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Position Paper. The role of iron deficiency in patients with chronic heart failure and current corrective approaches

Keywords Chronic heart failure; iron deficiency; anemia; ferric carboxymaltosate; functional ability; ferritin; transferrin saturation

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Further to the discussions, a position paper with the following main provisions was elaborated:

1. Iron Deficiency (ID) must be regarded as an independent clinically significant concomitant condition, with the prevalence reaching 50% among Chronic Heart Failure (CHF) patients in Russia.
2. According to observation studies iron deficiency in patients with CHF adversely affects functional performance and is associated with increased hospitalization rates and mortality.
3. ID must be excluded in all CHF patients, regardless of haemoglobin levels; the severity of ID should be evaluated. Blood ferritin concentration and transferrin saturation (TSAT, transferrin saturation coefficient) are currently optimal parameters for defining ID.
4. According to current data, therapy aimed only at increasing blood haemoglobin concentrations does not seem to have advantages in influencing the prognosis and clinical manifestations of CHF, while the elimination of ID in CHF patients leads to significant clinical benefits even in the absence of anaemia.
5. According to recently available data (the results of Randomized Clinical Trials, RCTs), the intravenous use of ferric carboxymaltose should be considered the most consistent approach for the treatment of ID in CHF patients.

Introduction

Chronic heart failure (CHF) is characterised by reduced tissue oxygen and nutrient supply. There is also an activation of neural and endocrine systems and an increased level of inflammation in these patients, often associated with ID (in about 50% of patients) and anaemia (in about 40% of patients) [1, 2].

Results of relatively recent major studies aimed at eliminating either anaemia or ID, showed a significant difference between the effects of such interventions. According to current data, therapy aimed at increasing haemoglobin concentration does not seem to have advantages, while the elimination of ID leads to

significant clinical benefits, including benefits in CHF patients without anaemia.

Most clinical guidelines, including the European Society of Cardiology, the American College of Cardiology and the American Association of Cardiology guidelines, consider anaemia in CHF patients as a clinically significant concomitant disease [3]. In the treatment of anaemia in such patients the possible elimination of anaemia is the main focus, even though in many cases it is not possible to reveal a specific cause. A special role in the treatment is attributed to the identification of ID and its elimination by the intravenous administration of ferric carboxymaltose. At the same time, the European Society of Cardiology experts do not recommend the use of erythropoiesis-stimulating medicinal products in CHF patients [3].

Iron deficiency prevalence and significance in CHF patients

Patients with CHF are often diagnosed with concurrent ID, which is of great clinical importance. ID both negatively affects the intensity and quality of erythropoiesis, and also leads to a functional deterioration in tissues not related to haematopoiesis (e.g., in skeletal muscles and myocardium) where iron plays a role of a key factor in the functioning of proteins that are involved in vital cellular processes – in particular, oxygen storage (as a component of myoglobin) and oxidative energy metabolism (as a component of oxidative enzymes and proteins of the mitochondrial respiratory chain) [4, 5]. Clinical studies revealed that ID was associated with a decreased functional performance in CHF patients [6–9], decreased health-related quality of life [10, 11], as well with an increased risk of repeated hospitalizations [12] and mortality [6, 13, 14]. Furthermore, this association was observed both with and without anaemia.

Results of many international studies showed a high ID prevalence among CHF patients, reaching 37–70% [6, 13, 15–18]. The prevalence CHF in the population of Russia has not yet been adequately studied.

Current approaches to iron deficiency diagnosis in CHF patients

Blood ferritin concentration and TSAT measurement is the standard method for ID diagnosis, which is also used in large RCTs with CHF patients (in CHF patients the criteria for ID are ferritin concentration ≤100 mg/l or ferritin concentration 100 to 300 mg/l in combination with TSAT < 20%). However, it should be noted that these are not formally validated criteria. Moreover, ferritin is an acute phase protein and its concentration is dependent on various different factors.

The results of the first study [19] have recently been published, where the validity of biomarkers (ferritin concentration and TSATs) confirming ID criteria in CHF patients was assessed. In this study bone marrow iron staining was used as the «gold standard» for ID diagnosis. The sensitivity and specificity of the standard ID criterion (ferritin concentration ≤100 mg/l or ferritin concentration 100 to 300 mg/l in combination with TSAT <20%) were 82% and 72%, respectively. The sensitivity and specificity of TSAT ≤19.8%, reached 94 and 84%, respectively (p <0.05 compared to the standard criterion of ID). The sensitivity and specificity of reduced blood iron concentration to ≤13 μmol/L were 84% and 88%, respectively (p <0.05 compared to the standard criterion of ID).

It should also be noted that the meta-analysis results of clinical trials also showed no improved prognosis after using iron preparations in CHF patients with TSAT of ≥20.1%, but an improved prognosis in CHF patients with lower TSAT values was demonstrated [20].

Based on a recent systematic review, Cacoub P. et al. concluded that TSAT value to a greater extent reflects the amount of iron available for bone marrow erythropoiesis compared to blood ferritin level [21]. Since TSAT is characterized by lower variability compared to ferritin levels, especially in patients with chronic inflammatory diseases, a reduced TSAT can be considered a more acceptable diagnostic criterion for ID.

The efficacy of different forms of iron preparations in CHF patients

In studies evaluating erythropoiesis-stimulating therapy, iron preparations were initially used as concomitant treatment [3]. Later, awareness of high ID prevalence (in about 70% of patients with anaemia and generally in about 50% of CHF patients), as well as observed negative ID clinical consequences and newly available intravenous iron preparations, prompted the development of studies evaluating the efficacy of iron preparations without concomitant erythropoiesis-stimulating therapies. Initially these studies included patients with anaemia, but later they began to include patients with ID with or without concomitant anaemia. During the phase II IRON-OUT study (Oral Iron Repletion Effects On Oxygen Uptake in Heart Failure) it was reported that the use of oral medicinal products, despite their ease of use, has limitations in CHF patients due to impaired iron absorption, as well as low patient adherence to therapy (as a result of associated gastrointestinal adeverse reactions) [22].

Several RCTs investigated the efficacy of intravenous iron [23–26]. All these studies included patients

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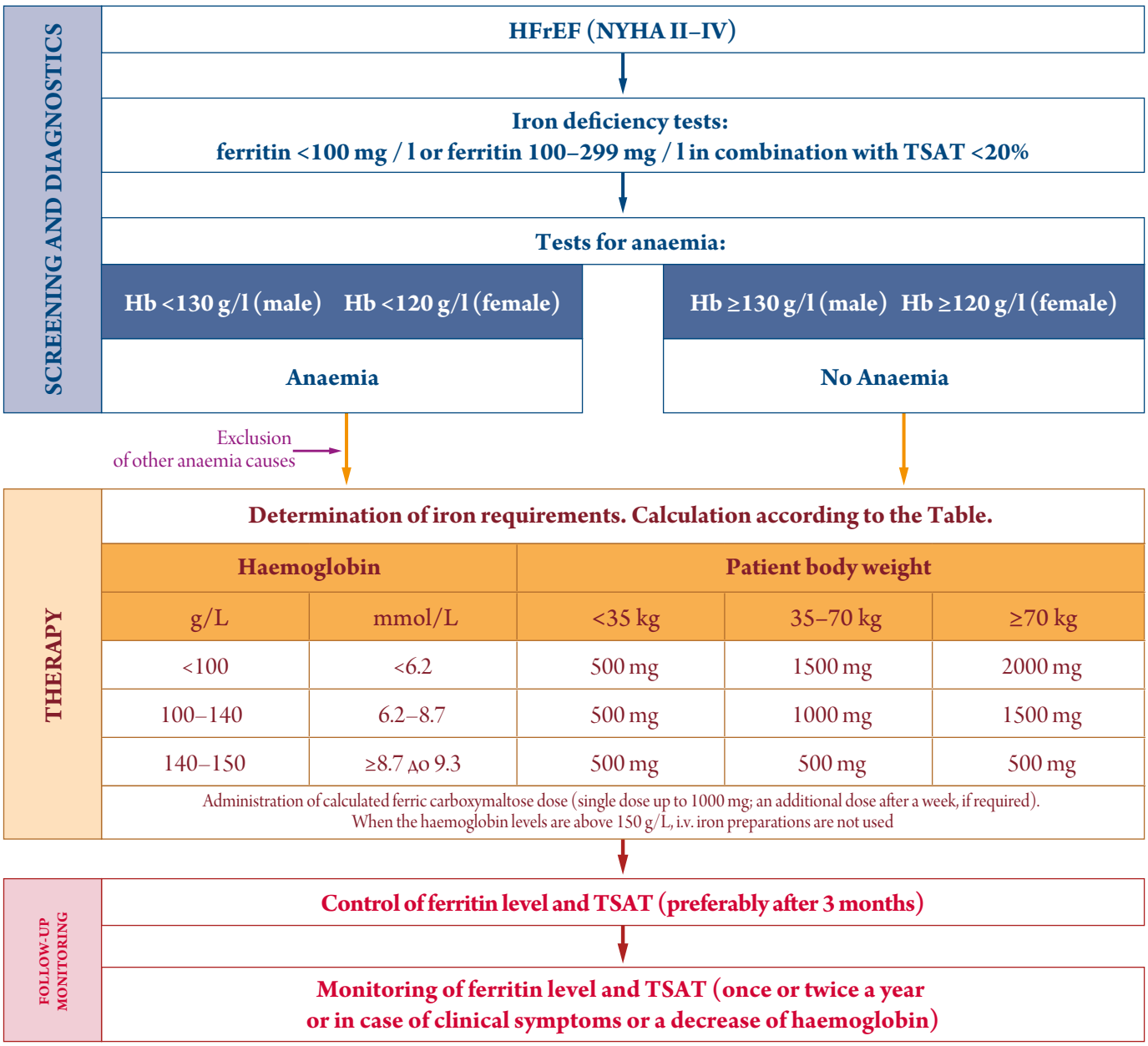
with certain levels of ferritin and TSAT. Generally, the results of these studies were similar, despite the differences in treatment and follow-up strategies: in a short-term period the intravenous administration of iron led to an improved grade within the NYHA (New York Heart Association), an improved exercise tolerance and an improved quality of life. In two largest RCTs – FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure) and CONFIRM-HF (Ferric Carhoxymaltose Evaluation on Performance in Patients with Iron Deficiency in Combination with Chronic Heart Failure) a statistically significant increase in blood haemoglobin concentrations was also registered. But the effect of therapy was similar regardless of whether anaemia was present or not [25, 26]. In the EFFECT-HF (Effect of Ferric Carhoxymaltose on Exercise Capacity in Patients with Iron Deficiency and Chronic Heart Failure) RCT where the efficacy of intravenous ferric carboxymaltose was compared to standard treatment for CHF patients with ID (n = 172) there was an increase of maximum oxygen consumption in the intravenous ferric carboxymaltose group compared to the control treatment-free group [27].

Figure 1. Clinical decision algorithm for the treatment of iron deficiency in CHF patients



CHF– chronic heart failure; HFrEF – heart failure with reduced ejection fraction ;
NYHA – New York Heart Association; TSAT – transferrin saturation coefficient;
FCM – ferric carboxymaltose. Hb – blood haemoglobin concentration.

The clinical decision algorithm for the treatment of iron deficiency in CHF patients proposed by the experts [28] is presented in Figure 1.

Diagnosis of anaemia in patients with chronic heart failure

According to a strict definition anaemia is an absolute decrease in the number of red blood cells in the body that can be estimated by a complex and expensive analysis of blood volume using radioactive medicinal products. However, in clinical practice we use indirect parametrs such as the blood haemoglobin levels and haematocrit to diagnose anaemia. It should be noted that both of these parameters depend on the degree of blood thickening, and the so-called pseudoanaemia often develops due to haemodilution in CHF patients also having volume overload [29].

According to the World Health Organization, anaemia is diagnosed in men and women when haemoglobin levels drop below 13 and 12 g/dl, respectively. The validity of such anaemia definition has never been formally confirmed, but in the general population of individuals with normal renal function, the concentration of blood erythropoietin increases exponentially when haemoglobin levels drop below 13 and 12 g/dl in men and women, respectively [30]. According to various studies, there is a large variability of anaemia prevalence in CHF patients (ranging from 17 to 70%), which may be due to differences in the criteria of anaemia, differences in patient demographic characteristics and concomitant diseases, as well as to differences in the types of studies of severity in chronic heart failure [31–33].

Aetiology and pathophysiological components of iron deficiency and anaemia development in chronic heart failure

The development of anaemia in CHF is determined by many factors. The highest risk of development is observed in patients with Chronic Kidney Disease (CKD) or diabetes mellitus, as well as in elderly patients [32, 33]. CHF can cause the development of anaemia due to various mechanisms; furthermore, anaemia and heart failure can also have several common risk factors.

As mentioned above, CHF patients often suffer concomitant ID that is observed in approximately 50% of patients [6, 13, 34]. The cause of iron deficiency may be due to a combined effect of various factors: nutritional iron deficiency, impaired iron absorption in the digestive tract, and gastro-intestinal bleeding. Chronic inflammation may also play a role in the functional iron deficiency [35].

In CHF patients, there can either be high levels of erythropoietin (with a phenomenon of erythropoietin resistance) or low levels (in patients with concomitant CKD, since erythropoietin is synthesized in kidneys) [36]. With a decreased bone marrow sensitivity to erythropoietin due to internal defects of the bone marrow, the blood erythropoietin concentration in CHF patients increases [37]. This leads to an excessive increase of erythropoietin blood concentration at the background of its normal production in CHF patients. In these patients, an increased blood erythropoietin level is associated with increased risks of adverse outcomes [38].

Drug therapy in CHF patients can also lead to anaemia. Angiotensin-converting enzyme inhibitors are known to suppress haematopoiesis due to the effect on N-acetyl-seryl-aspartyl-lysyl-proline, thus leading to an increased risk of anaemia. These effects were established in SOLVD studies (Studies of Left Ventricular Dysfunction) in the enalapril treatment group [39, 40]. In addition, there is evidence that carvedilol can lower the haemoglobin concentration due to β^2-adrenergic blockade [41].

The clinical consequences of anaemia in patients with chronic heart failure

In healthy individuals tissue oxygen supply in case of haemoglobin concentration decreased to a level as low as 5 g/dl can be compensated by an increase in both heart rate and stroke volume, i.e. due to mechanisms that are always impaired in CHF patients [42]. The development of anaemia in CHF patients may lead to a decreased tissue oxygen supply and thus to aggravation of such disease clinical manifestations as shortness of breath and fatigue, and, consequently, to further deterioration of exercise tolerance and quality of life [43]. The results of meta-analysis, which included a total of 153,180 CHF patients, showed an increased risk of mortality in the presence of anaemia (standardized risk ratio 1.46, 95% CI, 1.26–1.69) with no differences in effect on prognosis between patients with reduced and normal left ventricular ejection fraction [31]. The results of two observational studies showed the effective elimination of anaemia in more than 40% of CHF outpatients [32, 33]. Moreover, the prognosis in these patients did not differ from the prognosis in patients without anaemia, while the persistence of anaemia was associated with a decreased survival. It should be noted that the frequency of iron and erythropoiesis-stimulating agents use during this study was relatively low (21 and 8%, respectively), and the decrease of anaemia severity or its elimination was mainly explained by the effects of CHF treatment, in particular, by a decrease in volume overload, thus eliminating pseudoanaemia [32]. In CHF patients

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anaemia is often combined with CKD and/or ID CHF, which is accompanied by the progression of both CKD and CHF and is associated with an unfavorable prognosis [44].

Transfusion therapy

Red blood cells transfusion is often considered in the presence of severe clinically manifestating anaemia [1]. However, data on the efficacy of such a treatment strategy in CHF patients is limited. Transfusion therapy has only a transient effect and is associated with an additionally increased risk in CHF patients due to volume overload, or ischaemia-associated complications. Regardless of the fact that small clinical studies showed the safety of blood transfusion and its advantage (compared to the treatment without blood transfusions in patients with similar characteristics), two large observational studies including CHF patients showed that blood transfusions were associated with increased disease clinical manifestations and poor prognosis [45, 46]. Given the risk of acute haemolytic reactions, infections, acute lung damage, allergic reactions and the lack of benefits of broad blood transfusion indications, stricter indications for haemotransfusions are currently recommended (for example, with a blood haemoglobin threshold level of 7–8 g/dl [47].

The use of erythropoiesis-stimulating agents

Exogenous administration of erythropoietin is approved for the treatment of CKD-associated or chemotherapy-induced anaemia. The efficacy of anaemia treatment in CHF patients using erythropoiesis-stimulating medicinal products was studied in RED-HF RCT (Reduction of Events by Darbepoetin Alfa in Heart Failure) that included 2,278 patients [48]. In this study, CHF patients with clinical manifestations, LVEF ≤40%, and anaemia (haemoglobin level 9 to 12 g/dl), were assigned to darbepoetin-alpha (target haemoglobin concentration of up to 13–14.5 g/dl) or placebo. It should be noted that concomitant therapy with iron (administered either orally or intravenously) was allowed in both groups. In the intervention group, the median haemoglobin concentration increased, but there was no statistically significant effect on the main combined endpoint including all-cause mortality or hospitalization rate due to worsening of chronic heart

failure, as well as on other adverse outcomes. At the same time, the darbepoetin alpha group compared to placebo showed increased ischaemic stroke incidence by 1.7% (p = 0.03), as well as increased embolic or thrombotic complications incidence by 3.5% (p=0.009) [48, 49].

Conclusion

In summary, despite the fact that anaemia is often associated with ID, the prevalence of isolated ID in CHF patients is high, and the benefits of iron treatment appear not only due to the effect on hematopoiesis. However, according to the data available, and according to expert opinion [1], it is reasonable to monitor iron status in all CHF patients, regardless of haemoglobin concentration. Available evidence (results of RCTs) showed that intravenous ferric carboxymaltose should be considered the most consistent approach for the treatment of ID in CHF patients [25, 26].

Anaemia in CHF patients is still a clinically significant concurrent condition. Even though, most clinical trials did not confirm the advantage of eliminating anaemia in these cases per se. Despite the justification of searching for a specific anaemia cause in CHF patients, there is no evidence for the efficacy of increasing haemoglobin levels using erythropoiesis-stimulating medicinal products.

This type of treatment did not affect the risk of mortality and the frequency of repeated hospitalizations due to the worsening of CHF, but led to increased ischaemic stroke incidence, thus mitigating the small positive effect of erythropoietin on CHF clinical manifestations.

In contrast, the use of intravenous iron to correct iron deficiency anaemia in CHF patients seems to be the most promising approach in the treatment of anaemia in such cases. Furthermore, the effect of this therapy in these patients is not limited by only an increase in blood haemoglobin levels.

REFERENCES

1. Beverborg N.G., van Veldhuisen D.J., van der Meer P. Anemia in Heart Failure. Still Relevant? J Am Coll Cardiol HF 2018;6:201–208. DOI: 10.1016/j.jchf.2017.08.023.
2. van Veldhuisen D.J., Anker S.D., Ponikowski P., Macdougall I.C. Anemia and iron deficiency in heart failure: mechanisms and therapeutic approaches. Nat Rev Cardiol 2011;8:485–493. DOI: 10.1038/nrcardio.2011.77.
3. Ponikowski P., Voors A.A., Anker S.D., Bueno H., Cleland J.G.F., Coats A.J.S., Falk V., González-Juanatey J.R., Harjola V.P., Jankowska E.A., Jessup M., Linde C., Nihoyannopoulos P., Parissis J.T., Pieske B., Riley J.P., Rosano G.M.C., Ruilope L.M., Ruschitzka F., Rutten F.H., van der Meer P.; ESC Scientific Document Group. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016; 37:2129–2200. DOI: 10.1093/eurheartj/ehw128.
4. Beard J.L. Iron biology in immune function, muscle metabolism and neuronal functioning. J Nutr 2001;131:568S–580S. DOI: 10.1093/jn/131.2.568S
5. Anker S.D., Colet J.C., Filippatos G., Willenheimer R., Dickstein K., Drexler H., Lüscher T.F., Mori C., von Eisenhart Rothe B., Pocock S., Poole-Wilson P.A, Ponikowski P.; FAIR-HF committees and investigators. Rationale and design of Ferinject assessment in patients with IRon deficiency and chronic Heart Failure (FAIR-HF) study: a randomized, placebo-controlled study of intravenous iron supplementation in patients with and without anaemia. Eur J Heart Fail 2009;11:1084–1091. DOI: 10.1093/eurjhf/hfp140.
6. Okonko D.O., Mandal A.K., Missouris C.G., Poole-Wilson P.A. Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival. J Am Coll Cardiol 2011;58:1241–1251. DOI: 10.1016/j.jacc.2011.04.040.
7. Jankowska E.A., Rozentryt P., Witkowska A., Nowak J., Hartmann O., Ponikowska B., Borodulin-Nadzieja L., von Haehling S., Doehner W., Banasiak W., Polonski L., Filippatos G., Anker S.D., Ponikowski P. Iron deficiency predicts impaired exercise capacity in patients with systolic chronic heart failure. J Card Fail 2011;17:899–906. DOI: 10.1016/j.cardfail.2011.08.003.
8. Haas J.D., Brownlie T. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. J Nutr 2001;131:676S–690S. DOI: 10.1093/jn/131.2.676S.
9. Enjuanes C., Bruguera J., Grau M., Cladellas M., Gonzalez G., Meroño O., Moliner-Borja P., Verdú J.M., Farré N., Comín-Colet J. Iron status in chronic heart failure: impact on symptoms, functional class and submaximal exercise capacity. Rev Esp Cardiol (Engl Ed) 2016;69:247–255. DOI: 10.1016/j.rec.2015.08.018.
10. Comin-Colet J., Enjuanes C., Gonzalez G., Torrens A., Cladellas M., Meroño O., Ribas N., Ruiz S., Gómez M., Verdú J.M., Bruguera J. Iron deficiency is a key determinant of health-related quality of life in patients with chronic heart failure regardless of anaemia status. Eur J Heart Fail 2013;15:1164–1172. DOI: 10.1093/eurjhf/hft083.
11. Enjuanes C., Klip I.T., Bruguera J., Cladellas M., Ponikowski P., Banasiak W., van Veldhuisen D.J., van der Meer P., Jankowska E.A., Comín-Colet J. Iron deficiency and health-related quality of life in chronic heart failure: results from a multicenter European study. Int J Cardiol 2014;174:268–275. DOI: 10.1016/j.ijcard.2014.03.169.
12. Nunez J., Comin-Colet J., Minana G., Núñez E., Santas E., Mollar A., Valero E., García-Blas S., Cardells I., Bodí V., Chorro F.J., Sanchis J. Iron deficiency and risk of early readmission following a hospitalization for acute heart failure. Eur J Heart Fail 2016;18:798–802. DOI: 10.1002/ejhf.513.
13. Klip I.T., Comin-Colet J., Voors A.A., Ponikowski P., Enjuanes C., Banasiak W., Lok D.J., Rosentryt P., Torrens A., Polonski L., van Veldhuisen D.J., van der Meer P., Jankowska E.A. Iron deficiency in chronic heart failure: an international pooled analysis. Am Heart J 2013;165:575–582.e3. DOI: 10.1016/j.ahj.2013.01.017.
14. Jankowska E.A., Rozentryt P., Witkowska A., Nowak J., Hartmann O., Ponikowska B., Borodulin-Nadzieja L., Banasiak W., Polonski L., Filippatos G., McMurray J.J., Anker S.D., Ponikowski P. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. Eur Heart J 2010;31:1872–1880. DOI: 10.1093/eurheartj/ehq158.
15. Nanas J.N., Matsouka C., Karageorgopoulos D., Leonti A., Tsolakis E., Drakos S.G., Tsagalou E.P., Maroulidis G.D., Alexopoulos G.P., Kanakakis J.E., Anastasiou-Nana M.I. Etiology of anemia in patients with advanced heart failure. J Am Coll Cardiol 2006;48:2485–2489. DOI: 10.1016/j.jacc.2006.08.034.
16. Parikh A., Natarajan S., Lipsitz S.R., Katz S.D. Iron deficiency in community-dwelling US adults with self-reported heart failure in the National Health and Nutrition Examination Survey III: prevalence and associations with anemia and inflammation. Circ

ISSN 0022-9040. Kardiologiia. 2020;60(1). DOI: 10.18087/cardio.2020.1.n961

Heart Fail 2011;4:599–606. DOI: 10.1161/CIRCHEARTFAILURE.111.960906.
17. Yeo T.J., Yeo P.S., Ching-Chiew Wong R., Ong H.Y., Leong K.T., Jaufeerally F., Sim D., Santhanakrishnan R., Lim S.L., Chan M.M.Y., Chai P., Low A.F., Ling L.H., Ng T.P., Richards A.M., Lam C.S. Iron deficiency in a multi-ethnic Asian population with and without heart failure: prevalence, clinical correlates, functional significance and prognosis. Eur J Heart Fail 2014;16:1125–1132. DOI: 10.1002/ejhf.161.
18. von Haehling S., Gremmler U., Krumm M., Mibach F., Schön N., Taggeselle J., Dahm J.B., Angermann C.E. Prevalence and clinical impact of iron deficiency and anaemia among outpatients with chronic heart failure: The PrEP Registry. Clin Res Cardiol 2017;106:436–443. DOI: 10.1007/s00392-016-1073-y.
19. Grote Beverborg N., Klip I.T., Meijers W.C., Voors A.A., Vegter E.L., van der Wal H.H., Swinkels D.W., van Pelt J., Mulder A.B., Bulstra S.K., Vellenga E., Mariani M.A., de Boer R.A., van Veldhuisen D.J., van der Meer P. Definition of Iron Deficiency Based on the Gold Standard of Bone Marrow Iron Staining in Heart Failure Patients. Circ Heart Fail 2018;11(2):e004519. DOI: 10.1161/CIRCHEARTFAILURE.117.004519.
20. Anker S.D., Kirwan B.A., van Veldhuisen D.J., Filippatos G., Comin-Colet J., Ruschitzka F., Lüscher T.F., Arutyunov G.P., Motro M., Mori C., Roubert B., Pocock S.J., Ponikowski P. 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;20:125–133. DOI: 10.1002/ejhf.823.
21. Cacoub P., Vandewalle C., Peoc'h K. Using transferrin saturation as a diagnostic criterion for iron deficiency: A systematic review. Crit Rev Clin Lab Sci. 2019;56:526–532. DOI: 10.1080/10408363.2019.1653820.
22. Lewis G.D., Semigran M.J., Givertz M.M., Malhotra R., Anstrom K.J., Hernandez A.F., Shah M.R., Braunwald E. Oral iron therapy for heart failure with reduced ejection fraction: design and rationale for oral iron repletion effects on oxygen uptake in heart failure. Circ Heart Fail 2016;9:e000345. DOI: 10.1161/CIRCHEARTFAILURE.115.000345.
23. Toblli J.E., Lombraña A., Duarte P., Di Gennaro F. Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. J Am Coll Cardiol 2007;50:1657–1665. DOI: 10.1016/j.jacc.2007.07.029.
24. Okonko D.O., Grzeslo A., Witkowski T., Mandal A.K., Slater R.M., Roughton M., Foldes G., Thum T., Majda J., Banasiak W., Missouris C.G., Poole-Wilson P.A., Anker S.D., Ponikowski P. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. J Am Coll Cardiol 2008;51:103–112. DOI: 10.1016/j.jacc.2007.09.036.
25. Anker S.D., Comin Colet J., Filippatos G., Willenheimer R., Dickstein K., Drexler H., Lüscher T.F., Bart B., Banasiak W., Niegowska J., Kirwan B.A., Mori C., von Eisenhart Rothe B., Pocock S.J., Poole-Wilson P.A., Ponikowski P.; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009;361:2436–2448. 10.1056/NEJMoa0908355.
26. Ponikowski P., Van Veldhuisen D.J., Comin-Colet J., Ertl G., Komajda M., Mareev V., McDonagh T., Parkhomenko A., Tavazzi L., Levesque V., Mori C., Roubert B., Filippatos G., Ruschitzka F., Anker SD.; CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J 2015;36:657–668. DOI: 10.1093/eurheartj/ehu385.
27. Van Veldhuisen D.J., Ponikowski P., van der Meer P., Metra M., Böhm M., Doletsky A., Voors A.A., Macdougall I.C., Anker S.D., Roubert B., Zakin L., Cohen-Solal A.; EFFECT-HF Investigators. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. Circulation 2017;136:1374–1383. DOI: 10.1161/CIRCULATIONAHA.117.027497.
28. McDonagh T., Damy T., Doehner W., Lam C.S.P., Sindone A., van der Meer P., Cohen-Solal A., Kindermann I., Manito N., Pfister O., Pohjantähti-Maaroos H., Taylor J., Comin-Colet J. Screening, diagnosis and treatment of iron deficiency in chronic heart failure: putting the 2016 European Society of Cardiology heart failure guidelines into clinical practice. Eur J Heart Fail 2018;20:1664–1672. DOI: 10.1002/ejhf.1305.
29. Adlbrecht C., Kommata S., Hülsmann M., Szekeres T., Bieglmayer C., Strunk G., Karanikas G., Berger R., Mörtl D., Kletter K., Maurer G., Lang I.M., Pacher R. Chronic heart failure leads to an expanded plasma volume and pseudoanaemia, but does not lead to a reduction in the body's red cell volume. Eur Heart J 2008;29:2343–2350. DOI: 10.1093/eurheartj/ehn359.
30. Grote Beverborg N., Verweij N., Klip I.T., van der Wal H.H., Voors A.A., van Veldhuisen D.J., Gansevoort R.T., Bakker S.J., van der Harst P., van der Meer P. Erythropoietin in the general population: reference ranges and clinical, biochemical and genetic correlates. PLoS One 2015;10:e0125215.
31. Groenveld H.F., Januzzi J.L., Damman K., van Wijngaarden J., Hillege H.L., van Veldhuisen D.J., van der Meer P. Anemia and mortality in heart failure patients. a systematic review and meta-analysis. J Am Coll Cardiol 2008;52:818–827. DOI: 10.1016/j.jacc.2008.04.061.
32. Tang W.H., Tong W., Jain A., Francis G.S., Harris C.M., Young J.B. Evaluation and long-term prognosis of new-onset, transient, and persistent anemia in ambulatory patients with chronic heart failure. J Am Coll Cardiol 2008;51:569–576. DOI: 10.1016/j.jacc.2007.07.094.
33. Waldum B., Westheim A.S., Sandvik L., Flønæs B., Grundtvig M., Gullestad L., Hole T., Os I. Baseline anemia is not a predictor of all-cause mortality in outpatients with advanced heart failure or severe renal dysfunction. Results from the Norwegian Heart Failure Registry. J Am Coll Cardiol 2012;59:371–378. DOI: 10.1016/j.jacc.2011.10.864.
34. Nanas J.N., Matsouka C., Karageorgopoulos D., Leonti A., Tsolakis E., Drakos S.G., Tsagalou E.P., Maroulidis G.D., Alexopoulos G.P., Kanakakis J.E., Anastasiou-Nana M.I. Etiology of anemia in patients with advanced heart failure. J Am Coll Cardiol 2006;48:2485–2489. DOI: 10.1016/j.jacc.2006.08.034.
35. van der Meer P., Lok D.J., Januzzi J.L., de la Porte P.W., Lipsic E., van Wijngaarden J., Voors A.A., van Gilst W.H., van Veldhuisen D.J. Adequacy of endogenous erythropoietin levels and mortality in anaemic heart failure patients. Eur Heart J 2008;29:1510–1515. DOI: 10.1093/eurheartj/ehn205.
36. Westenbrink B.D., Visser F.W., Voors A.A., Smilde T.D., Lipsic E., Navis G., Hillege H.L., van Gilst W.H., van Veldhuisen D.J. Anaemia in chronic heart failure is not only related to impaired renal perfusion and blunted erythropoietin production, but to fluid retention as well. Eur Heart J 2007;28:166–171. DOI: 10.1093/eurheartj/ehl419.
37. Westenbrink B.D., Voors A.A., De Boer R.A., Schuringa J.J., Klinkenberg T., van der Harst P., Vellenga E., van Veldhuisen D.J., van Gilst W.H. Bone marrow dysfunction in chronic heart failure patients. Eur J Heart Fail 2010;12:676–684. DOI: 10.1093/eurjhf/hfq061.
38. van der Meer P., Voors A.A., Lipsic E., Smilde T.D., van Gilst W.H., van Veldhuisen D.J. Prognostic value of plasma erythropoietin on mortality in patients with chronic heart failure. J Am Coll Cardiol 2004;44:63–67. doi: 10.1016/j.jacc.2004.03.052.
39. van der Meer P., Lipsic E., Westenbrink B.D., van de Wal R.M., Schoemaker R.G., Vellenga E., van Veldhuisen D.J., Voors A.A., van Gilst W.H. Levels of hematopoiesis inhibitor N-acetyl-seryl-aspartyl-lysyl-proline partially explain the occurence of anemia in heart failure. Circulation 2005;112:1743–1747. DOI: 10.1161/CIRCULATIONAHA.105.549121.
40. Ishani A., Weinhandl E., Zhao Z., Gilbertson D.T., Collins A.J., Yusuf S., Herzog C.A. Angiotensin-converting enzyme inhibitor as a risk factor for the development of anemia, and the impact of incident anemia on mortality in patients with left ventricular dysfunction. J Am Coll Cardiol 2005;45:391–399. DOI: 10.1016/j.jacc.2004.10.038.
41. Komajda M., Anker S.D., Charlesworth A., Okonko D., Metra M., Di Lenarda A., Remme W., Moullet C., Swedberg K., Cleland J.G., Poole-Wilson P.A. The impact of new onset anaemia on morbidi-

ty and mortality in chronic heart failure: results from COMET. Eur Heart J 2006;27:1440–1446. DOI: 10.1093/eurheartj/ehl012.
42. Weiskopf R.B., Viele M.K., Feiner J., Kelley S., Lieberman J., Noorani M., Leung J.M., Fisher D.M., Murray W.R., Toy P., Moore M.A. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA 1998;279:217—221. DOI: 10.1001/jama.279.3.217.
43. Weiskopf R.B., Viele M.K., Feiner J., Kelley S., Lieberman J., Noorani M., Leung J.M., Fisher D.M. Ebner N., Jankowska E.A., Ponikowski P., Lainscak M., Elsner S., Sliziuk V., Steinbeck L., Kube J., Bekfani T., Scherbakov N., Valentova M., Sandek A., Doehner W., Springer J., Anker S.D., von Haehling S. The impact of iron deficiency and anaemia on exercise capacity and outcomes in patients with chronic heart failure. Results from the studies investigating co-morbidities aggravating heart failure. Int J Cardiol 2016;205:6–12. DOI: 10.1016/j.ijcard.2015.11.178.
44. Klip I.T., Jankowska E.A., Enjuanes C., Voors A.A., Banasiak W., Bruguera J., Rozentryt P., Polonski L., van Veldhuisen D.J., Ponikowski P., Comin-Colet J., van der Meer P. The additive burden of iron deficiency in the cardiorenal-anaemia axis: scope of a problem and its consequences. Eur J Heart Fail 2014;16:655–662. DOI: 10.1002/ejhf.84.
45. Garty M., Cohen E., Zuchenko A., Behar S., Boyko V., Iakobishvili Z., Mittelman M., Battler A., Shotan A., Gottlieb S., Caspi A., Hasdai D. Blood transfusion for acute decompensated heart failure-friend or foe? Am Heart J 2009;158:653–658. DOI: 10.1016/j.ahj.2009.08.001.
46. Kao D.P., Kreso E., Fonarow G.C., Krantz M.J. Characteristics and outcomes among heart failure patients with anemia and renal insufficiency with and without blood transfusions (public discharge data from California 2000-2006). Am J Cardiol 2011;107:69–73. DOI: 10.1016/j.amjcard.2010.08.046.
47. Qaseem A., Humphrey L.L., Fitterman N., Starkey M., Shekelle P.; Clinical Guidelines Committee of the American College of Physicians. Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2013;159:770–779. DOI: 10.7326/0003-4819-159-11-201312030-00009.
48. Swedberg K., Young J.B., Anand I.S., Cheng S., Desai A.S., Diaz R., Maggioni A.P., McMurray J.J., O'Connor C., Pfeffer M.A., Solomon S.D., Sun Y., Tendera M., van Veldhuisen D.J.; RED-HF Committees; RED-HF Investigators. Treatment of anemia with darbepoetin alfa in systolic heart failure. N Engl J Med 2013;368:1210–1219. DOI: 10.1056/NEJMoa1214865.
49. Bello N.A., Lewis E.F., Desai A.S., Anand I.S., Krum H., McMurray J.J., Olson K., Solomon S.D., Swedberg K., van Veldhuisen D.J., Young J.B., Pfeffer M.A. Increased risk of stroke with darbepoetin alfa in anaemic heart failure patients with diabetes and chronic kidney disease. Eur J Heart Fail 2015;17:1201–1207. DOI: 10.1002/ejhf.412.

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