Management of Iron Deficiency in Heart Failure

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Abstract

Anemia is a common finding in patients with heart failure (HF). The cause for anemia is multifactorial, with iron deficiency being the most common cause. Anemia with HF is an established predictor of morbidity and mortality. Iron deficiency in systolic HF, even without anemia, has been associated with increased mortality, increased hospitalizations, and decreased functional capacity and quality of life measures. Data from several randomized controlled trials and meta-analyses of iron deficiency and systolic HF show a beneficial effect for intravenous (IV) iron in terms of quality of life and functional capacity (improvements in 6-min walk test, and improvements in New York Heart Association functional class), as well as decreased hospitalizations for HF and reduction in cardiovascular mortality rates. Limited evidence exists for a beneficial effect of IV iron in diastolic dysfunction. Patients with symptomatic systolic HF should undergo an anemia diagnostic work-up. When iron deficiency (defined as ferritin <100 ng/mL or serum ferritin 100–299 ng/mL and transferrin saturation <20%) is present, current evidence supports treating HF patients with iron deficiency with IV iron.

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Prevalence of Anemia in Heart Failure

Anemia is a common finding in patients with heart failure (HF), with a variable reported prevalence between 4 and 61% [1–4]. This variability might be due to the heterogeneity of HF and the spectrum of HF severity in the different studies. Indeed, in studies of advanced HF, presenting as poorer functional capacity, HF was associated with a higher prevalence of anemia [5].

Causes of Anemia

The development of anemia with HF can result from various etiologies such as a blunted erythropoietin response [6], dilutional anemia, and anemia of chronic disease, with iron deficiency being the most common cause [7]. Iron deficiency may be either absolute iron deficiency or functional iron deficiency. Absolute iron deficiency is defined by severely reduced or absent storage iron in bone marrow, liver, and spleen. Functional iron deficiency is defined by normal or increased total body iron stores which are unavailable for incorporation into erythroid precursors

Oren Zusman passed away.

for erythropoiesis [8]. Absolute iron deficiency in HF may result from appetite loss, poor nutrition, decreased gastrointestinal absorption of iron due to edema, and gastrointestinal blood loss due to the use of anti-aggregants and anticoagulants [9]. Functional iron deficiency, referred to as iron-restricted erythropoiesis, is a form of anemia of chronic inflammation mediated through hepcidin, a peptide that inhibits intestinal iron absorption and iron release from the circulating macrophages [10]. Inflammation in HF can induce hepcidin expression independent of iron stores and inappropriately limit iron absorption.

Outcomes of Anemia in HF

Anemia with HF is an established predictor of morbidity and mortality. In a systematic review of 153,180 patients with HF, 48% died within 6 months (adjusted hazard ratio [HR] 1.46; 95% confidence interval [CI] 1.26–1.69) [11]. Data from a Canadian cohort demonstrated that the risk of death was 1.34 times higher in HF patients with anemia compared to those without anemia [12]. Corroborating the above, a retrospective analysis of the Valsartan Heart Failure Trial data indicated that higher levels of hemoglobin (Hb) as a continuous measure were associated with an increased survival in HF patients (HR 0.78) [3].

Outcomes of Iron Deficiency in HF

Traditionally, iron deficiency has been considered to have clinical consequences only in the presence of anemia. In systolic HF, iron deficiency has been shown to constitute a strong independent predictor of unfavorable outcome [13]. In a prospective observational study of 546 patients with stable systolic HF, iron deficiency, with and without anemia, was an independent predictor for death or heart transplant [13]. Moreover, iron deficiency with or without anemia decreases aerobic performance and is associated with the development of fatigue [14]. In a single-center cross-sectional study of 538 stable patients with chronic HF, iron deficiency had an independent and linear association with submaximal exercise capacity according to the 6-min walk (6MWD) test and with symptomatic functional limitation according to the advanced New York Heart Association (NYHA) functional class [15]. Iron deficiency in HF has also been associated with increased hospitalizations [16]. Health-related quality of life (QoL) measures have been shown to be significantly impaired in HF and iron deficiency as well [17].

In this context, anemia can be viewed as the last stage of the same process of iron deficiency, and benefit from treatment might possibly be seen early in the course of HF, before the progression of iron deficiency to iron deficiency anemia. However, as anemia might serve as a surrogate for the severity of HF rather than a therapeutic target per se, time to intervene, dosage, and targets need to be clearly defined.

Intravenous Iron Treatment

Evidence from Randomized Controlled Trials

One of the first studies to examine intravenous (IV) iron in patients with HF was published in 2006 by Bolger et al. [18]. This was a single-arm study which included 16 patients with systolic HF who received 1 g iron sucrose daily for 12 days. Iron deficiency was inappropriately defined in this study by a ferritin level <400 ng/mL. The investigators reported benefit in functional capacity as was evidenced by improved 6MWD test and by the Minnesota Living with Heart Failure Questionnaire (MLHFQ). In 2007, Toblli et al. [16] randomized 40 patients with HF and an ejection fraction (EF) <40% to either normal saline or 200 mg IV iron sucrose weekly for 5 weeks. Inclusion criteria were anemia and a Hb concentration <12.5 g/dL in men and <11.5 g/dL in women, plus iron deficiency defined by serum ferritin <100 ng/mL and/or transferrin saturation (TSAT) of <20%. Patients who received IV iron had lower NT-pro-brain natriuretic peptide, better functional capacity, and fewer hospitalizations throughout 6 months of follow-up.

In 2009, Okonko et al. [19] randomized 35 patients with an EF <45%, anemia (defined as a Hb concentration <12.5 g/dL), and evidence of iron lack (defined as either ferritin <100 ng/mL or ferritin between 100 and 300 ng/mL and TSAT <20%) to a total of 1,400 mg iron sucrose or normal saline. Although no differences were noted in peak oxygen consumption or the duration of treadmill exercise ($p = 0.08$ for both), marked improvements were noted in the endpoints of NYHA functional class and patient global assessment. The observed improvement was greater if anemia was present.

The study with the greatest magnitude of benefit observed with IV iron in HF patients comes from the FAIR-HF trial [20]. It included 459 patients with HF with NYHA classifications II or III, an EF ≤ 40 –45%, evidence of iron deficiency (defined as a ferritin level either <100 ng/mL or between 100 and 299 ng/mL if TSAT <20%), and a Hb concentration of 9.5–13.5 g/dL. Another cohort

consisted of patients without anemia. The patients were randomly assigned in a 2:1 ratio to receive either 200 mg IV ferric carboxymaltose (FCM) or saline. The protocol mandated a maintenance dose every 4 weeks with re-initiation if serum ferritin, Hb, or TSAT fell below pre-defined values. Endpoints were assessed at 24 weeks. According to patient global assessment, 50 versus 28% of the patients showed an improvement with the use of FCM (odds ratio [OR] for improvement, 2.51; 95% CI 1.75–3.61). In the group assigned to FCM, 47% presented with a NYHA functional class I or II at week 24, as compared with 30% assigned to placebo (OR for improvement by one class, 2.40; 95% CI 1.55–3.71). The results were consistent irrespective of anemia status. Significant improvements were also reported in the treatment arm on the 6MWD test and QoL questionnaire. The difference in serum ferritin levels was 246 ng/mL, and the difference in Hb concentration was 0.5 g/dL, primarily due to the difference in anemic patients (0.9 g/dL in anemic patients vs. 0.1 g/dL in those without anemia). In the placebo arm, there was a near-normal Hb concentration (12.5 g/dL at the end of the trial). One can conclude that benefits from FCM were exerted even in the absence of prior anemia. The rates of death or adverse events in both arms were comparable.

The CONFIRM-HF [21] trial, published in 2015, was a placebo-controlled multicenter trial that enrolled 304 ambulatory symptomatic patients with HF with left ventricular EF $\leq 45\%$ and iron deficiency randomized 1:1 to treatment with FCM or saline and followed them for 52 weeks. This trial has the longest published follow-up period in HF patients treated with iron. Treatment with FCM significantly improved the 6MWD test at week 24 (difference FCM vs. placebo: 33 + 11 min; $p = 0.002$). This treatment effect of FCM was consistent in the various subgroups and remained consistent up to week 52 (difference FCM vs. placebo: 36 + 11 min; $p < 0.001$). In addition, improvements in NYHA class and other functional/QoL measures were reported with statistical significance noted from week 24 and onwards. Furthermore, treatment with FCM was associated with a significant reduction in the risk of hospitalizations for worsening HF (HR 0.39, 95% CI 0.19–0.82; $p = 0.009$). Mortality and incidence of adverse events were similar between the study groups.

Altogether, although the combined evidence from the aforementioned trials demonstrated improvement in the functional capacity and QoL after IV iron, this therapy only partially translated to a reduction in HF hospitalizations and did not translate to a survival benefit.

Evidence from Meta-Analyses

In 2012, Avni et al. [22] published a meta-analysis which included the above-mentioned three randomized controlled trials [16, 19, 20]. A total of 370 patients were treated with IV iron, compared with 224 controls. The primary endpoint was the effect of IV iron on QoL measures and functional capacity. There was a significant improvement in QoL measures in the treatment arm according to the MLHFQ score at 26 weeks, with a mean difference of -18.00 in the score ($-22.54, -13.46, I^2 = 0\%$). The point estimate for an improvement in the NYHA classification favored IV iron. IV iron reduced the number of hospitalizations, C-reactive protein levels, and increased the score of the 6MWD test and mean left ventricular EF. Iron indices were significantly improved, yet Hb levels remained unchanged. No increase in the rate of adverse events was reported.

Another meta-analysis, which included the CONFIRM-HF, reported on 907 patients [23]. Compared with placebo or with no treatment, IV iron significantly reduced hospitalization for HF (OR 0.28, 95% CI 0.16–0.49). However, no difference in all-cause mortality was noted (OR 0.81, 95% CI 0.42–1.57). When these two endpoints were combined to a composite endpoint (four studies), the risk of hospitalizations for HF and death was significantly lower in the IV iron group (OR 0.47, 95% CI 0.29–0.76). There was no increase in the risk of adverse events [23].

In a patient-level meta-analysis, Anker et al. [24] combined data from the FAIR-HF, CONFIRM-HF, and two other, then unpublished, trials (FER-CAR-01 and EMPHASIS-HF). All trials compared FCM with placebo. In total, 839 patients, of whom 504 were randomized to FCM, were included. Compared with placebo, patients treated with FCM had lower rates of recurrent cardiovascular (CV) hospitalizations and CV mortality (risk ratio [RR] 0.59, 95% CI 0.40–0.88; $p = 0.009$). FCM also reduced the rates of recurrent hospitalizations due to HF and CV mortality (RR 0.53, 95% CI 0.33–0.86; $p = 0.011$), recurrent CV hospitalizations, and all-cause mortality (RR 0.60, 95% CI 0.41–0.88; $p = 0.009$). The administration of IV FCM was not associated with an increased risk for adverse events.

Cost and Adverse Events

In all the above-mentioned studies, IV iron was not associated with adverse events. This is in-line with a meta-analysis which reported the safety of iron formulations in different clinical settings and even more so in the sub-

group with patients with HF, where the RR for severe adverse events was 0.45 versus any comparator (95% CI 0.29–0.70) [25].

The conglomerate evidence from the studies supports the effectiveness and safety of IV iron therapy. Supporting the benefit of IV iron, in a cost-effectiveness study in Nordic countries [26], quality-adjusted life years were higher (increase of 0.050 quality-adjusted life years per patient) in the IV iron-treated group compared with placebo. Per-patient costs were, in fact, lower in all countries, with reductions ranging from EUR 36 to EUR 484. The main driver for decreased costs was fewer hospitalizations.

Iron in Diastolic HF

Although limited data exists, patients with HF with reduced left ventricular EF (HFrEF) and preserved left ventricular EF (HFpEF) show similar rates of iron deficiency [27–29]. Several studies have demonstrated that patients with HFpEF with iron deficiency suffered from a similar impact on health-related QoL as patients with HFrEF [17, 28]. Moreover, in both HFrEF and HFpEF, concomitant iron deficiency informs for all-cause mortality independent of the presence or absence of anemia [29]. Evidence for improved outcomes after IV iron therapy is lacking. Small-scale studies treating HFpEF patients with erythropoietin-stimulating agents or oral iron reported no effect on left ventricular end-diastolic volume and left ventricular mass and no improvement in the submaximal exercise capacity or QoL [30, 31]. These findings are consistent with a report from Kasner et al. [32], who did not find an association between functional iron deficiency and exercise capacity in patients with HFpEF. This important issue should be further elucidated in a dedicated larger-scale study: the ongoing FAIR-HF-HFpEF study. This randomized trial will address whether treatment with IV iron for patients with HFpEF and iron deficiency (defined as ferritin <100 ng/mL or serum ferritin 100–299 ng/mL and TSAT <20%), both with or without anemia, can improve exercise capacity as measured by the 6MWD test and symptoms without significant toxicity. Study completion date is expected to be approximately July 2019.

Iron Formulations and Route in HF

Most trials assessed IV iron formulations. In HF, iron deficiency is both absolute and functional, and levels of hepcidin are elevated. Due to a hepcidin dysregulation in

HF, iron absorption is reduced [33]. Recruitment of iron stores from the reticuloendothelial cells and hepatocytes is impaired in the presence of hepcidin. The oral route might not lead to repletion, although it is attractive due to low cost. IV administration bypasses the “inflammatory block” of available iron and allows faster repletion without gastrointestinal perturbation.

The IRON-OUT study [34] randomized 225 patients with reduced EF to oral iron polysaccharide or placebo. The primary endpoint, change in peak oxygen consumption (VO_2) at 16 weeks, was not significantly different between the arms (+23 vs. –2 mL/min; difference, 21 mL/min, 95% CI –34 to +76; $p = 0.46$). Similarly, at 16 weeks, there were no significant differences between the treatment groups in changes in the 6MWD test (–13 m, 95% CI –32 to 6), NT-pro-brain natriuretic peptide levels (159 pg/mL, 95% CI –280 to 599), or KCCQ score (1, 95% CI –2.4 to 4.4), all $p > 0.05$. In this study, the median hepcidin levels increased from 6.7 to 8.9 ng/mL ($p = 0.007$) in the oral iron group, but the between-group comparison of change in hepcidin levels was not statistically significant (+1.5 ng/mL, 95% CI –0.6 to 3.7; $p = 0.17$). Changes in TSAT ($r = -0.29$; $p = 0.004$), ferritin ($r = -0.30$; $p = 0.004$), and soluble transferrin receptor levels ($r = 0.48$; $p < 0.001$) at 16 weeks were correlated with baseline hepcidin levels. The negative results of this trial are in contradistinction to the reported benefits of IV iron and provided a pathophysiologic explanation through the correlation of baseline hepcidin.

The IV formulations used for HF are FCM and iron sucrose, but others, such as ferumoxytol, low-molecular-weight iron dextran, iron isomaltoside, and ferric gluconate, are likely to show equivalent benefit. No direct comparison of products exists for HF with iron deficiency; however, extrapolating from other studies [35–37], one can assume similar effects. Not all formulations are available in all countries, and costs vary.

Conclusions and Recommendations

In conclusion, anemia is common in HF and is a negative prognostic marker. Iron deficiency is the most common cause and is an independent risk factor for long-term outcomes. Data from randomized controlled trials in patients with iron deficiency and systolic HF show a beneficial effect for IV iron in terms of QoL and functional status. A recent meta-analysis shows that, in HF patients, IV iron also reduced the rates of recurrent HF hospitalizations and CV mortality and recurrent CV hos-

pitalizations and CV mortality. Evidence for improved outcomes in patients with HFpEF treated with IV iron is lacking.

In all patients with systolic HF, an anemia diagnostic work-up is warranted, although in many patients, no specific cause is found. This recommendation is consistent with the 2016 European Society of Cardiology (ESC) guidelines [38]. As for the recommendation regarding treatment, the ESC guidelines state that “IV FCM should be considered in symptomatic patients (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and TSAT <20%) in order to alleviate HF symptoms, and improve exercise capacity and QoL.” This is a class IIa recommendation with level of evidence A. The 2017 update of the joint guidelines of the American Heart Association

(AHA) and American College of Cardiology (ACC) states that “in patients with NYHA functional class II–III and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L if TSAT <20%) IV iron might be reasonable to improve functional status and quality of life.” The level of evidence is IIb. No specific type of iron formulation was recommended [39].

We agree with these recommendations. We believe that current evidence supports treating HF patients with iron deficiency with IV iron.

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In memory, this paper is dedicated to Oren Zusman.

References

- 1 Felker GM, Adams KF Jr, Gattis WA, O'Connor CM. Anemia as a risk factor and therapeutic target in heart failure. *J Am Coll Cardiol*. 2004 Sep;44(5):959–66.
- 2 Wexler D, Silverberg D, Sheps D, Blum M, Keren G, Iaina A, et al. Prevalence of anemia in patients admitted to hospital with a primary diagnosis of congestive heart failure. *Int J Cardiol*. 2004 Jul;96(1):79–87.
- 3 Anand IS, Kuskowski MA, Rector TS, Florea VG, Glazer RD, Hester A, et al. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. *Circulation*. 2005 Aug;112(8):1121–7.
- 4 Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol*. 2001 Oct;38(4):955–62.
- 5 Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol*. 2000 Jun;35(7):1737–44.
- 6 Opasich C, Cazzola M, Scelsi L, De Feo S, Bosimini E, Lagioia R, et al. Blunted erythropoietin production and defective iron supply for erythropoiesis as major causes of anaemia in patients with chronic heart failure. *Eur Heart J*. 2005 Nov;26(21):2232–7.
- 7 Nanas JN, Matsouka C, Karageorgopoulos D, Leonti A, Tsolakis E, Drakos SG, et al. Etiology of anemia in patients with advanced heart failure. *J Am Coll Cardiol*. 2006 Dec;48(12):2485–9.
- 8 Auerbach M, Adamson JW. How we diagnose and treat iron deficiency anemia. *Am J Hematol*. 2016 Jan;91(1):31–8.
- 9 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 Mar;34(11):816–29.
- 10 Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science*. 2004 Dec;306(5704):2090–3.
- 11 Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, et al. Anemia and mortality in heart failure patients: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2008 Sep;52(10):818–27.
- 12 Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. *Circulation*. 2003 Jan;107(2):223–5.
- 13 Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J*. 2010 Aug;31(15):1872–80.
- 14 Haas JD, Brownlie T 4th. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. *J Nutr*. 2001 Feb;131(2 2S-2):676S–88S.
- 15 Enjuanes C, Bruguera J, Grau M, Cladellas M, Gonzalez G, Meroño O, et al. Iron Status in Chronic Heart Failure: Impact on Symptoms, Functional Class and Submaximal Exercise Capacity. *Rev Esp Cardiol (Engl Ed)*. 2016 Mar;69(3):247–55.
- 16 Toblli JE, 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 Oct;50(17):1657–65.
- 17 Enjuanes C, Klip IT, Bruguera J, Cladellas M, Ponikowski P, Banasiak W, et al. Iron deficiency and health-related quality of life in chronic heart failure: results from a multicenter European study. *Int J Cardiol*. 2014 Jun;174(2):268–75.
- 18 Bolger AP, Bartlett FR, Penston HS, O'Leary J, Pollock N, Kaprielian R, et al. Intravenous iron alone for the treatment of anemia in patients with chronic heart failure. *J Am Coll Cardiol*. 2006 Sep;48(6):1225–7.
- 19 Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, et al. 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 Jan;51(2):103–12.
- 20 Anker SD, Comin Colet J, Filippatos G, Wilenheimer R, Dickstein K, Drexler H, et al.; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009 Dec;361(25):2436–48.
- 21 Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al.; 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 Mar;36(11):657–68.
- 22 Avni T, Leibovici L, Gafer-Gvili A. Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis. *Eur J Heart Fail*. 2012 Apr;14(4):423–9.

- 23 Qian C, Wei B, Ding J, Wu H, Wang Y. The Efficacy and Safety of Iron Supplementation in Patients With Heart Failure and Iron Deficiency: A Systematic Review and Meta-analysis. *Can J Cardiol*. 2016 Feb;32(2):151–9.
- 24 Anker SD, Kirwan BA, van Veldhuisen DJ, Filippatos G, Comin-Colet J, Ruschitzka F, 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 Jan;20(1):125–33.
- 25 Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A. The safety of intravenous iron preparations: systematic review and meta-analysis. *Mayo Clin Proc*. 2015 Jan; 90(1):12–23.
- 26 Hofmarcher T, Cabrales Alin D, Linde C. Cost effectiveness of implementing ESC guidelines for treatment of iron deficiency in heart failure in the Nordic countries. *Scand Cardiovasc J*. 2018 Nov:1–26.
- 27 Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, et al. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J*. 2013 Apr; 165(4):575–582.e3.
- 28 Comín-Colet J, Enjuanes C, González G, Torrens A, Cladellas M, Meroño O, et al. 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 Oct;15(10):1164–72.
- 29 Drozdz M, Jankowska EA, Banasiak W, Ponikowski P. Iron Therapy in Patients with Heart Failure and Iron Deficiency: Review of Iron Preparations for Practitioners. *Am J Cardiovasc Drugs*. 2017 Jun;17(3):183–201.
- 30 Vullaganti S, Goldsmith J, Teruya S, Alvarez J, Helmke S, Maurer MS. Cardiovascular effects of hemoglobin response in patients receiving epoetin alfa and oral iron in heart failure with a preserved ejection fraction. *J Geriatr Cardiol*. 2014 Jun;11(2):100–5.
- 31 Maurer MS, Teruya S, Chakraborty B, Helmke S, Mancini D. Treating anemia in older adults with heart failure with a preserved ejection fraction with epoetin alfa: single-blind randomized clinical trial of safety and efficacy. *Circ Heart Fail*. 2013 Mar;6(2):254–63.
- 32 Kasner M, Aleksandrov AS, Westermann D, Lassner D, Gross M, von Haehling S, et al. Functional iron deficiency and diastolic function in heart failure with preserved ejection fraction. *Int J Cardiol*. 2013 Oct;168(5):4652–7.
- 33 Sandek A, Bjarnason I, Volk HD, Crane R, Meddings JB, Niebauer J, et al. Studies on bacterial endotoxin and intestinal absorption function in patients with chronic heart failure. *Int J Cardiol*. 2012 May;157(1):80–5.
- 34 Lewis GD, Malhotra R, Hernandez AF, McNulty SE, Smith A, Felker GM, et al.; NHLBI Heart Failure Clinical Research Network. 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. *JAMA*. 2017 May;317(19): 1958–66.
- 35 Macdougall IC, Strauss WE, McLaughlin J, Li Z, Dellanna F, Hertel J. A randomized comparison of ferumoxytol and iron sucrose for treating iron deficiency anemia in patients with CKD. *Clin J Am Soc Nephrol*. 2014 Apr; 9(4):705–12.
- 36 Adkinson NF, Strauss WE, Macdougall IC, Bernard KE, Auerbach M, Kaper RF, et al. Comparative safety of intravenous ferumoxytol versus ferric carboxymaltose in iron deficiency anemia: A randomized trial. *Am J Hematol*. 2018 May;93(5):683–90.
- 37 Hetzel D, Strauss W, Bernard K, Li Z, Urbaniene A, Allen LF. A Phase III, randomized, open-label trial of ferumoxytol compared with iron sucrose for the treatment of iron deficiency anemia in patients with a history of unsatisfactory oral iron therapy. *Am J Hematol*. 2014 Jun;89(6):646–50.
- 38 Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al.; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016 Jul; 37(27):2129–200.
- 39 Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al.; American College of Cardiology Foundation. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol*. 2017 Aug;70(6): 776–803.