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Iron deficiency, heart failure and cerebrovascular events: what is the connection?

Niedobór żelaza, niewydolność serca, incydenty mózgowo-naczyniowe — jaki jest związek?

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Abstract

Heart failure (HF) is the leading cause of hospitalization among patients aged 65 years and older. One of the most common comorbidities in HF is iron deficiency (ID), being present in about 50% of all HF patients. ID in HF has been shown to reduce exercise capacity, increase the risk of cerebrovascular events, and increase patient morbidity and mortality. The association between heart failure with reduced ejection fraction (HFrEF) and ID has already been proven to lead to an increased risk of cardiovascular events, and some research is establishing a similar relation between heart failure with preserved ejection fraction (HFpEF) and ID. ID can lead to hypercoagulability, which in HF may be associated with an increased risk of stroke/TIA (transient ischemic attack).

Although current HF treatment guidelines recognize ID as a significant problem, ID is still rarely recognized and undertreated.

Key words: iron deficiency, heart failure, stroke, transient ischemic attack, cerebrovascular events

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Introduction

Iron deficiency (ID) is currently one of the most prominent nutrient deficiencies worldwide [1]. There are many possible causes of ID, such as increased demand and loss of iron, decreased absorption and inadequate dietary intake, and impaired iron release [2, 3]. According to current ESC guidelines, ID in HF patients is defined as either a serum ferritin concentration < 100 µg/mL or as 100–299 µg/mL with transferrin saturation (TSAT) < 20% [4].

However, ID still continues to be undertreated and underdiagnosed in the clinical setting [5]. Concurrent ID and HF can have profound negative effects on the patient's condition leading to a decreased exercise capacity and quality of life (QoL), higher morbidity, and mortality [4, 6, 7]. ID may also cause a wide range of hematological complications within patients, such as predisposing the patient to thromboembolic events [8].

The aim of this paper is to emphasize connections made through the most current literature on the issue of cerebrovascular events connected with ID in HF patients and to indicate the most needed directions of further research.

Iron deficiency

Iron is an essential mineral for the body and is vital for a multitude of different functions, such as oxygen transport, metabolism and storage, cardiac and skeletal

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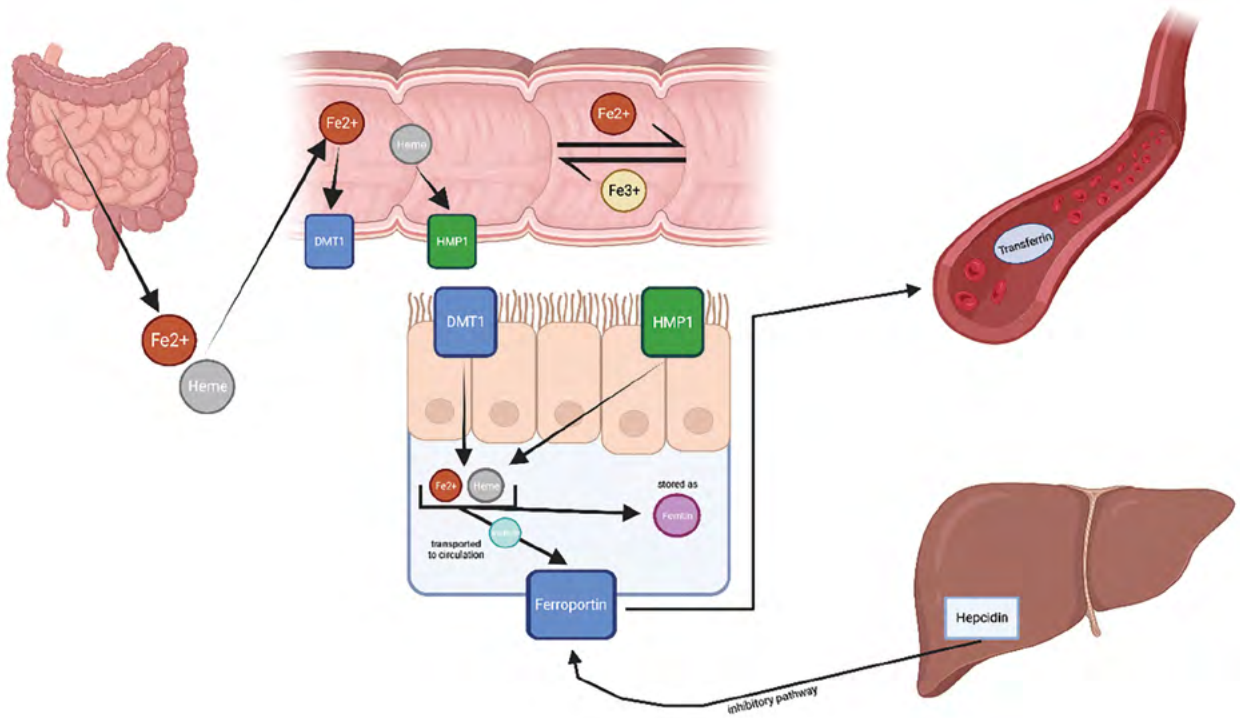

Figure 1. Iron metabolism in the body; DMT1 — divalent-metal-transporter-1; Fe2+ — ferrous iron form; Fe 3+ — ferric iron form; HMP1 — heme-carrier-protein-1

muscle metabolism, erythropoiesis, mitochondrial preservation and function, a cofactor for various enzymes or cellular metabolism [5, 7, 9]. Iron exists either in the ferrous form (Fe^{2+}), during absorption in the small intestine, or bound intracellularly to ferritin or as the ferric form (Fe^{3+}) coupled to the transport protein transferrin during circulation [5].

Iron homeostasis is solely regulated by absorption, as no means of iron excretion exists [9]. In the physiological state, only about 5–10% of the dietary iron is absorbed.

Iron absorption, taking place mainly in the duodenum and upper jejunum [5], can occur in three pathways according to the chemical form of iron present. Those pathways are shown in Figure 1. Free ferrous ions are absorbed *via* the divalent-metal-transporter-1 pathway, whereas heme-bound iron is absorbed *via* the heme-carrier-protein-1 pathway. In the enterocyte, iron can be stored bounded by ferritin or it can be transported directly to the basolateral side by mobilferrin to release iron to the circulation *via* the intramembranous channel ferroportin. Hepcidin, produced in the liver, is the main regulator of iron absorption as it binds to ferroportin to decrease its expression as well as by inhibiting the mobilization of stored iron in macrophages of the reticuloendothelial system [10].

Iron deficiency anemia (IDA) is a consequence of prolonged ID where the ID is severe enough to reduce erythropoiesis in the bone marrow [11]. The prevalence of iron deficiency has been extensively studied and well summarized by Savarese et al. [12], about one in every two persons with HF has ID. It seems that regardless of anemia, ID is present in about 50% of patients with HF [12]. On the contrary, ID and anemia in HF coexist rarely [13]. Moreover, anemia does not influence mitochondrial functions, and its treatment relieved HF symptoms, but at the same time increased thromboembolic events' risk [13]. IDA leads to structural and functional alterations in tissues with a high mitotic index and oxygen demand, such as neoplastic, immune and cardiac cells, which are especially sensitive to anemia [5]. It has a significant impact on HF pathology and is an established predictor of a worse prognosis [10]. Previous studies have shown accelerated left ventricular (LV) remodeling, mitochondrial damage, and low iron content in cardiomyocytes in HF patients, possibly explaining reduced peak oxygen consumption and LV dysfunction associated with HF [7]. Furthermore, skeletal muscle dysfunction can ultimately lead to inspiratory muscle weakness, dramatically lowering the QoL of HF patients [5]. Impaired exercise capacity is the result of crucial patient characteristics and multisystem dysfunction, including aging, impaired pulmonary reserve, peripheral and respiratory skeletal muscle dysfunction as well as ID [14, 15].

Despite the significant prevalence of ID in HF, the etiology is often unrecognized [3]. The main suggested mechanisms include reduced iron intake and absorption,

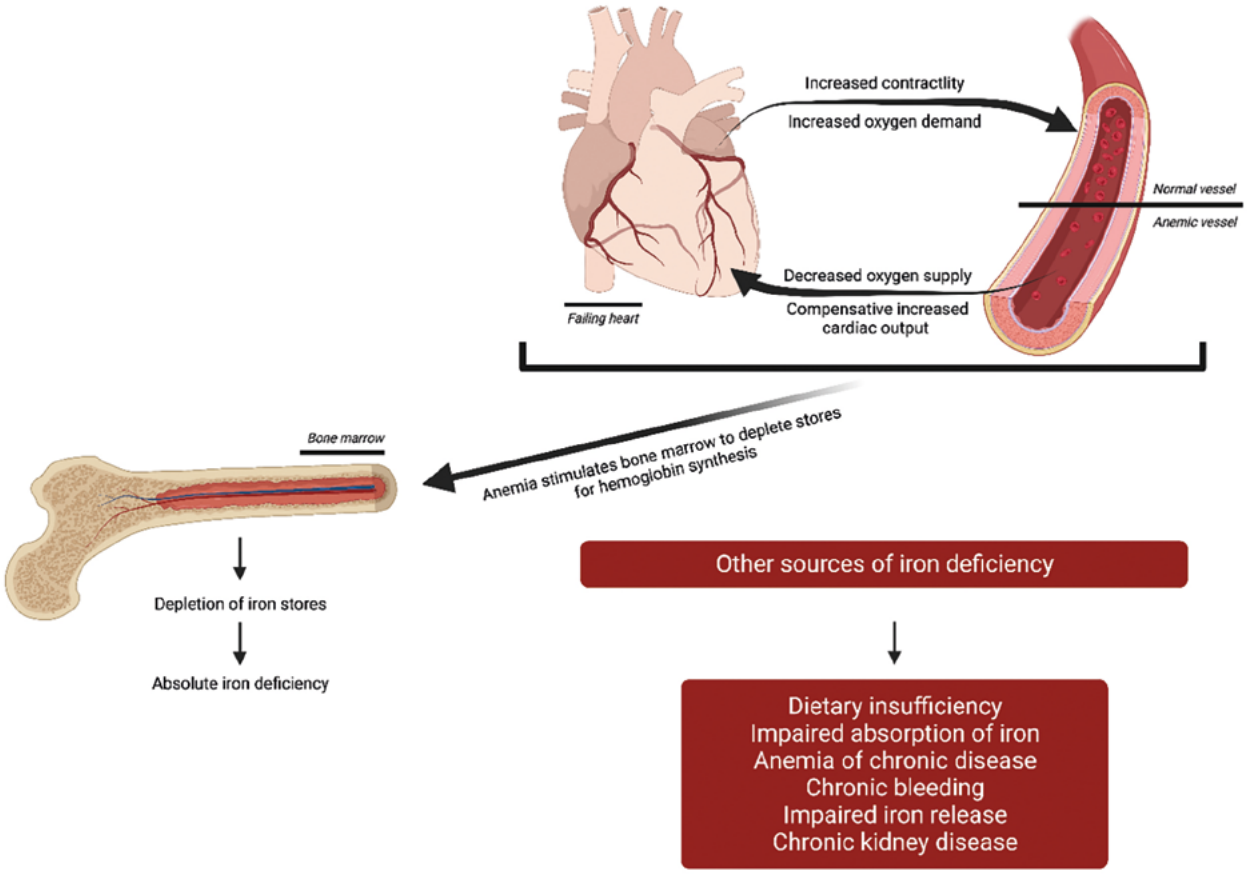

Figure 2. Iron deficiency etiology in heart failure

increased iron loss, and impaired iron release [2]. The summary of the possible etiologies of ID in HF is seen in Figure 2.

Reduced iron intake

Iron requirements and thus recommended iron intake depend mainly on sex, age and pregnancy status. In a large international HF cohort, Van Der Wal et al. [3] showed that a poor nutritional status with low serum albumin level might bean etiological pathway for ID in HF. As iron intake was not studied itself, and the underlying reason for the poor nutritional status is not clear yet, further studies need to be done. A cross-sectional study from Christina Andreae [16] identified a significant prevalence of loss of appetite with a high risk of weight loss in patients with HF. It needs to be emphasized that increasing the intake of iron such as in oral iron therapy is not effective and due to excessive polypharmacy and possible side effects is not recommended [5].

Reduced iron absorption

Venous congestion leads to gastrointestinal wall edema, which might reduce the absorption of nutrients such as iron [3]. Other factors like concomitant diseases such as inflammatory bowel disease or the high prevalence of proton pump inhibitor usage in HF patients, might also play an etiological role in ID in HF [3]. Furthermore, recent studies showed that hepcidin levels are decreased in HF patients, suggesting that the iron concentration is a dominating factor over the inflammatory state to determine the rate of hepcidin synthesis [3, 5, 10]. In conclusion, ID is more likely caused by an absolute decrease in iron availability than by a metabolic mechanism induced by a chronic inflammatory state [5].

Increased iron loss

Increased iron loss is another factor that contributes ID in HF. Firstly, as a recent study by Meijers et al. [17] identified HF as a novel risk for incident cancer, blood loss, and as a consequence, iron loss in HF might therefore be due to malignancies or gastrointestinal diseases such as gastritis or peptic ulcers [2]. Secondly, patients with ID have a higher prevalence of antiplatelet use [3]. Thus, iron loss in these patients might be due to an increased tendency for bleeding.

Table 1. A review of current literature regarding heart failure and iron deficiency and its correlation with cerebrovascular events

Author	Year	Type of study	N	Results/conclusions
Gillum et al. [24]	1995	Follow-up of a national cohort	5033	There is a significant U-shaped association of transferrin saturation with risk of incident stroke
Dubyk et al. [26]	2012	Prospective, cohort	94	IDA as a risk factor in elderly patients at hospital admission for TIA or first stroke
Shovlin et al. [27]	2014	Prospective, cohort	497	Iron deficient patients with pulmonary malformations at a higher risk of ischemic stroke
Potaczek et al. [28]	2016	Prospective, cohort	229	ID may represent a riskfactor for thrombosis recurrence
Adelborg et al. [19]	2017	General population cohort	1 446 765	HF is an important risk factor for all types of stroke.
Gill et al. [29]	2018	Mendelian randomized	48 972	Higher iron status is associated with increased stroke risk
Tang et al. [30]	2020	Prospective, cohort	795	ID and CC are risk factors for thromboembolic diseases
Szulc-Bagrowska et al. [31]	2022	Retrospective, observational	150	ID in HF is associated with ahigher risk of stroke/TIA
Doehner et al. [32]	2022	Prospective, observational	746	ID and anemia significantly lower functional capacity after acute stroke

CC — contraceptives; ID — iron deficiency; IDA — iron deficiency anemia; HF — heart failure; TIA — transient ischemic attack

All in all, the etiology of ID in HF is highly complex, multifactorial, and not well understood. Further research on the etiopathogenesis of ID in HF needs to be conducted to establish recognized causal factors which can help in finding sufficient treatment of ID in HF, as a predictor of a worse prognosis [7].

Stroke and ID in heart failure

The etiology of HF varies depending on the phenotype. HFrEF results as a consequence of the necrosis of cardiomyocytes, due to myocardial ischemia, myocarditis, or cardiotoxins, and it has the predisposition to affect males more [18]. HFpEF occurs most often in patients suffering non-cardiac comorbidities such as hypertension, pulmonary disease, diabetes mellitus, sleep apnea or obesity and it has the predisposition to affect females more often [18]. It is known that HF, even in its earliest stage, is a risk factor for stroke [19, 20]. Among stroke patients, 9% had HF as the cause of the event [20]. Furthermore, 10–24% of stroke patients also have HF [20]. The Framingham Heart Study emphasized that patients with HF are two to 3 times more likely to suffer from a stroke than those without HF [21]. On the other hand, one of the pathomechanisms of HF is chronic inflammation which may either be a consequence of HF or it may precede and be one of the causative factors which led to HF. In consequence, chronic inflammation leads to hypercoagulability. Finally, endothelial damage is also responsible for the pathogenesis of HF, which may be caused by various different vasculopathies [20, 21]. The above-mentioned factors form the Virchow's Triad, which are at the same time the most important elements for the formation of thrombosis [22]. That makes HF a disease of a higher risk of thromboembolism forming.

Aside from the already proven fact that ID in HF patients leads to a decreased QoL and exercise tolerance, as well as to increased patient mortality and morbidity [4], it should also be The combination of both these diseases may prove deleterious consequences in patients ultimately leading to an increased probability of stroke occurring. Kandinata et al. [23] presented a case of a 34-year-old patient with ID who suffered from a stroke. It implies that ID may be a great predictive value for stroke, and even greater if it is combined with comorbidities. Gillum et al. proved there may be a U-shaped connection between iron status and the risk of stroke [24]. However, the data on iron status and its influence on stroke prevalence is limited and conflicting, there is a need to conduct further research on the prognostic significance and treatment ID in patients with cerebrovascular events [12]. Current trends indicate thepossible use of hematologic parameters such as ID as biomarkers in HF [25].

Table 1 presents selected studies regarding HF and ID and their correlation with cerebrovascular events.

Significance and solutions — IRONMAN study

The only efficacious and recommended treatment for reversing ID is intravenous (IV) ferric carboxymaltose. However, the approved treatment of ID in the setting of left ventricle ejection fraction < 50%, there is currently no approved treatment for ID in the setting of HFpEF [4]. To our knowledge, IRONMAN was the first large clinical trial that investigated

Table 2. A comparison of selected clinical trials regarding intravenous iron administration in HF patients

	FAIR-HF [36]	CONFIRM-HF [37]	EFFECT-HF [38]	AFFIRM-HF [34]	IRONMAN [33]
Type of study	Prospective, randomized, multicenter	Prospective, randomized, multicenter	Prospective, randomized, open-label, SoC-controlled	Prospective, randomized, multicenter	Prospective, randomized, open-label, SoC-controlled
N	FCM: 305 Placebo: 154	FCM: 152 Placebo: 152	FCM: 88 SoC: 86	FCM: 559 Placebo: 551	FDI: 569 SoC: 568
Study population	Chronic HF NYHA class II (LVEF ≤ 40%) or III (LVEF ≤ 45%) with ID	Chronic HF NYHA class II/III (LVEF ≤ 45%) BNP > 100 pg/mL and/or NT-proBNP > 400 pg/mL with ID	Chronic HF NYHA class II/III (LVEF ≤ 45%) BNP > 100 pg/mL and/or NT-proBNP > 400 pg/mL with ID Peak VO_2 10–20 mL/kg/min	Acute HF Hospitalized for acute HF, treated with at least 40 mg furosemide (or equivalent) LVEF < 50% with ID	Chronic HF NYHA II–IV and recent HF hospitalization or elevated NPs (LVEF ≤ 45%) Ferritin < 100 µg/L or TSAT < 20%
Primary endpoint result	Improvement in self-reported PGA (50% for FCM vs. 28% placebo; OR 2.51; 95% CI: 1.75–3.61; p < 0.001) and NYHA class I/II at 24 week (47% vs. 30%; OR 2.40; 95% CI: 1.55–3.71; p < 0.001)	Change in 6WMT distance from baseline to week 24 for FCM vs. placebo — both LS means ± SE (18 ± 8 meters vs. 16 ± 8 meters; difference FCM vs. placebo: 33 ± 11 meters; p = 0.002)	Change from baseline in peak VO_2 at week 24 for FCM vs. control (SoC) — LS mean ± SE (−0.16 ± 0.387 vs. −1.19 ± 0.389 mL/min/kg; p = 0.020) Sensitivity analysis in which missing data were not imputed for FCM vs. control: (−0.16 ± 0.37 vs. −0.63 ± 0.38 mL/min/kg; p = 0.23)	Composite of total HF hospitalizations and CV deaths up to 52 weeks after randomization for FCM vs. placebo (293 primary events [57.2 per 100 patient-years] vs. 372 [72.5 per 100 patient-years] RR 0.79; 95% CI: 0.62–1.01; p = 0.059) (Pre-COVID-19 sensitivity analysis: 274 primary events [55.2 per 100 patient-years] vs. 363 [73.5 per 100 patient-years] RR 0.75; 95% CI: 0.59–0.96; p = 0.024)	Composite of CV deaths and hospitalizations for HF for FDI vs. SoC: (336 primary events [22.4 per 100 patient-years] vs. 411 [27.5 per 100 patient-years] RR 0.82; 95% CI: 0.66–1.02; p = 0.070)
Secondary endpoint result	Improvement (p < 0.001) with FCM vs. placebo in: • Self-reported PGA at weeks 4 and 12 • 6 MWT distance at weeks 4, 12, and 24 • QoL (EQ-5D visual assessment) at weeks 4, 12, and 24 • Overall KCCQ score at weeks 4, 12, and 24	Improvements with FCM vs. placebo in: • PGA at week 12 (p = 0.035) week 24 (p = 0.047), weeks 36 and 52 (both p < 0.001) • NYHA class at week 24 (p = 0.004) and weeks 36 and 52 (both p < 0.001) • 6 MWT difference in changes at week 36 (42 meters with 95% CI of 21–62; p < 0.001) and week 52 (36 meters with 95% CI of 16–57; p < 0.001) • Fatigue score at week 12 (p = 0.009), week 24 (p = 0.002), week 36 (p < 0.001), and week 52 (p = 0.002)	• Improvements with FCM vs. control in: • NYHA class at weeks 6, 12 and 24 (with imputation; all p < 0.05) • PGA at weeks 12 and 24 (with imputation; p < 0.05)	Total CV hospitalizations and CV deaths with FCM vs. placebo: • 370 vs. 451 (RR 0.80; 95% CI: 0.64–1.00; p = 0.050) CV deaths • 77 (14%) vs. 78 (14%) (HR 0.96; 95% CI: 0.70–1.32; p = 0.81) lower number HF hospitalizations • 217 vs. 294 (RR 0.74; 95% CI: 0.58–0.94; p = 0.013) treatment for time to first hospitalization or CV death — 181 (32%) vs. 209 (38%) (HR 0.80; 95% CI: 0.66–0.98; p = 0.030)	Composite of CV deaths or hospital admission for HF, stroke or MI with FDI vs. placebo: 209 vs. 246 (RR 0.83; 95% CI: 0.69–1.00; p = 0.045)

6 MWT — 6-min walking test; AFFIRM-AHF — Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency; BNP — brain natriuretic peptide; CONFIRM-HF — Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure; CI — confidence interval; CV — cardiovascular; EFFECT-HF — Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure; EQ-5D — EuroQol-5 Dimension; FAIR-HF — Ferinject Assessment in patients with IRon deficiency and chronic Heart Failure; FCM — ferric carboxymaltose; FDI — ferric derisomaltose; HF — heart failure; HR — hazard ratio; ID — iron deficiency; IRONMAN — Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK; KCCQ — Kansas City Cardiomyopathy Questionnaire; LS — least squares; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NYHA — New York Heart Association; PGA — patient global assessment; OR — odds ratio; QoL — quality of life; RR — rate ratio; SE — standard error; SoC — standard of care; TSAT — transferrin saturation

the long-term effect of IV ferric derisomaltose (FDI) administration on cardiovascular (CV) outcomes, including recurrent hospitalizations for HF [33]. 1137 patients were randomized, 569 received IV FDI treatment and 568 usual care. The primary endpoint, which included a composite of CV deaths and hospitalizations for HF occurred for FDI treatment vs. standard of care: (336 primary events [22.4 per 100 patient-years] vs. 411 [27.5 per 100 patient-years] RR [rate ratio] 0.82; 95% CI [confidence interval]: 0.66–1.02; p = 0.070) [33], what was on the borderline of statistical significance, such as in AFFIRM trial [34]. IRONMAN study proved that IV administration of iron reduced the combined secondary endpoint (CV death, hospital admissions for stroke, HF, and myocardial infarction) (HR = 0.82; 95% CI: 0.69–1.00; p = 0.045) [33]. The recommended COVID-19 analysis showed consistent results (HR = 0.78; 95% CI: 0.62–0.98; p = 0.030 respectively) [33]. To our knowledge, previous studies of ID in HF did not include stroke hospitalization as endpoint, which needs to be strongly emphasized [33]. Subsequently, important differences between IRONMAN and another clinical trial regarding ID, for instance, AFFIRM-AHF, are worth noticing [34]. Firstly, the follow-up was longer in IRONMAN (median follow-up 2.7 years [IQR 1.8–3.6]) than in AFFIRM-AHF, in which IV iron treatment was finalized after 24 weeks [33, 34]. Hence, IRONMAN study confirmed the long-term safety of IV FDI, since there were no excessive serious adverse events [33]. Subsequently, there was no collection of phosphate samples in IRONMAN, since the risk of hypophosphataemia is significantly lower in FDI [35]. A comparison of selected clinical trials is shown in Table 2.

Conclusions

HF with ID may predispose the patient to a higher risk of suffering from cerebrovascular events. Numerous studies emphasize that ID in clinical practice is often unrecognized and definitely underdiagnosed even though it is in the ESC treatment guidelines for HF. Better screening for ID should be implemented to reverse this health issue. HF with ID should be recognized and promptly treated by the clinician and the risk of stroke should be assessed as ID is a positive predictive value for stroke. Finally, upcoming randomized clinical trials should focus on assessing whether IV iron administration is an effective treatment for ID in HF patients with LVEF ≥ 45%

Conflict of interest

None declared.

Streszczenie

Niewydolność serca (HF) jest główną przyczyną hospitalizacji wśród pacjentów w wieku 65 lat i starszych. Jedną z najczęstszych chorób współistniejących w HF jest niedobór żelaza (ID), występujący u około 50% wszystkich pacjentów z HF. Wykazano, że ID w HF zmniejsza wydolność wysiłkową, zwiększa ryzyko incydentów naczyniowo-mózgowych, chorobowość i śmiertelność pacjentów. Udowodniono, że związek między niewydolnością serca z obniżoną frakcją wyrzutową (HFrEF) a ID prowadzi do zwiększonego ryzyka incydentów sercowo-naczyniowych, a niektóre badania wskazują na podobny związek między niewydolnością serca z zachowaną frakcją wyrzutową (HFpEF) a ID. ID może prowadzić do nadkrzepliwości, co w HF może wiązać się ze zwiększonym ryzykiem udaru mózgu/przemijającego ataku niedokrwiennego.

Chociaż obecne wytyczne dotyczące leczenia HF uznają ID za istotny problem, jest ono nadal rzadko rozpoznawane i niedostatecznie leczone.

Słowa kluczowe: niedobór żelaza, niewydolność serca, udar mózgu, TIA, incydenty mózgowo-naczyniowe

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References

1. Micronutrients. https://www.who.int/health-topics/micronutrients (20.12.2022).
2. Kumar A, Sharma E, Marley A, et al. Iron deficiency anaemia: pathophysiology, assessment, practical management. BMJ Open Gastroenterol. 2022; 9(1): e000759, doi: 10.1136/bmjgast-2021-000759, indexed in Pubmed: 34996762.
3. van der Wal HH, Grote Beverborg N, Dickstein K, et al. Iron deficiency in worsening heart failure is associated with reduced estimated protein intake, fluid retention, inflammation, and antiplatelet use. Eur Heart J. 2019; 40(44): 3616–3625, doi: 10.1093/eurheartj/ehz680, indexed in Pubmed: 31556953.
4. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021; 42(36): 3599–3726, doi: 10.1093/eurheartj/ehab368, indexed in Pubmed: 34447992.
5. Loncar G, Obradovic D, Thiele H, et al. Iron deficiency in heart failure. ESC Heart Fail. 2021; 8(4): 2368–2379, doi: 10.1002/ehf2.13265, indexed in Pubmed: 33932115.

6. Alcaide-Aldeano A, Garay A, Alcoberro L, et al. Iron deficiency: impact on functional capacity and quality of life in heart failure with preserved ejection fraction. J Clin Med. 2020; 9(4): 1199, doi: 10.3390/jcm9041199, indexed in Pubmed: 32331365.
7. Nakano H, Nagai T, Sundaram V, et al. Impact of iron deficiency on long-term clinical outcomes of hospitalized patients with heart failure. Int J Cardiol. 2018; 261: 114–118, doi: 10.1016/j.ijcard.2018.03.039, indexed in Pubmed: 29580659.
8. Evstatiev R, Bukaty A, Jimenez K, et al. Iron deficiency alters megakaryopoiesis and platelet phenotype independent of thrombopoietin. Am J Hematol. 2014; 89(5): 524–529, doi: 10.1002/ajh.23682, indexed in Pubmed: 24464533.
9. von Haehling S, Ebner N, Evertz R, et al. Iron deficiency in heart failure: an overview. JACC Heart Fail. 2019; 7(1): 36–46, doi: 10.1016/j.jchf.2018.07.015, indexed in Pubmed: 30553903.
10. Magrì D, De Martino F, Moscucci F, et al. Anemia and iron deficiency in heart failure: clinical and prognostic role. Heart Fail Clin. 2019; 15(3): 359–369, doi: 10.1016/j.hfc.2019.02.005, indexed in Pubmed: 31079694.
11. Bermejo F, García-López S, Bermejo F, et al. A guide to diagnosis of iron deficiency and iron deficiency anemia in digestive diseases. World J Gastroenterol. 2009; 15(37): 4638–4643, doi: 10.3748/wjg.15.4638, indexed in Pubmed: 19787826.
12. Savarese G, von Haehling S, Butler J, et al. Iron deficiency and cardiovascular disease. Eur Heart J. 2023; 44(1): 14–27, doi: 10.1093/eurheartj/ehac569, indexed in Pubmed: 36282723.
13. Zhang H, Zhabyeyev P, Wang S, et al. Role of iron metabolism in heart failure: From iron deficiency to iron overload. Biochim Biophys Acta Mol Basis Dis. 2019; 1865(7): 1925–1937, doi: 10.1016/j.bbadis.2018.08.030, indexed in Pubmed: 31109456.
14. Del Buono MG, Arena R, Borlaug BA, et al. Exercise intolerance in patients with heart failure. J Am Coll Cardiol. 2019; 73(17): 2209–2225, doi: 10.1016/j.jacc.2019.01.072, indexed in Pubmed: 31047010.
15. Alnuwaysir RIS, Hoes MF, van Veldhuisen DJ, et al. Iron deficiency in heart failure: mechanisms and pathophysiology. J Clin Med. 2021; 11(1): 125, doi: 10.3390/jcm11010125, indexed in Pubmed: 35011874.
16. Andreae C, van der Wal MHL, van Veldhuisen DJ, et al. Changes in appetite during the heart failure trajectory and association with fatigue, depressive symptoms, and quality of life. J Cardiovasc Nurs. 2021; 36(6): 539–545, doi: 10.1097/JCN.0000000000000756, indexed in Pubmed: 33136703.
17. Meijers WC, Maglione M, Bakker SJL, et al. Heart failure stimulates tumor growth by circulating factors. Circulation. 2018; 138(7): 678–691, doi: 10.1161/CIRCULATIONAHA.117.030816, indexed in Pubmed: 29459363.
18. Simmonds SJ, Cuijpers I, Heymans S, et al. Cellular and molecular differences between HFpEF and HFrEF: a step ahead in an improved pathological understanding. Cells. 2020; 9(1): 242, doi: 10.3390/cells9010242, indexed in Pubmed: 31963679.
19. Adelborg K, Szépligeti S, Sundbøll J, et al. Risk of stroke in patients with heart failure: a population-based 30-year cohort study. Stroke. 2017; 48(5): 1161–1168, doi: 10.1161/STROKEAHA.116.016022, indexed in Pubmed: 28377383.
20. Kim W, Kim EJ. Heart failure as a risk factor for stroke. J Stroke. 2018; 20(1): 33–45, doi: 10.5853/jos.2017.02810, indexed in Pubmed: 29402070.
21. Mahmood SS, Levy D, Vasan RS, et al. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. Lancet. 2014; 383(9921): 999–1008, doi: 10.1016/s0140-6736(13)61752-3, indexed in Pubmed: 24084292.
22. Kushner A, West WP, Khan Suheb MZ, Pillarisetty LS. Virchow Triad. StatPearls Publishing, Treasure Island (FL) 2022.
23. Kandinata NN, Breehl L, Chhetri B, et al. Stroke secondary to iron deficiency anemia: a case report. Cureus. 2021; 13(11): e19526, doi: 10.7759/cureus.19526, indexed in Pubmed: 34804746.
24. Gillum RF, Sempos CT, Makuc DM, et al. Serum transferrin saturation, stroke incidence, and mortality in women and men. The NHANES I Epidemiologic Followup Study. National Health and Nutrition Examination Survey. Am J Epidemiol. 1996; 144(1): 59–68, doi: 10.1093/oxfordjournals.aje.a008855, indexed in Pubmed: 8659486.
25. Castiglione V, Aimo A, Vergaro G, et al. Biomarkers for the diagnosis and management of heart failure. Heart Fail Rev. 2022; 27(2): 625–643, doi: 10.1007/s10741-021-10105-w, indexed in Pubmed: 33852110.
26. Dubyk MD, Card RT, Whiting SJ, et al. Iron deficiency anemia prevalence at first stroke or transient ischemic attack. Can J Neurol Sci. 2012; 39(2): 189–195, doi: 10.1017/s0317167100013214, indexed in Pubmed: 22343152.
27. Shovlin CL, Chamali B, Santhirapala V, et al. Ischaemic strokes in patients with pulmonary arteriovenous malformations and hereditary hemorrhagic telangiectasia: associations with iron deficiency and platelets. PLoS One. 2014; 9(2): e88812, doi: 10.1371/journal.pone.0088812, indexed in Pubmed: 24586400.
28. Potaczek DP, Jankowska EA, Wypasek E, et al. Iron deficiency: a novel risk factor of recurrence in patients after unprovoked venous thromboembolism. Pol Arch Med Wewn. 2016; 126(3): 159–165, doi: 10.20452/pamw.3311, indexed in Pubmed: 26942727.
29. Gill D, Monori G, Tzoulaki I, et al. Iron status and risk of stroke. Stroke. 2018; 49(12): 2815–2821, doi: 10.1161/STROKEAHA.118.022701, indexed in Pubmed: 30571402.
30. Tang X, Fang M, Cheng R, et al. Iron-deficiency and estrogen are associated with ischemic stroke by up-regulating transferrin to induce hypercoagulability. Circ Res. 2020; 127(5): 651–663, doi: 10.1161/CIRCRESAHA.119.316453, indexed in Pubmed: 32450779.
31. Szulc-Bagrowska J, Sawościan M, Kołodziejczyk K, et al. Niedobór żelaza u pacjentów z niewydolnością serca a większa częstość udarów mózgu. Folia Cardiol. 2022; 17(5): 283–288, doi: 10.5603/fc.a2022.0031.
32. Doehner W, Scherbakov N, Schellenberg T, et al. Iron deficiency is related to low functional outcome in patients at early rehabilitation after acute stroke. J Cachexia Sarcopenia Muscle. 2022; 13(2): 1036–1044, doi: 10.1002/jcsm.12927, indexed in Pubmed: 35166066.
33. 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, indexed in Pubmed: 36347265.
34. Ponikowski P, Kirwan BA, Anker S, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. Lancet. 2020; 396(10266): 1895–1904, doi: 10.1016/s0140-6736(20)32339-4, indexed in Pubmed: 33197395.
35. Wolf M, Rubin J, Achebe M, et al. Effects of iron isomaltoside vs ferric carboxymaltose on hypophosphatemia in iron-deficiency ane-

mia: two randomized clinical trials. JAMA. 2020; 323(5): 432–443, doi: 10.1001/jama.2019.22450, indexed in Pubmed: 32016310.

36. 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, indexed in Pubmed: 19920054.
37. 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, indexed in Pubmed: 25176939.
38. van Veldhuisen DJ, Ponikowski P, van der Meer P, et al. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. Circulation. 2017; 136(15): 1374–1383, doi: 10.1161/CIRCULATIONAHA.117.027497, indexed in Pubmed: 28701470.