DĄBEK, Katarzyna, OCHWAT, Michał, SUDOŁ, Maria, PIEKARSKA, Martyna, MIERZWA, Gabriela, KAJTEL, Aleksandra, and SKOWRONEK, Anna. Effect of Intravenous Iron Supply in Patients with Heart Failure with Reduced Ejection Fraction. Quality in Sport. 2024;35:56338. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.35.56338
https://apcz.umk.pl/QS/article/view/56338

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 21.11.2024. Revised: 05.12.2024. Accepted: 12.12.2024. Published: 12.12.2024.

Effect of Intravenous Iron Supply in Patients with Heart Failure with Reduced Ejection Fraction – a Literature Review

Katarzyna Dąbek

Country Hospital in Strzyżów

700-lecia 1, 38-100 Strzyżów

dabekkatarzyna63@gmail.com

ORCID: 0009-0002-2592-0148

Michał Ochwat

Independent Public Health Care Facility No. 1 in Rzeszów

Czackiego 3, 35-051 Rzeszów

michalochwat.michu@gmail.com

ORCID: 0009-0000-1225-5519

Maria Sudoł
5 Military Clinical Hospital with Polyclinic SPZOZ
Wrocławska 1-3, 30-901 Kraków
sudol.m@o2.pl
ORCID: 0009-0009-7204-3097

Martyna Piekarska
Independent Public Health Care Center
of the Ministry of Internal Affairs and Administration in Krakow
Kronikarza Galla 25, 30-053 Kraków
piekarskamartyna@hotmail.com
ORCID: 0009-0008-0698-3307

Gabriela Mierzwa
Nowodworskie Medical Center
Miodowa 2, 05-100 Nowy Dwór Mazowiecki
gabrielamierzwa0@gmail.com
ORCID: 0009-0000-5548-2316

Aleksandra Kajtel
The University Hospital in Krakow
Macieja Jakubowskiego 2, 30-688 Kraków
akajtel@gmail.com
ORCID: 0009-0004-2576-1209

Anna Skowronek
The University Hospital in Krakow
Macieja Jakubowskiego 2, 30-688 Kraków
aniasko99@gmail.com
ORCID: 0009-0005-8567-6695

Corresponding author: Katarzyna Dąbek
Country Hospital in Strzyżów, 700-lecia 1, 38-100 Strzyżów
dabekkatarzyna63@gmail.com

ABSTRACT

Introduction and Purpose

Iron deficiency in patients with heart failure is a common problem of which they are often unaware. It is associated with a worse prognosis compared to patients suffering with heart failure without iron deficiency. An important point in the diagnosis in patients with heart failure would be the determination of iron in the blood, in order to catch patients eligible for intravenous iron administration. The aim of the study was to investigate whether intravenous iron administration could affect quality of life in these patients and further reduce hospital admissions for heart failure exacerbations and deaths caused by cardiovascular events.

Material and Methods

A comprehensive literature review was conducted using the PubMed and Google Scholar database. We used the key words: 'heart failure' in combination with medical terms referring to iron status or its therapeutic use , "iron deficiency", "intravenous iron", "intravenous ferric carboxymaltose", "intravenous ferric derisomaltose" in various combinations.

Results and conclusions

Intravenous iron administration in patient with heart failure with reduced ejection fraction and iron deficiency reduces symptoms, improves quality of life, exercise tolerance and reduces hospital admissions for heart failure. It is very important to actively look for iron deficiency in patients with heart failure, and then patients who meet the criteria should be provided with an intravenous iron administration.

Keywords: heart failure, iron deficiency, intravenous ferric carboxymaltose, intravenous ferric derisomaltose

The role of iron

Iron is a crucial microelement for the body's homeostasis, cellular energy and metabolism [1]. Iron can move between two oxidative states Fe^{3+} or Fe^{2+}, that allows it to be a cofactor for different enzymes and the catalyst for biochemical reactions [2].

Iron is a component of proteins with specific cellular functions such as enzymes, transport and structural proteins, that's why iron plays a very essential role in many physiological processes: as a component of haemoglobin it ensures proper oxygen transport, as a component of myoglobin it enables oxygen storage in the body, as a component of oxidative enzymes and respiratory chain protein it is involved in energy production in the mitochondria [3]. In addition, iron is involved in the metabolism of cardiac and skeletal muscle and provides synthesis, degradation of proteins, lipids, ribonucleic acids and mitochondrial function [1].

Iron is also used for optimal haematopoiesis and is important in maintaining cellular energy and metabolism of cells with high mitogenic potential like hematopoietic or immune cells and high energy requirements like hepatocytes, adipocytes, bone and cardiac myocytes or kidney cells [4].

The presence of iron deficiency can have multiple clinical consequences. In addition to its direct effect on erythropoiesis, it can also lead to complications related to oxidative metabolism, cellular energetics, and immune mechanisms [4]. Since cardiac myocytes are particularly sensitive to depletion of iron stores, abnormal myocardial and skeletal muscle energy production and utilization contribute to the pathophysiology of heart failure [5].

Table 1.The importance of iron to the body (based on [5]).

Results of iron deficiency		
-Mitochondrial dysfunction - Deranged activity of enzymes -Apoptosis	Abnormal heart remodelling	- Impaired exercise capasity - Increased morbidity and mortality

Heart failure

Heart failure (HF) is a disease entity with diverse etiology and pathogenesis that is a main cause of morbidity and mortality in adults worldwide [6]. The disorder is caused by structural or functional impairment of ventricular filling or ejection of blood [7]. Currently, patients with heart failure are most commonly classified as suffering from:

- heart failure with reduced ejection fraction (HFrEF): left ventricular ejection fraction (LVEF) <40%,
- heart failure with mildly reduced ejection fraction (HFmrEF): LVEF 40-49%
- heart failure with preserved ejection fraction (HFpEF): LVEF ≥50% [8].

Acute or chronic heart failure is a major cause of recurrent hospitalizations and early readmissions, accounting for particularly high morbidity and costs. Patients have a lower quality of life and their survival is severely compromised [9].

ESC guidelines for the management of HF emphasize the need to address risk factors and comorbidities that exacerbate HF symptoms and adversely affect prognosis [10]. Among the relevant risk factors, the current guidelines highlight anaemia and iron deficiency, which also worsens the prognosis of patients with HF independently of anaemia comorbidities [11].

Anaemia versus iron deficiency

According to the World Health Organization (WHO), anaemia is defined as hemoglobin concentration of less than 12.0 g/dl in women and 13.0 g/dl in men (table 2) [12,13].

In different studies, we can see large discrepancies in the prevalence of anaemia in patients with HF (the range includes 5-70%), it depends on the definition of anaemia used and the clinical characteristics of the patients included in the study. Anaemia increases in proportion to age, severity of heart failure and comorbidities, in addition, it more often affects the female sex [6].

Table 2. Definitions of anaemia (according to the World Health Organization) and iron deficiency in patients with heart failure (based on [12,6]).

Anaemia
Peripheral blood haemoglobin concentration: <12.0 g/dl in women <13.0 g/dl in men Iron deficiency: Ferritin concentration <100 μg/l or 100-299 μg/l with Tsat < 20%.

Tsat - transferrin saturation

Iron deficiency can occur independently of the presence of anaemia or lead to its development [14]. Iron deficiency with or without anaemia is associated with poorer quality of life, reduced aerobic capacity and exercise intolerance, and a worse prognosis [15].
A multicenter study of a population of patients with HF showed the prevalence of iron deficiency in 58% of patients, meanwhile, anaemia was diagnosed in only 35% of patients [16]. Iron deficiency, independent of anemia, has been shown to be associated with increased mortality, hospitalization and early readmission. Interestingly, patients with isolated iron deficiency had a worse prognosis compared to those with anaemia and no iron deficiency [9].

The trials on intravenous iron supplementation in heart failure

Iron is an essential nutrient; as a cofactor, it is involved in many important cellular functions [1]. Patients with HFrEF are particularly susceptible to iron deficiency, which is associated in them with reduced exercise capacity, lower quality of life (QoL) and worse prognosis, regardless of the presence of anaemia [17].

This issue has led to trials of intravenous iron supplementation in heart failure patients who meet criteria for iron deficiency. CONFIRM-HF, AFFIRM-AHF, IRONMAN and FAIR-HF are multicentres, randomized, placebo-controlled trials that have demonstrated symptomatic benefit after the inclusion of intravenous (i.v.) iron treatment in patients with heart failure with reduced ejection fraction and iron deficiency (table 3).

CONFIRM-HF involved 304 patients. They were treated on an outpatient basis. Patients suffered from symptomatic heart failure with left ventricular ejection fraction ≤45%, iron deficiency (ferritin <100ng/ml or 100-300ng/ml with transferrin saturation <20%, haemoglobin (Hb) <15 g/dl) and elevated natriuretic peptide levels. Participants were randomly assigned (1:1) to receive treatment with i.v. iron, as ferric carboxymaltose (FCM) or placebo as saline for 52 weeks. The change in distance in the 6-minute walk test (6MWT) by 24 week was the primary endpoint. In the secondary endpoints researchers assessed changes in New York Heart Association (NYHA) class, Patient Global Assessment (PGA), 6MWT distance, health-related quality of life (QoL), Fatique Score at weeks 6,12, 24, 36 and 52, and the effect of FCM on the rate of hospitalization for worsening HF. The results showed a reduction in the risk of hospitalization for heart failure exacerbation. Additionally NYHA class, PGA, QoL and Fatigue Score improved in patients, who were treated with FCM [18].

AFFIRM-AHF involved 1108 patients, who were hospitalized for acute heart failure with left ventricular ejection fraction <50% and iron deficiency (ferritin <100 μg/L or 100-299 μg/L with transferrin saturation <20%). Participants were randomly assigned (1:1) to receive treatment with intravenous iron in the form of iron carboxymaltose or saline as placebo for 24 weeks. The

composite number of hospitalizations for heart failure and death from cardiovascular causes through week 52 was the primary endpoint. In results, the risk of hospitalization for heart failure decreased, with no clear effect on the risk of cardiovascular death [19].

IRONMAN involved 1137 patients, who were treated on an outpatient basis. Patients suffered from heart failure with left ventricular ejection fraction ≤45% in the previous 24 months and iron deficiency (ferritin <100 μg/L or transferrin saturation <20%). Participants were randomly assigned (1:1) to receive intravenous ferric derisomaltose or saline as placebo. A mean follow-up lasted 2.7 years (IQR 1.8-3.6). The primary endpoint was recurrent hospital admissions for heart failure and death from cardiovascular causes. Researchers found that ferric derisomaltose administration was associated with a lower risk of hospitalization for heart failure and death from cardiovascular causes [20].

The FAIR-HF trial enrolled 459 patients with a left ventricular ejection fraction ≤40% in patients with NYHA class II or ≤45% in patients with NYHA class III and iron deficiency (ferritin <100 μg/L or ferritin 100-299 μg/L if transferrin saturation <20%) and a haemoglobin level was 95-135 g/L. Patients were randomly allocated (2:1) to receive intravenous iron carboxymaltose or placebo as saline. Patient self-assessment of global assessment and NYHA functional class were the primary endpoints, both at week 24. Researchers found that intravenous iron carboxymaltose treatment in patients with chronic heart failure and iron deficiency, with or without anaemia, improved symptoms, functional capacity and quality of life [21].

Table 3. The comparison of trials over intravenous iron treatment.

	CONFRIM-HF	AFFIRM-AHF	IRONMAN	FAIR-HF
Patient population	Ambulatory, symptomatic HF, LVEF ≤45%, NYHA II/III, F<100 or Tsat<20 + F100-300, Hb<15	Hospitalized HF, LVEF<50%, NT-proBNP↑, Hb 8–15, *F* < 100 or *Tsat* < 20% + F 100–299	Hospitalized HF or ambulatory HF with NT-proBNP↑/ BNP↑, LVEF≤45%, Tsat<20 or F<100	LVEF ≤45%, NYHA II-III, F<100 or Tsat<20 + F100-299, Hb 9.5-13.5
Number of patients, (FAS)	304	1108	1137	459

Randomisation (i.v. iron:control)	(1:1)	(1:1)	(1:1)	(2:1)
Comparator	ferric carboxymaltose vs placebo	ferric carboxymaltose vs placebo	ferric derisomaltose vs placebo	ferric carboxymaltose vs placebo
Double-blind	Yes	Yes	Yes	Yes
Study duration	52 weeks	52 weeks	Median follow-up 2,7 years (IQR 1,8–3,6)	24 weeks
Primary endpoint(s)	Change in 6MWT from baseline to 24 week	Composite of total hospitalisations for heart failure and cardiovascular death up to 52 weeks	Recurrent hospital admissions for heart failure and cardiovascular death	The self-reported PGA and NYHA functional class, both at 24 week

6MWT, 6-minute walk test; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro b-type natriuretic peptide; HF, heart failure; PGA, patient global assessment; NYHA, New York Association; Hb, haemoglobin (g/dl); FAS, full analysis set; LVEF, left ventricular ejection fraction; Tsat, transferrin saturation; F, ferritin (ng/ml)

Oral iron treatment as an alternative method

IRONOUT HF was designed to test whether, oral iron supplementation in patients who suffer from heart failure with iron deficiency improves exercise capacity after 16 weeks of therapy. The trial included 225 patients with HFrEF (<40%) and iron deficiency (ferritin 15-100 ng/ml or ferritin 101-299 ng/ml if transferrin saturation <20%). Participants were randomly allocated (1:1) to oral iron polysaccharide or placebo for 16 weeks. A change in peak oxygen uptake (VO2) during 16 weeks was the primary endpoint. In the result it was found that high-dose oral iron did not improve exercise capacity over 16 weeks in patients with HFrEF with iron deficiency [22].

Conclusions

Iron deficiency is common in patients with heart failure and indicates a poorer prognosis [23]. Based on the findings of the presented trials, intravenous iron supply in heart failure patients with reduced ejection fraction and iron deficiency reduces symptoms, improves quality of life

and exercise tolerance, which has not been demonstrated with oral iron therapy [22,24]. The totality of evidence suggests that intravenous iron administration reduces hospital admissions for heart failure [20]. However, there are still uncertain results showing a reduction in cardiovascular mortality [25]. The consistency of findings suggests that intravenous iron therapy has an overall benefit in a broad group of patients with iron-deficient heart failure, which may be independent of the type of intravenous iron complex used [20].

DISCLOSURE

Author`s contribution:

Conceptualization: Katarzyna Dąbek, Michał Ochwat
Methodology: Katarzyna Dąbek, Martyna Piekarska
Software: Michał Ochwat, Aleksandra Kajtel
Check: Anna Skowronek, Gabriela Mierzwa
Formal analysis: Maria Sudoł, Martyna Piekarska
Investigation: Katarzyna Dąbek, Michał Ochwat
Resources: Maria Sudoł, Gabriela Mierzwa
Data curation: Anna Skowronek, Aleksandra Kajtel
Writing -rough preparation: Katarzyna Dąbek, Michał Ochwat, Maria Sudoł
Writing -review and editing: Anna Skowronek, Aleksandra Kajtel
Visualization: Martyna Piekarska
Supervision: Gabriela Mierzwa, Anna Skowronek
Project administration: Katarzyna Dąbek

All authors have read and agreed with the published version of the manuscript.

Funding Statement:

The study did not receive special funding.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Conflict of Interest Statement:

The authors declare no conflicts of interest.

Acknowledgements:

Not applicable

References:

1. Cairo G, Bernuzzi F, Recalcati S. A precious metal: Iron, an essential nutrient for all cells. *Genes Nutr*. 2006;1(1):25-39. doi:10.1007/BF02829934
2. Anderson GJ, Vulpe CD. Mammalian iron transport. *Cell Mol Life Sci*. 2009;66(20):3241-3261. doi:10.1007/s00018-009-0051-1
3. Núñez J, Comín-Colet J, Miñana G, et al. Iron deficiency and risk of early readmission following a hospitalization for acute heart failure [published correction appears in Eur J Heart Fail. 2022 Mar;24(3):591. doi: 10.1002/ejhf.2396]. *Eur J Heart Fail*. 2016;18(7):798-802. doi:10.1002/ejhf.513
4. Jankowska EA, Rozentryt P, Witkowska A, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure [published correction appears in Eur Heart J. 2011 May;32(9):1054]. *Eur Heart J*. 2010;31(15):1872-1880. doi:10.1093/eurheartj/ehq158
5. Jankowska EA, von Haehling S, Anker SD, Macdougall IC, Ponikowski P. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. *Eur Heart J*. 2013;34(11):816-829. doi:10.1093/eurheartj/ehs224

6. Tymińska A, Sypień P, Ozierański K, Opolski G. Anemia and iron deficiency in patients with heart failure — diagnostic and therapeutic management. Folia Cardiologica. 2017 September, 12(4), 422 – 430. doi: 10.5603/FC.2017.0077
7. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation. 2022 May 3;145(18):e1033. doi: 10.1161/CIR.0000000000001073] [published correction appears in Circulation. 2022 Sep 27;146(13):e185. doi: 10.1161/CIR.0000000000001097] [published correction appears in Circulation. 2023 Apr 4;147(14):e674. doi: 10.1161/CIR.0000000000001142]. *Circulation*. 2022;145(18):e895-e1032. doi:10.1161/CIR.0000000000001063
8. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail*. 2020;22(8):1342-1356. doi:10.1002/ejhf.1858
9. Rocha BML, Cunha GJL, Menezes Falcão LF. The Burden of Iron Deficiency in Heart Failure: Therapeutic Approach. *J Am Coll Cardiol*. 2018;71(7):782-793. doi:10.1016/j.jacc.2017.12.027
10. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [published correction appears in Eur Heart J. 2021 Dec 21;42(48):4901. doi: 10.1093/eurheartj/ehab670]. *Eur Heart J*. 2021;42(36):3599-3726. doi:10.1093/eurheartj/ehab368
11. Skotnicka J, Błaszczak K, Witkowska M, Turek M, Witkowski M, Ślósarz T, Krupa P, Kaczorowski R, Forenc T, Wojciechowska K. Changes in the Treatment and Prevention of Heart Failure Based on the 2023 Focused Update of the 2021 European Society of Cardiology Guidelines. *Quality in Sport*. 24, (Oct. 2024), 54787. DOI:https://doi.org/10.12775/QS.2024.24.54787.
12. Nutritional anaemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser*. 1968;405:5-37.
13. Masini G, Graham FJ, Pellicori P, et al. Criteria for Iron Deficiency in Patients With Heart Failure. *J Am Coll Cardiol*. 2022;79(4):341-351. doi:10.1016/j.jacc.2021.11.039
14. Cohen-Solal A, Leclercq C, Deray G, et al. Iron deficiency: an emerging therapeutic target in heart failure. *Heart*. 2014;100(18):1414-1420. doi:10.1136/heartjnl-2014-305669

15. Klip IT, Comin-Colet J, Voors AA, et al. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J*. 2013;165(4):575-582.e3. doi:10.1016/j.ahj.2013.01.017
16. Enjuanes C, Klip IT, Bruguera J, et al. Iron deficiency and health-related quality of life in chronic heart failure: results from a multicenter European study. *Int J Cardiol*. 2014;174(2):268-275. doi:10.1016/j.ijcard.2014.03.169
17. Anker SD, Kirwan BA, van Veldhuisen DJ, et al. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. *Eur J Heart Fail*. 2018;20(1):125-133. doi:10.1002/ejhf.823
18. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†. *Eur Heart J*. 2015;36(11):657-668. doi:10.1093/eurheartj/ehu385
19. Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial [published correction appears in Lancet. 2021 Nov 27;398(10315):1964. doi: 10.1016/S0140-6736(21)02492-2]. *Lancet*. 2020;396(10266):1895-1904. doi:10.1016/S0140-6736(20)32339-4
20. Kalra PR, Cleland JGF, Petrie MC, et al. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. *Lancet*. 2022;400(10369):2199-2209. doi:10.1016/S0140-6736(22)02083-9
21. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009;361(25):2436-2448. doi:10.1056/NEJMoa0908355
22. Lewis GD, Malhotra R, Hernandez AF, et al. Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency: The IRONOUT HF Randomized Clinical Trial [published correction appears in JAMA. 2017 Jun 20;317(23):2453. doi: 10.1001/jama.2017.7019]. *JAMA*. 2017;317(19):1958-1966. doi:10.1001/jama.2017.5427
23. Jankowska EA, Kasztura M, Sokolski M, et al. Iron deficiency defined as depleted iron stores accompanied by unmet cellular iron requirements identifies patients at

the highest risk of death after an episode of acute heart failure. *Eur Heart J*. 2014;35(36):2468-2476. doi:10.1093/eurheartj/ehu235

24. Sawicki KT, Ardehali H. Intravenous Iron Therapy in Heart Failure With Reduced Ejection Fraction: Tackling the Deficiency. *Circulation*. 2021;144(4):253-255. doi:10.1161/CIRCULATIONAHA.121.054271
25. Graham FJ, Pellicori P, Ford I, Petrie MC, Kalra PR, Cleland JGF. Intravenous iron for heart failure with evidence of iron deficiency: a meta-analysis of randomised trials. *Clin Res Cardiol*. 2021;110(8):1299-1307. doi:10.1007/s00392-021-01837-8