the quality of life of patients.

Keywords
Heart failure, iron deficiency, iron supplement, quality of life, anemia, hemoglobin

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Introduction

Iron depletion is the main cause of anemia. Despite this known depletion, there are a number of issues concerning the best choice of supplementation therapy. The drugs that are frequently provided for anemia are ferrous sulfate, ferrous gluconate, or ferrous fumarate. These ferrous (Fe^{2+}) forms are more soluble than the dietary ferric (Fe^{3+}) form, with twice the absorbability.[1,2]

Approximately 30%–40% of patients with chronic heart failure (CHF) develop anemia.[3] If iron deficiency in CHF is defined as a serum ferritin level $< 100\,\mu g/L$, along with a transferrin saturation level (TSAT = serum iron level divided by transferrin level multiplied by 100) of $< 20\%$, approximately 24% of all patients with CHF and approximately 40% of non-anemic patients have iron deficiency.[4] There are several possible reasons for iron deficiency in patients with CHF. Some patients with CHF are anemic not because their red cell mass is low, but because their plasma volume is high, which is described as hemodilution.[5] Proteinuria is often found in CHF and it may cause loss of erythropoietin via the urine, as well as cause a loss of transferrin, which can lead to iron deficiency anemia.[6] A further explanation is that anemia may be part of a long-lasting inflammation (e.g. anemia of chronic disease). Some studies have suggested that approximately 60% of patients with CHF may have anemia of chronic disease, as established by low ferrous levels and iron binding capacity, but elevated ferritin levels.[7] A drawback of ferritin is that it is an acute phase reactant and its level may be elevated during inflammation. For practical purposes, TSAT may be used to provide the real amount of serum that is iron bound with ferritin.[8,9]

The precise cut-off to define anemia in CHF has mostly been arbitrary. According to the World Health Organization (WHO), anemia is defined as when hemoglobin concentrations are < 13 g/dL for men or < 12 g/dL for women, but some authors use more conservative definitions to ensure a higher level of confidence.[9] The prevalence and severity of anemia increase during progression of CHF.[6] Some studies have established the importance of anemia correction in patients with CHF. The treatment strategies are treatment with erythropoietin, iron supplementation, or both of them.[10] The majority of these studies were carried out using intravenous formulation, but little observation has been carried out with oral formulations of iron.

Anemia is an independent prognostic factor of morbidity and mortality in patients with CHF. Previous studies have shown the beneficial effect of treating anemia in patients with CHF. This study aimed to examine the frequency of iron deficiency anemia (IDA) in patients with

CHF and its correlation with the New York Heart Association (NYHA) class. We also investigated the effects of oral ferrous and ferric supplementation therapy on the 6-month prognosis of CHF and quality of life, as measured by the 6-minute walking test (6MWT) in patients with IDA.

Patients & methods

We enrolled 201 patients in this prospective study who had been admitted to hospital for chronic decompensated heart failure (HF). The Ethical Committee of the Medical Faculty at the University of Nis approved the research (No. 14-9475-5/-96/07), which was conducted at the Clinic for Cardiovascular Diseases, Clinical Centre Nis, during 2016. All participants ($n = 201$) gave written informed consent for their participation in this study before enrolment. The research was conducted according World Medical Association Declaration of Helsinki. We used the WHO definition for anemia. Inclusion criteria were serum ferritin levels < 100 μg/L and TSAT levels $< 20\%$. The exclusion criteria were known and treated anemia, allergy or intolerance to iron supplements, duodenal or gastric ulcerations, gastrointestinal disease with impaired iron absorption, oncological diseases, surgery 6 months before inclusion in the study, active bleeding, and the requirement for blood transfusion (severe anemia). Patients with shock or sepsis were also excluded.

The patients were randomly assigned to two groups to receive different iron supplements. Once a patient consented to enter the study, an envelope was opened and the patient was then offered the allocated treatment regimen. The study was open-label because physicians and patients were aware of the treatment assignment. Patients in the first group with IDA received ferrous fumarate (Heferol® capsule, 350 mg, which correlates to 115 mg of elemental iron; Vifor Inc., St Gallen, Switzerland) twice daily, 1 hour before a meal simultaneously with ascorbic acid at a dose of 500 mg (group I). Patients in the second group with IDA were assigned to receive a ferric hydroxide polymaltose complex (Ferrum Sandos® 357 mg, which correlates with 100 mg of elemental iron; Vifor Inc.) without ascorbic acid (group II).

A routine clinical examination was carried out for all participants upon admission. This examination included taking a detailed medical history, a physical examination, standard laboratory analyses, a 12-lead chest electrocardiogram, a chest X-ray, and echocardiography. In anemic patients, we measured ferritin levels and carried out the total iron binding capacity test (TIBC), which shows the levels of transferrin bound with iron. Before hospital discharge, all patients underwent the 6MWT according to a standardized protocol to measure their physical capacity.[11] The primary endpoints during the 6 months of follow-up were death and rehospitalization due to cardiac diseases (acute myocardial infarction, cardiac arrhythmia, pulmonary edema, acutely decompensated HF, and cardiac arrest). Six months after their initial hospitalization, patients underwent a physical examination, and blood samples were taken for a complete blood count test. Furthermore, the 6MWT was carried out at this time, as well as an echocardiographic examination (left ventricular ejection fraction [LVEF] was measured according to Simpson's rule). The patients were also interviewed regarding tolerability of the iron supplements. At the time of hospital discharge, all patients received optimal medical therapy according to the latest guidelines from the European Society of Cardiology.[12]

Statistical analysis

The data are presented as descriptive statistics in the form of the arithmetic mean and

standard deviation, median and interquartile differences, minimal and maximum values, and absolute and relative numbers. The normality of the data was tested using the Kolmogorov–Smirnov test. A t-test was used to compare the two groups. The Mann–Whitney U test was used if the data distribution was not normal . If normal distribution was not satisfied when comparing the data sets, the Kruskal–Wallis test was used. To compare descriptive values, the chi-square test or Fisher's Exact Probability Test was used. Logistic regression analysis was used to determine the odds ratio (OR) for each of the risk factors investigated. Statistical data processing was carried out using the SPSS 17.0 program package (SPSS Inc., Chicago, IL, USA). Statistical significance was determined for a p value of < 0.05.

Results

The baseline characteristics of the groups are shown in Table 1. Group I comprised 100 patients, among whom 56 (56%) were men and the mean age was 73.3 ± 9.77 years. In group II, we enrolled 101 patients, 65.3% (66) of whom were men, and the mean age was 70.76 ± 9.81 years. There were no significant differences in age and sex between the groups ($F = 3.404$, $p = 0.06$; chi-square test $= 1.8$, $p = 0.113$, respectively). There were no significant

Table 1. Baseline characteristics of the patients.

	Group I (n = 100)		Group II (n = 101)	
	Mean	SD	Mean	SD
Age (years)	73.31	9.766	70.76	9.811
Systolic BP (mmHg)	136.00	34.60	132.87	25.90
Diastolic BP (mmHg)	79.95	21.69	80.35	14.88
Heart rate (bpm)	97.90	33.89	97.51	23.75
Duration of HF (years)	1.68	1.18	1.70	1.08
TnI (ng/mL)	0.036	0.003	0.012	0.008
BNP (pg/mL)	1163.07	1213.02	1141.37	1153.66
Glucose (mmol/L)	9.12	4.926	8.39	4.924
Creatinine (μmol/L)	143.13	83.325	140.97	91.114
Urea (mmol/L)	11.41	6.745	12.56	60.594
BUN (mmol/L)	450.35	140.911	490.97	132.388
Cholesterol (mmol/L)	4.84	1.483	4.43	1.488
Triglycerides (mmol/L)	1.57	0.943	1.60	0.566
Albumin (g/dL)	34.59	5.871	32.92	4.052
AST (U/L)	71.46	103.911	71.62	66.639
ALT (U/L)	55.97	79.562	61.78	63.352
WBC	11.54	5.16	12.02	5.51
PLT	227.48	87.36	324.33	93.095
Fe (μmol/L)	5.73	2.52	5.42	1.82
CRP (mg/L)	41.85	62.635	39.16	55.963
Fibrinogen (g/L)	5.12	2.140	8.76	2.096
Transferrin (μmol/L)	15.7	2.8	14.44	3.1

SD - standard deviation, BP - blood pressure, HF - heart failure, TnI - cardiac troponin I, BNP - brain natriuretic peptide, BUN - blood urea nitrogen, AST - aspartate aminotransferase, ALT - alanine aminotransferase, WBC - white blood cells, PLT - platelets, Fe - iron, CRP - C-reactive protein.

differences in comorbidities and the number of active smokers between the groups (Table 2). In group I, 49% (49) of the patients had IDA, and in group II, 53.3% (54) of the patients were anemic.

Table 2. Comorbidities in both groups of patients.

Co-morbidity	Group I (% of patients), n = 100	Group II (% of patients), n = 101
Arterial hypertension	85	75.2
Diabetes mellitus	54	55.4
Chronic renal failure	40	46.5
COPD	25	22.8
CVI	7	7.9
Hyperthyreosis	1	3
Hypothyreosis	6	9.9
Depression	7	12.9
Permanent atrial fibrillation	43	40.6
Pacemaker	4	4.6
Active smoker	19	27.7

COPD - chronic obstructive pulmonary disease, CVI - cerebrovascular insult.

Baseline hematological parameters are shown in Tables 1 and 3. The main reasons for HF are shown in Table 4. There were significantly more patients with diastolic HF in group I than in group II (39% versus 23.8%, $p = 0.01$). Patients with renal dysfunction were more likely to have anemia compared with those without renal dysfunction (65.5% versus 34.5%, $p < 0.001$). A total of 88.1% of patients received furosemide intravenously during hospitalization. However, the use of furosemide or its dosage did not correlate with hematological parameters that we measured.

There were significant improvements in hemoglobin values, hematocrit, red blood cell count, 6MWT distance, and NYHA class after 6 months compared with initial admission to hospital in both groups (all $p < 0.01$, Tables 3, 5), irrespective of the presence of anemia. Anemic patients from group II tolerated iron supplements significantly better than those in group I ($p = 0.037$). Forty-one (20.4%) patients had mild intolerance, such as nausea,

Table 3. Parameters measured at the beginning and at the end of the study.

	Group I (n = 100)			Group II (n = 101)		
	Mean	SD	Difference (p)	Mean	SD	Difference (p)
Hb at baseline (g/L)	115.22	22.27	t = 21.48,	117.85	24.51	t = 8.206,
Hb after 6 months (g/L)	125.67	21.18	p < 0.001	122.41	23.03	p < 0.001
Hct at baseline	33.45	5.40	t = 21.38,	32.9495	7.87	t = 16.336,
Hct after 6 months	38.65	6.69	p < 0.001	34.5644	8.23	p < 0.001
RBC at baseline ($\times 10^{12}$)	3.95	0.73	t = 18.25,	3.4991	0.86	t = 7.807,
RBC after 6 months ($\times 10^{12}$)	4.23	0.77	p < 0.001	3.6264	0.86	p < 0.001
Ferritin at baseline (μg/L)	8.66	4.15	t = 7.81,	8.52	3.91	t = 7.60,
Ferritin after 6 months (μg/L)	36.77	24.93	p < 0.001	37.84	29.74	p < 0.001
TSAT at baseline (%)	8.7	4.1	t = 7.72,	8.5	3.9	t = 8.21,
TSAT after 6 months (%)	29.7	18.05	p < 0.001	31.9	22.2	p < 0.001
6MWT at baseline (m)	376.10	125.73	t = 5.36,	299.75	121.90	t = 2.682,
6MWT after 6 months (m)	438.17	113.09	p < 0.0001	335.13	93.15	p < 0.001
LVEF at baseline (%)	40.81	14.87	t = 0.223,	38.46	10.64	t = 0.785,
LVEF after 6 months (%)	40.71	12.35	p = 0.8	38.63	10.46	p = 0.4

SD - standard deviation, Hb - hemoglobin, RBC - red blood cells, TSAT - transferrin saturation, 6MWT - 6-minute walking test, LVEF- left ventricular ejection fraction.

Table 4. Main reasons for heart failure.

Main reason for heart failure	Group I (n = 100)	Group II (n = 101)
Dilatative cardiomyopathy	45 (45%)	37 (36.6%)
Coronary artery disease	49 (49%)	56 (55.4%)
Arterial hypertension	6 (6%)	8 (7.9%)
Chi square test = 1.56, p = 0.6		

Table 5. NYHA class in both groups of patients.

	Group I		Group II	
NYHA class	At baseline (n = 100)	After 6 months n = 91	At baseline (n = 101)	After 6 months n = 84
1	0	10 (11%)	0	5 (6%)
2	45 (45%)	51 (56%)	37 (36.6%)	44 (52%)
3	49 (49%)	30 (33%)	56 (55.4%)	35 (42%)
4	6 (6%)	0	8 (7.9%)	0

Wilcoxon signed rank test, $p < 0.0001$.

Table 6. Parameters measured at baseline and after 6 months.

Parameter	Group I (n = 100)	Group II (n = 101)	Chi-square test	p
No of re-hospitalizations	10 (10)	14 (13.9)	0.713	0.266
Mortality during 6 months, n (%)	9 (9)	17 (16.8)	2.737	0.07
Intolerability of iron supplementation, n (%)	26 (26)	15 (14.9)	3.846	0.037

vomiting, abdominal pain, diarrhea, and constipation after taking the supplements, but these were sporadic. The majority of these patients were in group I (Table 6). None of the patients stopped taking iron supplements.

There was a significant correlation between hemoglobin at baseline and creatinine levels (Pearson correlation: −0.339, $p < 001$), as well as between hemoglobin at the end of the study and baseline creatinine levels (Pearson correlation: −0.367, $p < 001$). There were no correlations between hemoglobin at the beginning and at the end of the study with inflammatory markers (white blood cells, fibrinogen, C-reactive protein), LVEF, brain natriuretic peptide (BNP), and duration of HF or type of HF (systolic/diastolic HF) measured at baseline. Hemoglobin levels at baseline in patients with NYHA class 2 were significantly higher compared with those in patients with NYHA class 4 (119.15 versus 102.86 g/dL, $p = 0.042$). At the end of the study, this significance was lost. Patients with chronic obstructive pulmonary disease had significantly higher hemoglobin levels at baseline than those in patients without that comorbidity (123.00 versus 114.52 g/dL, $p = 0.028$). Furthermore, hemoglobin levels in those with renal failure were significantly lower at the beginning of the

study than in those without renal failure (109.51 versus 121.91 g/dL, $p < 0.001$). Other comorbidities that were investigated were not associated with different hemoglobin levels. Hemoglobin levels were not correlated with age, but they were significantly lower in women at baseline (111.71 versus 119.67 g/dL, $p = 0.018$) and at the end of the study compared with men (119.87 versus 126.72 g/dL, $p = 0.032$).

Six months after the admission to hospital, there was a significant decrease in the number of anemic patients in group I because of acute heart decompensation compared with the initial time of admission (49 [49%] to 45 [45%]). In group II, the number of anemic patients did not change after 6 months, despite an increase in hemoglobin levels (54 [53.5%] versus 54 [53.5%]). In group I, hemoglobin levels significantly increased during the 6-month period compared with the initial time of admission, irrespective of whether patients had anemia at baseline (without anemia: 133.76 ± 9.47 versus 142.20 ± 11.90 g/L, $p < 0.001$; with anemia: 95.92 ± 13.55 versus 108.47 ± 13.63 g/L, $p < 0.001$). Hemoglobin levels in group II were also increased after 6 months (without anemia: 138.98 ± 13.65 versus 140.17 ± 13.96 g/L, $p < 0.001$; with anemia: 96.46 ± 15.2 versus 105.20 ± 13.56 g/L, $p < 0.001$).

The patients in group II tended to have higher mortality rate than did those in group I ($p = 0.07$). In group II, there were more patients with systolic than with diastolic HF. In logistic regression analysis, LVEF affected mortality during the 6-month period (OR = 0.946, 95% confidence interval [CI] = 0.909–0.984, $p = 0.006$). NYHA class 4 was associated with an increased risk of mortality (OR = 0.197, 96% CI = 0.047–0.822), as well as high BNP levels (OR = 1.1, 95% CI = 0.99–1.2, $p = 0.005$). Fibrinogen levels had a borderline significant effect on mortality during the follow-up period (OR = 1.1613, 95% CI = 0.997–2.609, $p = 0.052$).

Interestingly, none of the parameters of interest had any effect on re-hospitalization. Only the presence of hyperthyreosis was associated with an increased risk of re-hospitalization (OR = 0.126, 95% CI = 0.017–0.938, $p = 0.043$), which could be associated with more prevalent rhythm disturbances in this group of patients.[11]

Discussion

Our study showed that optimal management of HF, which also included oral iron supplementation in IDA, significantly improved hemoglobin levels, NYHA functional class, and 6MWT distance. Patients with HF syndrome not only require optimal treatment for HF, but also prevention and treatment for comorbidities. This approach improves the prognosis for this severe syndrome.[10,13] The etiology of anemia in patients with HF is complex and not well understood. In severe HF, iron deficiency tends to be the rule than the exception.[14] The majority of our patients had iron deficiency, irrespective of whether they had anemia. Many processes are involved in the pathophysiology of anemia in HF. Advanced anemia in HF could be a consequence of bone marrow suppression due to high levels of tumor necrosis factor-alpha in the circulation, and this interferes with the effects of erythropoietin. Additionally, the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers contributes to development of anemia because they decrease erythropoietin levels.[14,15] All of our patients had angiotensin-converting enzyme inhibitors or angiotensin receptor blockers as part of their therapy, which could have contributed to development of anemia.

In our patients, hemoglobin was not correlated with markers of inflammation or BNP levels, but it was strongly negatively

correlated with creatinine levels. Interaction between chronic renal failure, HF, and anemia is called cardio-renal anemia syndrome. Correction of anemia with subcutaneous erythropoietin and intravenous iron has beneficial effects on cardiac and renal function, and it even improves the diuretic response.[4,16] Patients with HF and relatively severe anemia (hemoglobin levels < 11 g/dL) and concomitant moderate to severe chronic kidney disease could be considered as potential candidates for erythropoietic therapy.[17] In both groups of our patients, the prevalence of anemia was approximately 50%, which is in line with previously published data.[18] Anemia was more frequent in female patients than in male patients and it was equally distributed between systolic and diastolic HF, which is also in line with previous reports.[19] However, anemia was not more frequent in older patients with HF.

Patients with NYHA class 4 more frequently have anemia than those with NYHA class 1 or 2.[10] However, in both groups of our patients with HF, anemia was equally distributed among the NYHA functional classes. This could be a consequence of the low percentage of patients in NYHA class 4 among our participants (7%). However, our patients with NYHA class 4 had significantly lower hemoglobin values than did those with NYHA class 2 at baseline. Anemia is a comorbidity that should be treated in patients with HF. The potential beneficial effects of this treatment are improved oxygen delivery and inhibition of cardiomyocyte apoptosis due to ischemia, slowing of adverse cardiac remodeling, improved tolerance of exercise, and improved health-related quality of life.[15]

The use of oral iron therapy is associated with frequent gastrointestinal side effects (20%–30%), and a long duration of therapy is required to replenish iron stores. These side effects lead to poor compliance. This is the main reason for switching to intravenous iron application, which is also accompanied by compliance or financial problems. Recently published, double-blind, placebo-controlled FAIR-HF and CONFIRM-HF trials showed that intravenous iron therapy was better tolerated than oral therapy.[20] The results from large-scale, multicenter, randomized, controlled trials for oral versus intravenous iron supplement therapy in HF are still long awaited.[15,21] A total of 20.4% of our patients had mild gastrointestinal side-effects on oral iron, but none of them stopped their therapy.

The recommendation by the World Health Organization to use Fe^{2+} iron supplements for treating iron deficiency anemia is under constant reassessment. This recommendation is based on research that showed that absorption of Fe^{2+} ions from the intestine is three times higher than that of Fe^{3+} iron. Recent studies have report conflicting results regarding the rate of success in anemia treatment by Fe^{2+} and Fe^{3+} preparations.[22,23] Few studies have shown improved gastrointestinal tolerance when using Fe^{3+} iron, which is a consequence of lower production of hydroxyl free radicals in the gastrointestinal mucosa and fewer side-effects.[24] Slow-release ferrous sulfate preparations are widely accepted as the iron supplements of choice for managing iron deficiency, irrespective of the indication. These supplements have shown good bioavailability, efficacy, and acceptable tolerability, as shown in several large clinical studies.[25] Accordingly, our patients had significantly fewer gastrointestinal side effects when using ferric supplements (group II) compared with those using ferrous supplements (group I), and the increase in hemoglobin was as effective as that with ferrous salts.

A 1-g increase in hemoglobin decreases the morbidity and mortality rates in patients with HF by 13%.[4] This association was not found in our patients, but the follow-up was only 6 months, and many

of the patients remained anemic, despite an increase in hemoglobin. However, as shown in other studies, treatment of iron-dependent anemia in HF significantly improved exercise tolerance (6MWD and NYHA class).[26] However, LVEF did not significantly increase in our patients as reported by other authors.[3] Bolger et al.[27] found that iron supplementation in anemic patients with HF improved their performance in the 6MWT (the distance walked was linearly correlated with hemoglobin) and the Patient's Global Assessment, Minnesota Living with Heart Failure Questionnaire scores.

Whether iron deficiency (absolute or relative) in HF is itself a comorbidity without anemia is still controversial.[10] In the FAIR-HF study, which enrolled 459 patients who were anemic and nonanemic with iron deficiency, all endpoints were similarly improved in both groups of participants.[28] This finding suggested that iron deficiency represents a significant comorbidity in CHF, even without anemia. The endpoints were variations of peak oxygen consumption as assessed by ergospirometry, functional class, BNP levels, quality of life scores, LVEF, adverse events, HF hospitalization, and death.[28]

Iron overload increases basal lipid peroxidation and accelerates ischemia-induced serum matrix metalloproteinase-9 levels in mice with thromboembolic stroke.[29] To the best of our knowledge, iron overload has not been investigated in patients with HF. However, hypothetically, iron overload could lead to worsening of HF because of accelerated loss of cardiomyocytes due to increased oxidative stress and adverse remodeling of the left ventricle.

In conclusion, our study shows that oral ferrous, as well as, ferric supplementation improves NYHA class and exercise tolerance in anemic patients with CHF. Ferric supplements are better tolerated than ferrous supplements. Standard testing in patients with HF should include serum iron levels, serum transferrin levels, the percentage of transferrin saturation, and serum ferritin levels, irrespective of whether anemia is present. Iron should be replaced orally or intravenously because correction of iron deficiency improves exercise tolerance and quality of life in patients with CHF. Further investigations are required with a larger number of patients. Additionally, the awareness of cardiologists regarding anemia in CHF should be improved.

This study has some limitations. The lack of a control group (a cohort not provided with iron) is a major limitation. The long-term safety and efficacy of iron supplements in HF is unclear. Therefore, there is no overriding clinical rule to supplement patients with ferritin levels above conventional cut-offs for iron deficiency (12–30 ng/mL). A control group in our study would have been useful to understand how much of the improvement in hemoglobin and the 6MWT was due to continued decongestion (and general clinical improvement) over the 6-month period versus iron supplementation.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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ORCID iD

Dragana Stanojevic https://orcid.org/0000-0003-3447-9817

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