

# Anaemia, iron deficiency and heart failure in 2020: facts and numbers

Vijay K. Chopra<sup>1\*</sup>  and Stefan D. Anker<sup>2</sup>

<sup>1</sup>Heart Failure Programme and Research, Max Super Specialty Hospital, Saket, New Delhi, India; <sup>2</sup>Department of Cardiology & Berlin Institute of Health Center for Regenerative Therapies (BCRT), German Center for Cardiovascular Research (DZHK), Partner Site Berlin, Charité-Universitätsmedizin Berlin (Campus CVK), Berlin, Germany

## Abstract

Anaemia is defined by WHO as Hb < 13.0 g/dL in male adults and <12.0 g/dL in female adults. It is a common comorbidity in patients of heart failure with both HFrEF and HFpEF. The incidence ranges between 30% and 50%, though in certain communities, it is likely to be higher still. Elderly age, severe heart failure, poor nutrition, and elevation of inflammatory markers are associated with a higher incidence of anaemia. However, the commonest contributing factor to anaemia in HF is iron deficiency. In a Canadian study of 12 065 patients, the incidence of absolute ID was 21% in anaemic patients. Many other western studies have also quoted incidences varying between 35% and 43%.

The earlier attempts to improve outcomes by supplementation with Erythropoietic-stimulating factors were unsuccessful and resulted in a higher incidence of thrombotic events. Iron deficiency (ID) has emerged as an important factor in patients of HF, even in those without anaemia and worsens outcomes. It is defined as Ferritin levels below 100 mcg/L or 100–299 µg/L with transferrin saturation of <20%. Attempts to correct ID by oral supplementation have been unsuccessful as seen in IRON-HF and IRONOUT-HF trials. FAIR-HF and CONFIRM-HF conclusively established the role of IV Iron in improving exercise capacity and quality of life in patients with HFrEF. ESC guidelines have given a class IC indication for testing all heart failure patients for ID, and an IIaA recommendation for its correction by IV ferric carboxymaltose was found to be deficient. Ongoing trials will establish the role of IV iron in improving mortality and in HFpEF patients and in patients with acute heart failure.

**Keywords** Intravenous; Heart failure with preserved ejection fraction

Received: 8 May 2020; Accepted: 15 May 2020

\*Correspondence to: Vijay K. Chopra, Heart Failure Programme and Research, Max Super Specialty Hospital, Saket, New Delhi, India.

Email: chopravk@gmail.com

## Introduction

Anaemia is defined by WHO as Hb < 13.0 g/dL in male adults and <12.0 g/dL in female adults.<sup>1</sup> It is one of the commonest associations in patients of HF<sup>2,3</sup> and has been shown to be associated with increased mortality in both acute and chronic heart failure.<sup>4,5</sup> The aetiology is varied, especially in countries like India where apart from other mechanisms, nutritional deficiency and worm infestations also play a part. ID has emerged as one of the most important causes of anaemia in patients of heart failure, though other causes need to be excluded as well. Iron is an essential element for humans due to its role in several functions in our bodies. There are several physiological conditions where its deficiency occurs. These are infancy, pregnancy, lactation, menstrual periods,

and old age. As a majority of patients of HF are in the elderly age group, it is also important to exclude other causes of anaemia such as GI malignancies which have been reported to be present in about 10% of patients undergoing endoscopic evaluation in a large study.<sup>6</sup> Over the past few years, a lot of research has been carried out into ID in conditions such as chronic kidney disease, HF, chronic inflammatory diseases, and cancer, and several mechanisms have been elucidated and corrective steps identified.

## Prevalence of anaemia in HF

Anaemia is highly prevalent in patients of heart failure. In the first multi-ethnic Asian-HF study, it was present in one third

to half the patients with HF and was shown to adversely impact QOL and survival, with remarkable differences among the different Asian ethnicities.<sup>7</sup> In a study by al-Jarallah *et al.*, the incidence of cardio renal anaemia syndrome was 27% and was associated with higher odds of all-cause mortality in acute HF patients in the Middle East, especially in those with HFrEF.<sup>8</sup> Malnutrition is an important factor contributing to anaemia in HF patients. It can be due to economic factors, loss of appetite, gut wall oedema interfering with absorption, and the presence of inflammatory cytokines. In a study by Chien *et al.*,<sup>9</sup> patients in both malnutrition and lower BMI (<25 kg/m<sup>2</sup>) strata demonstrated the lowest chance of survival compared with those with both better nutrition and higher BMI. Advanced stages of both HFrEF and HFpEF result in a high incidence of cardiac cachexia, which is a deleterious, highly catabolic condition, and is associated with significant incidence of anaemia. Low serum albumin in these patients signifies poor nutrition and is one of the important markers of poor prognosis.<sup>9</sup> However, the commonest contributing factor to anaemia in HF is iron deficiency. In a Canadian study of 12 065 patients, the incidence of absolute ID was 21% in anaemic patients.<sup>10</sup> Many other western studies have also quoted incidences varying between 35% and 43%.<sup>11,12</sup>

## Diagnosis of iron deficiency

Iron is present in circulating and stored forms. The stored iron may be in mobilizable or immobilizable forms. Hepcidin is a protein secreted by the liver<sup>13,14</sup> and controls the activity of ferroportin which, in turn, is an iron exporter out of different cell types. These are gut mucosal cells as well as the sites for iron storage, i.e. hepatocytes and macrophages. Once hepcidin binds with ferroportin, it gets destroyed by lysosomes, leading to reduced levels of ferroportin and reduced iron release.<sup>15</sup> Hepcidin levels are increased in heart failure. Thus, even if there is enough iron stored in the body, it is not available for various metabolic functions and haematopoiesis as it cannot be mobilized.

The generally accepted definition of iron deficiency is ferritin below 100 µg/L or ferritin levels of 100 to 299 µg/L along with TSAT of less than 20%.<sup>16</sup> Current ESC guidelines give a class IC indication to screen all HF patients for ID.<sup>16</sup>

## Iron metabolism

Iron itself is toxic to the cells because of its ability to generate reactive oxygen species. Therefore, it is present intracellularly as ferritin and in the intravascular compartment as a bound form with transferrin. Similarly, when administered intravenously, it is coated with another compound. The side effects of IV iron are due to the nature of this coating.

Iron is present in heme form in meat and non-heme form in vegetarian diet. Heme iron is absorbed much better from the gut. This is relevant in our country with a large population on vegetarian diet. Daily consumption of iron is 12–15 mg but only 1–2 mg is finally absorbed. The only natural form of iron excretion from the body is through exfoliation of gut mucosal cells.

The overall iron store in humans is 3–5 g, of which two-third resides in haemoglobin.<sup>13</sup> Stored iron bound to ferritin is much less, 800–1000 mg in men and 300–500 mg in women. Iron is required not only for oxygen transport but also for skeletal, neurological, and immune functions among others.

## History of treating iron deficiency

Researchers in Tel Aviv were the first to attempt exercise capacity and quality of life in late 1990s in patients with HF and anaemia by using a combination of IV iron and erythropoietin.<sup>17</sup> Over the next few months, they demonstrated a significant improvement in haemoglobin, LVEF, and functional class. This sparked off a lot of interest in this field. Several trials were carried out to improve Hb by using darbepoetin in HF patients in the belief that improvement in Hb will result in beneficial effects in HF patients. Finally, a large trial RED-HF<sup>18</sup> was launched where darbepoetin was given in HF patients with anaemia whose TSAT was over 20%. The trial was negative for improvements in cardiovascular outcomes, but there was a higher incidence of thromboembolic events and ischemic stroke. This laid to rest attempts to improve outcomes by using darbepoetin to improve Hb and cardiovascular outcomes, but sparked new interest in correcting ID rather than improving Hb.

## Oral iron therapy

Oral iron preparations are usually in ferrous form. The side effects include nausea, metallic taste in the mouth, abdominal bloating, flatulence, diarrhoea, and constipation, leading to its discontinuation in many cases. It needs to be taken at least 30 min before meals to increase its absorption. Increase in haemoglobin and reticulocyte count after 1–3 weeks indicates its success.

Two clinical trials assessed the efficacy of oral iron in patients of HF and iron deficiency. The first study named IRON-HF<sup>19</sup> was published in 2013. This compared placebo, IV iron, and oral iron in patients with LVEF < 40%, NYHA class II–IV, who had Hb 9–12 g/dL, a TSAT level of >20% and ferritin <500 µg/L. It could enrol only 23 patients. The peak oxygen consumption increased in IV iron group, but not in the other two. TSAT and ferritin levels also increased in IV iron

group, but only the latter change was statistically significant. No other similar study has been done. The data need to be interpreted with caution as most of the non-significant results could be due to beta error.

The second trial to test oral iron in HF was the IRONOUT-HF trial which enrolled 225 patients with HF, LVEF < 40%, and ID defined as ferritin levels of 15–100 µg/L or ferritin 101–299 µg/L with TSAT < 20%. Patients received either a placebo or a 150 mg oral iron polysaccharide for 16 weeks. The primary end point which was a change in peak oxygen uptake from baseline and the secondary end points did not differ in the two groups. The authors concluded that ‘these results do not support the use of oral iron supplementation in patients with HF with reduced ejection fraction.’<sup>20</sup>

## Intravenous iron therapy

Since oral iron therapy was ineffective, a number of trials have been carried out using IV iron. The earlier iron formulation, iron dextran, caused a lot of reactions and is not recommended. Current additions to the portfolio are iron sucrose, FCM, and ferumoxytol. Most studies in HF and ID have been carried out with iron sucrose or FCM.

The first large scale, double-blinded placebo-controlled trial was FAIR-HF, published in 2009.<sup>21</sup> The study enrolled 459 patients in NYHA class II (LVEF < 40%) or class III (LVEF < 45%) and Hb of 9.0–13.5 g/dL. Patients had ID defined as serum ferritin <100 µg/L or ferritin 100–299 µg/L with TSAT <20%. They were randomly allocated in 2:1 fashion to receive FCM or placebo. ID was calculated by Ganzoni’s formula and corrected by weekly doses of 200 mg. A maintenance dose of 200 mg per month was given. After 24 weeks of follow-up, 50% patients in FCM improved according to self-reported patient global assessment (PGS), the primary end point, as compared to 24% in the placebo group with odds ratio of being in a better rank: 2.51 ( $P < 0.001$ ). The secondary end points, NYHA class, 6 min walk test, and KCCQ also showed a statistically significant improvement. This improvement was regardless of the presence of anaemia at baseline. Based on this trial, IV FCM first entered in the recommendations of ESC guidelines.

The second large trial of FCM was CONFIRM-HF.<sup>22</sup> This double-blind placebo-controlled prospective randomized trial included patients with LVEF < 45%, NYHA class II or III with raised BNP or NT-ProBNP. Patients received 500–200 mg of FCM or placebo within the first 6 weeks followed by 500 mg FCM at weeks 12, 24, and 36 if they were still ID. At 24 weeks, the 6 min walk test improved significantly in patients of FCM as compared to those on placebo and the benefit was maintained at 52 weeks. A third trial named EFFECT-HF<sup>23</sup> studied the effect of IV FCM compared to standard of care in 174 patients in NYHA class II in a randomized

non-blinded fashion. At 24 weeks, peak oxygen consumption decreased in control group but was maintained in FCM group.

Two meta-analysis with regard to IV iron in HF were published in 2016 and 2017. Jankowska *et al.*<sup>24</sup> analysed five clinical studies which included 851 patients, of which 509 received iron sucrose or FCM. The analysis showed that IV iron in heart failure reduced the combined end point of all causes of death or CV hospitalization (OR 0.44;  $P < 0.0001$ ) and the combined end point of cardiovascular death or hospitalization due to worsening of HF (OR 0.39;  $P < 0.0001$ ). In addition, there was reduction in NYHA functional class ( $P = 0.001$ ), increase in 6 min walk test ( $P < 0.0001$ ) and improvement in quality of life using different assessment tools. A second meta-analysis published in 2017 included four randomized trials including 839 patients of which 504 received IV FCM.<sup>25</sup> Patients on FCM had lower incidence of CV mortality and recurrent CV hospitalizations ( $P < 0.01$ ). Recurrent HF hospitalizations and all-cause mortality also improved. These data strongly suggest the beneficial effect of IV iron in patients with HF and ID. A new trial, FAIR-HF 2, is currently under way. This trial will enrol 1200 patients with a primary end point of combined rate of recurrent HF hospitalizations and of CV death. It is expected to be completed in October 2020.

Apart from the improvement in clinical outcomes, correction of ID also results in substantial healthcare cost savings. A large retrospective claims database analysis of 172 394 patients showed that in patients with ID, those treated with IV iron had a significant reduction in mortality and the number of hospitalizations. The annual healthcare costs for HF patients with untreated incident ID/anaemia amounted to €17 347 with incremental cost of €849 ( $P < 0.01$ ) attributed to ID/anaemia.<sup>26</sup>

## Treatment of iron deficiency in HF guidelines

Since 2012, the ESC guidelines have recommended that all HF patients be screened for anaemia and ID using ferritin and TSAT giving it a Class I, level of evidence: C recommendation. After the publication of CONFIRM-HF results, in 2016 treatment recommendations were updated to Class IIa, level of evidence: A. The statement reads ‘IV FCM should be considered in symptomatic patients (Serum Ferritin <100 µg/L, or ferritin between 100 to 299 µg/L and TSAT < 20%) in order to alleviate HF symptoms and improve exercise capacity and quality of life’.<sup>16</sup> The ACC/AHA guidelines in 2017 state that ‘In patients with class II and III HF and iron deficiency, IV iron replacement might be reasonable to improve functional status and quality of life giving this recommendation an IIb level of evidence’.<sup>27</sup> While the European guidelines recommend only FCM, given the large body of evidence, the US guidelines do not specify any particular type of IV iron.

## Conclusions

Anaemia is a very common comorbid condition in patients of HF. The pathophysiology is diverse and includes nutritional deficiencies, loss of blood through GI tract, decreased iron absorption, and decreased release of stored iron. It is an independent predictor of reduced exercise capacity, quality of life, and recurrent hospitalizations. After the RED-HF trial conclusively proved that increasing haemoglobin to 12–13 g/dL by using erythropoietic factors does not improve outcomes in anaemia in HF, attention has shifted to the role of iron deficiency, which is very common in HF, even in patients who are not anaemic. The criteria for the diagnosis are now well established, and it is recommended that every patient with HF should be screened for ID. There is conclusive evidence that it reduces hospitalizations and improves quality of life. Some evidence of its effect on survival in these patients appears to be emerging, and the ongoing trials will further

answer this question. Most of the efficacy and safety data are with IV FCM. The data with IV iron in HFpEF are not clear yet, and the ongoing trial FAIR-HFpEF, which is expected to be completed in approximately 2 years, may answer this question. Likewise, the role of IV iron in acute HF is also not yet clear, and another ongoing trial, AFFIRM-AHF, expected to be completed by the end of 2020, may throw some light on this issue.

## Conflict of interest

VKC reports no conflict of interest. SDA reports receiving fees from Abbott Vascular, Bayer, Boehringer Ingelheim, Cardiac Dimension, Impulse Dynamics, Novartis, Servier, and Vifor Pharma, and grant support from Abbott Vascular and Vifor Pharma.

## References

- Nutritional anaemias. Report of a WHO scientific group. Geneva, World Health Organization, 1968. (WHO Technical Report Series, No. 405). [http://whqlibdoc.who.int/trs/WHO\\_TRS\\_405.pdf](http://whqlibdoc.who.int/trs/WHO_TRS_405.pdf)
- 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; **107**: 223–225.
- Adams KF Jr, Patterson JH, Oren RM, Mehra MR, O'Connor CM, Piña IL, Miller AB, Chiong JR, Dunlap SH, Cotts WG, Felker GM. Prospective assessment of the occurrence of anemia in patients with heart failure: results from the Study of Anemia in a Heart Failure Population (STAMINA-HFP) Registry. *Am Heart J* 2009; **157**: 926–932.
- Komajda M, Anker SD, Charlesworth A, Okonko D, Metra M, di Lenarda A, Remme W, Moulet C, Swedberg K, Cleland JGF, Poole-Wilson PA. The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. *Eur Heart J* 2006; **27**: 1440–1446.
- Von Haehling S, Schefold JC, Hodoscek LM, Doehner W, Mannaa M, Anker SD, Lainscak M. Anaemia is an independent predictor of death in patients hospitalized for acute heart failure. *Clin Res Cardiol* 2010; **99**: 107–113.
- Martens P, Minten L. Prevalence of underlying gastrointestinal malignancies in iron-deficient heart failure. *ESC Heart Fail* 2019 Feb; **6**: 37–44.
- Goh, V. J., Tromp J., Teng T.H. K., Tay W. T., van der Meer P., Ling L. H., Siswanto B. B., Hung C.L., Shimizu W., Zhang S., Narasimhan C., Yu C. M., Park S. W., Ngarmukos T., Liew H. B., Reyes E., Yap J., MacDonald M., Richards M. A., Anand I., Lam C. S.P., on behalf of the ASIAN-HF investigators, (2018) Prevalence, clinical correlates, and outcomes of anaemia in multi-ethnic Asian patients with heart failure with reduced ejection fraction. *ESC Heart Failure* 2018, : 570–578.
- Al-JarallahM RR, Al-Zakwani I, Dashti R, Bulbanat B, Sulaiman K, Alsheikh-Ali AA, Panduranga P, Al Habib KF, Al Suwaidi J, Al-Mahmeed W. Incidence and impact of cardiorenal anaemia syndrome on all-cause mortality in acute heart failure patients stratified by left ventricular ejection fraction in the Middle East. *ESC Heart Fail* 2019 Feb; **6**: 103–110.
- Chien SC, Lo CI, Lin CF, Sung KT, Tsai JP, Huang WH, Yun CH, Hung TC, Lin JL, Liu CY, Hou CJY, Tsai IH, Su CH, Yeh HI, Hung CL. Malnutrition in acute heart failure with preserved ejection fraction: clinical correlates and prognostic implications. *ESC Heart Fail* 2019 Oct; **6**: 953–964.
- Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12065 patients with new-onset heart failure. *Circulation* 2003. Jan 21; **107**: 223–225.
- Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadziejka L, Banasiak W, Polonski L, Filippatos G, McMurray JJV, Anker SD, Ponikowski P. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J* 2010; **31**: 1872–1880.
- Von Haehling S, Gremmler U, Krumm M, Mibach F, Schön N, Taggeselle J, Dahm JB, Angermann CE. 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.
- Ganz T, Nemeth E. Iron imports. IV. Hepcidin and regulation of body iron metabolism. *Am J Physiol Gastrointest Liver Physiol* 2006; **290**: G199–G203 Cross Ref PubMed.
- Crielaard BJ, Lammers T, Rivella S. Targeting iron metabolism in drug discovery and delivery. *Nat Rev Drug Discov* 2017; **16**: 2400–2423.
- Andrews NC. Closing the iron gate. *N Engl J Med* 2012; **366**: 376–377.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M. for the Authors/Task Force Members; Document Reviewers2016 ESC Guidelines 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 J Heart Fail* 2016; **18**: 891–975.
- Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, Brosh D, Laniado S, Schwartz D, Yachnin T, Shapira I, Gavish D, Baruch R, Koifman B, Kaplan C, Steinbruch S, Iaina A. 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 hospitalization. *J Am Coll Cardiol* 2000; **35**: 1737–1744.
18. Swedberg K, Young JB, Anand IS, Cheng S, Desai AS, Diaz R, Maggioni AP, McMurray J, O'Connor C, Pfeffer MA, Solomon SD, Sun Y, Tendera M, van Veldhuisen D, RED-HF Committees and Investigators (2013) Treatment of anaemia with darbepoetin alfa in systolic heart failure. *N Engl J Med* **368**:1210-1219. Cross Pub Med
  19. Beck-da-Silva L, Piardi D, Soder S, Rohde LE, Pereira-Barretto AC, de Albuquerque D, Bocchi E, Vilas-Boas F, Moura LZ, Montera MW, Rassi S, Clausell N. Iron-HF study. A randomized trial to assess the effects of iron in heart failure with anemia. *Int J Cardiol* 2013; **168**: 3439–3442.
  20. Lewis GD, Malhotra R, Hernandez AF, McNulty SE, Smith A, Felker GM, Tang WHW, LaRue SJ, Redfield MM, Semigran MJ, Givertz MM, van Buren P, Whellan D, Anstrom KJ, Shah MR, Desvigne-Nickens P, Butler J, Braunwald E, for the NHLBI Heart Failure Clinical Research Network, 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 16; **317**: 1958–1956.
  21. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, von Eisenhart Rothe B, Pocock SJ, Poole-Wilson PA, Ponikowski P, FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; **361**: 2436–2448.
  22. Ponikowski P, Van Veldhuisen DJ. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency CONFIRM-HF. *Eur Heart J* 2015 Mar 14; **36**: 657–668.
  23. Van Veldhuisen DJ, Ponikowski P, van der Meer P, Metra M, Böhm M, Doletsky A, Voors AA, Macdougall IC, Anker SD, Roubert B, Zakin L. for EFFECT-HF Investigators. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. *Circulation* 2017; **136**: 1374–1383.
  24. Jankowska EA, Tkaczyszyn M, Suchocki T, Drozd M, von Haehling S, Doehner W, Banasiak W, Filippatos G, Anker SD, Ponikowski P. Effects of intravenous iron therapy in iron deficient patients with systolic heart-failure: a meta-analysis of randomized controlled trials. *Eur J Heart Fail* 2016; **18**: 786–795.
  25. Anker S. D, Kirwan B.A., van Veldhuisen D.J., Filippatos G, Comin-Colet J, Ruschitzka F, Lüscher TF, Arutyunov GP, Motro M, Mori C, Roubert B. (2018) Effects of ferric carboxymaltose on hospitalizations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. *Eur J Heart Fail* **20**: 125-133.
  26. Jacob C, Alteviers J, Barck I, Hardt T, Braun S, Greiner W. Retrospective analysis into differences in heart failure patients with and without iron deficiency or anaemia. *ESC Heart Fail* 2019 Aug; **6**: 840–855.
  27. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR. 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 foundation/American Heart Association Task Force on Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017; **70**: 776–803.