Chapter 5

Heart Failure and Iron Deficiency

Francesco Fedele, Alessandra Cinque, Massimo Mancone, Viviana Maestrini and Carmen Caira

Additional information is available at the end of the chapter

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Abstract

Heart failure (HF) is a major public health problem because it is one of the most common causes of morbidity and mortality in Western countries, with a prevalence of 1–2% in the adult population, rising to ≥10% in those age >70 years. In addition to the "classic" co-morbidities, such as COPD, arterial hypertension, diabetes, renal failure, etc., there are other conditions frequently found in patients with heart failure that many times are underestimated. One example are anemia and iron deficiency (ID). ID, regardless of anemia impair exercise tolerance, symptoms and quality of life, with a strong negative prognostic impact on hospitalization and mortality rate. Despite strong evidence of high prevalence of ID in these patients and current guidelines recommendations, the diagnosis of ID and its monitoring over time still have low priority for physicians in clinical practice. Consequently ID is under-treated; furthermore current therapies, in particular i.v. iron as ferric carboxymaltose, though effective, turn out to be poorly managed by clinicians. ID should be considered more in real world HF healthcare settings to improve patients' quality of life and outcome.

Keywords: heart failure, heart disease, anemia, iron deficiency

1. Heart failure and comorbidity

Heart failure (HF) is a major public health problem because it is one of the most common causes of morbidity and mortality in Western countries, with a prevalence of 1–2% in the adult population, rising to ≥10% in those age >70 years [1]. Regardless of the cause, HF is a life threatening syndrome and therefore requires specific treatments aimed at reducing symptoms and improving quality and/or quantity of life. The overall aging of the population,

that has been recorded over the last few decades, has led to an increase in the prevalence of chronic pathologies, from which derives an increase in the number of elderly people that have more than one disease at the same time. Patients with HF have multiple co-morbid conditions and 60% of them have five or more [2, 3]. In addition to the "classic" co-morbidities, such as COPD, arterial hypertension, diabetes, renal failure, etc., there are other conditions frequently found in patients with heart failure that many times are underestimated. One example are anemia and iron deficiency (ID): the presence of ID, regardless of concomitant anemia, has been shown to worsen symptoms and patient prognosis.

Management of co-morbidities is a key point of HF patients care, to cut down this chronic epidemic disabling syndrome.

2. Iron deficiency in heart failure

2.1. Epidemiology

Iron deficiency (ID) is a frequent co-morbidity found in 35–50% of patients with HF; it is the most common cause of anemia in patients with HF but, most importantly, ID occurs in 46% of non-anemic patients with stable systolic HF [4, 5].

Despite its high prevalence, this co-morbidity was underdiagnosed for several years. ID can be present in patients with HF regardless of the presence of anemia and can be classified in absolute or functional ID, by determining ferritin levels: ferritin <100 μg/l if absolute ID, reflecting depleted iron stores due to low dietary intake, blood loss, etc., or ferritin between 100 and 300 μg/l and the transferrin saturation (<20%) if functional ID, when iron delivery to target cells is impaired despite normal or overly abundant iron stores, due to chronic inflammation, etc. [6, 7].

ID in chronic HF is more frequent in women and in patients with advanced HF, as shown by Klip data [4]: in an international cohort of 1506 patients with chronic HF, ID was closely related to disease severity, assessed using NYHA functional class (**Figure 1**) and NT-proBNP levels.

ID frequently overlaps with anemia and chronic kidney disease; in this study only the 7% of patients had anemia without ID (related to renal dysfunction, hemodilution, vitamins or folic deficiency, hematologic cause) [8–10].

As reported in a study of Ponikowski, ID prevalence was of 37% in a cohort of 546 CHF patients (32 ± 4 vs. 57 ± 10% in subjects without vs. with anemia) [11]. This study also showed that ID, but not anemia, was related to an increased risk of mortality after 3 years follow-up (**Figure 2**).

In the setting of acute heart failure patients, ID prevalence is even higher (50–80%) [12, 13].

In preserved ejection fraction HF it is also high, as showed in subgroups analysis.

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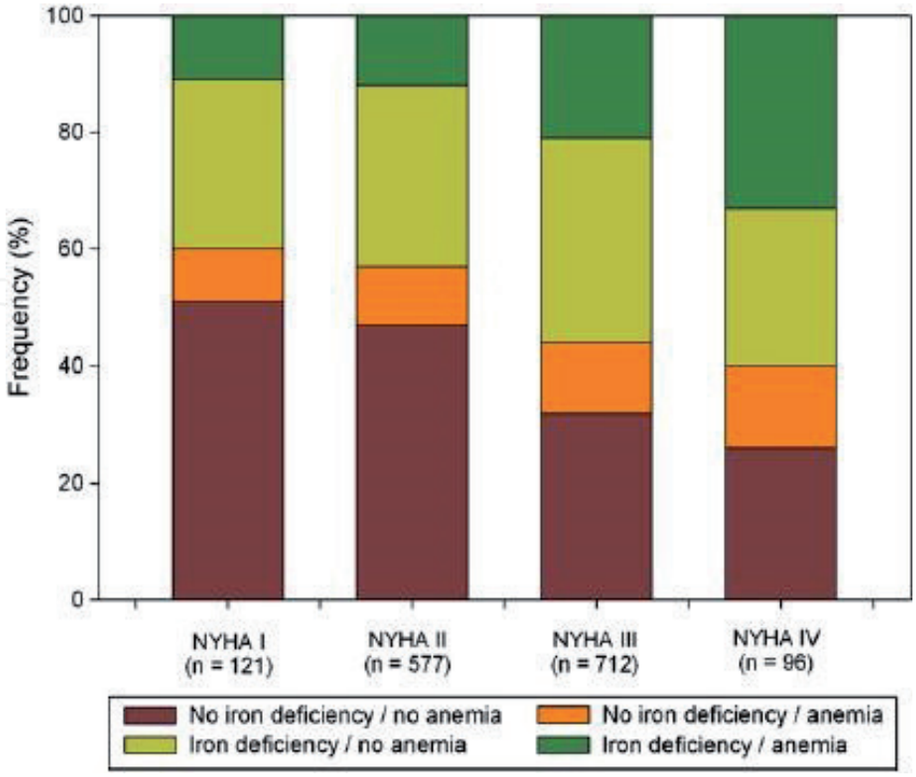

Figure 1. ID and anemia stratified by NYHA functional class. Modify by Iron deficiency in chronic heart failure: an international pooled analysis.

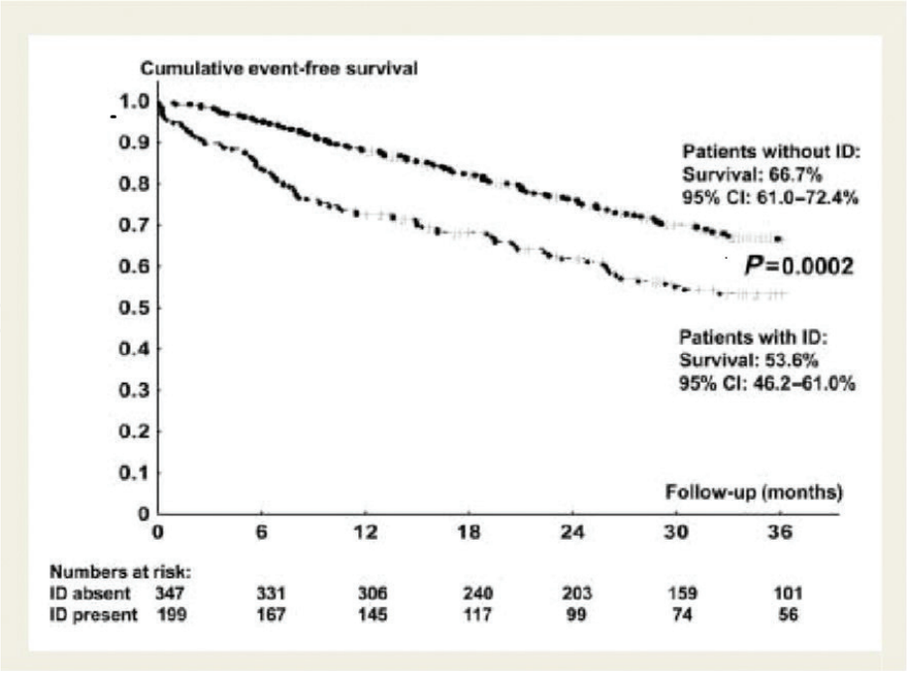

Figure 2. ID was related to an increased risk of mortality after 3 years follow-up. Modify by Iron deficiency: an ominous sign in patients with systolic chronic heart failure.

2.2. Clinical and prognostic impact

In patients with chronic HF, ID, regardless of the presence of anemia, is a strong and independent predictor of outcome, in fact it is associated with higher mortality and hospitalization rates [13, 14]. Moreover, ID has been shown to worsen HF symptoms and to impair exercise tolerance, with poor quality of life [11]. The explanation is simple and is related to the key role of iron in human homeostasis. Iron, as is well known, is essential for erythropoiesis, as part of the hemoglobin, ad so for oxygen transport. Moreover, as is perhaps less well known [15], iron is a fundamental co-factor for other several processes, such as normal activity of key enzymes of the citric acid cycle and ROS scavenging enzymes. It plays an important role in generation of ATP, necessary for all cellular process and for muscles contractility. Recent in vitro evidence show that ID directly affects human cardiomyocytes function, impairing mitochondrial respiration, and reducing contractility and relaxation. In this regard, a special characteristic of physical stress in heart failure is the early shift from aerobic to anaerobic metabolism due to the compromission of oxidative capacity [16]. It is therefore clear that ID can only worse exercise intolerance and sub-maximal exercise resistance, heavily compromising quality of life. Restoration of intracellular iron levels can reverse these effects [17]. Exercise tolerance was analyzed in 443 patients with systolic chronic heart failure: only ID (and not anemia) was significantly associated with reduced peak oxygen consumption (VO_2) (**Figure 3**) [18].

Another study from Okonko confirm these data on 157 chronic HF patients: ID was related to impaired exercise capacity and survival and appeared prognostically more ominous than anemia [19]. In the same way, it is known that ID therefore has a negative impact on Quality

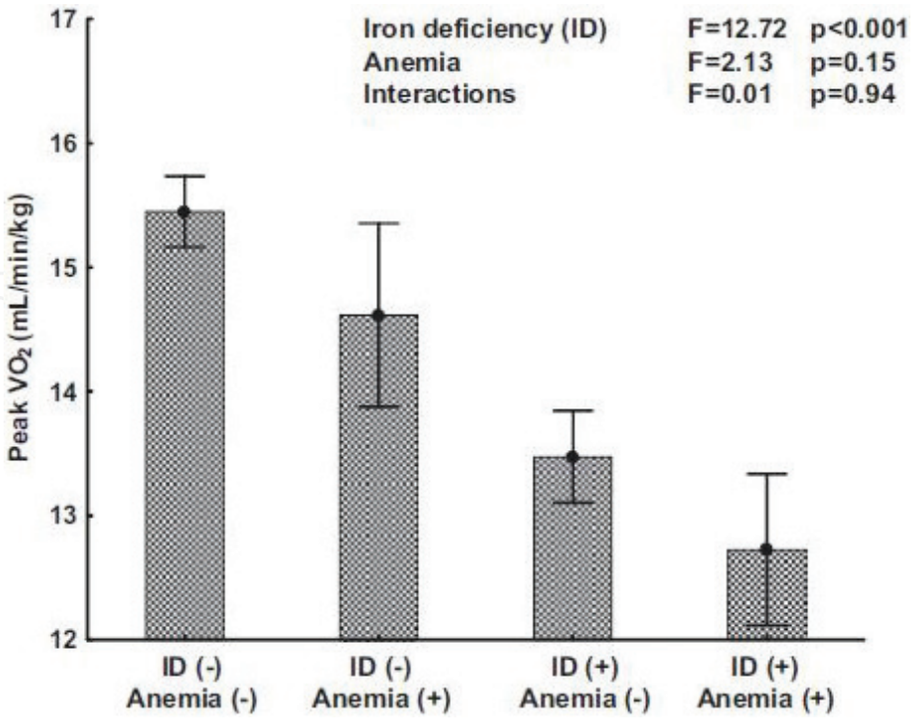

Figure 3. ID is significantly associated with reduced peak VO_2. Modify by Iron deficiency predicts impaired exercise capacity in patients with systolic chronic heart failure.

of Life, measured by Minnesota Living with Heart Failure questionnaire, and this is independent of the presence of anemia. Lower TSAT is related to lower QoL; the correlation is not so clear for hemoglobin level [20]. Furthermore, ID is a strong and independent predictor of outcome in HF patients, as shown in several studies. In the large international pooled cohort of 1506 chronic HF patients by Klip, ID identifies those with an enhanced risk for death, independently of other well-established predictors of outcome, and appears to have greater predictive power than anemia (**Figures 4** and **5**) [4].

For several years, we consider only anemia as negative prognostic factor, but definitely, the negative effect of iron deficiency seems to be stronger.

2.3. Treatments

Given the clinical importance of ID in HF patients, restoration of iron stores to normal levels should be a therapeutic goal in clinical practice [21], as well as addressing its underlying causes.

Regardless the known poor efficacy, oral iron supplementation is almost always the first line therapy for ID, due to their low cost and ease of administration. Ferrous sulfate is the most commonly used. However, gastrointestinal side effects are common and can often compromise the therapy compliance. Moreover, the enteric absorption may be reduced by quite a lot of factors: interaction with other drugs or food, edema and congestion of the gastrointestinal mucosa, high hepcidin level in HF [22].

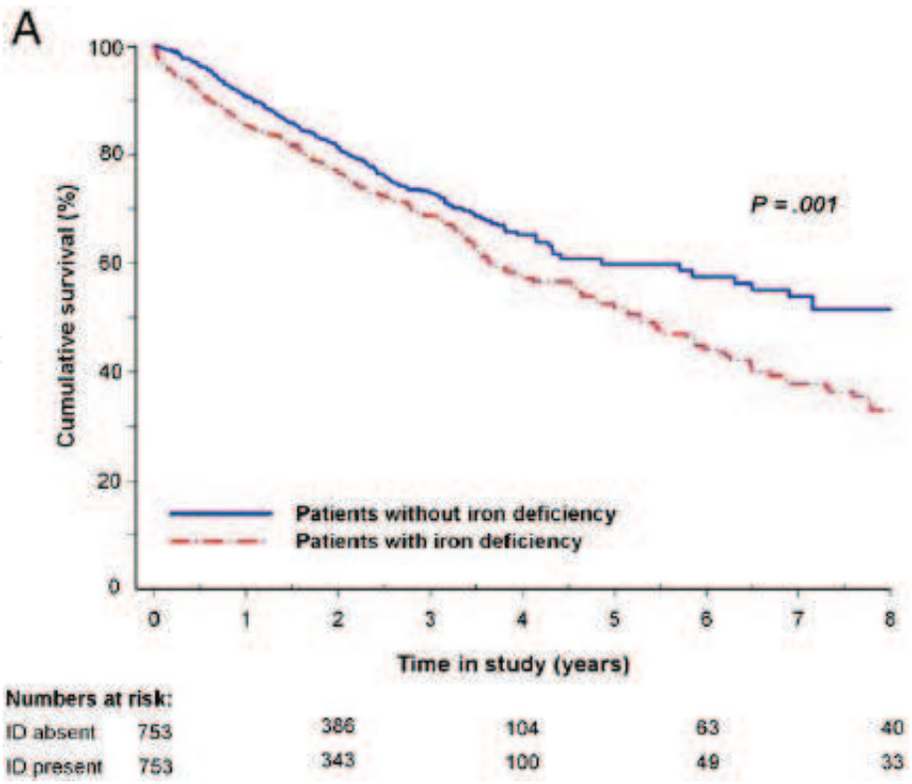

Figure 4. ID is a strong and independent predictor of outcome in HF patients. Modify by Iron deficiency in chronic heart failure: an international pooled analysis.

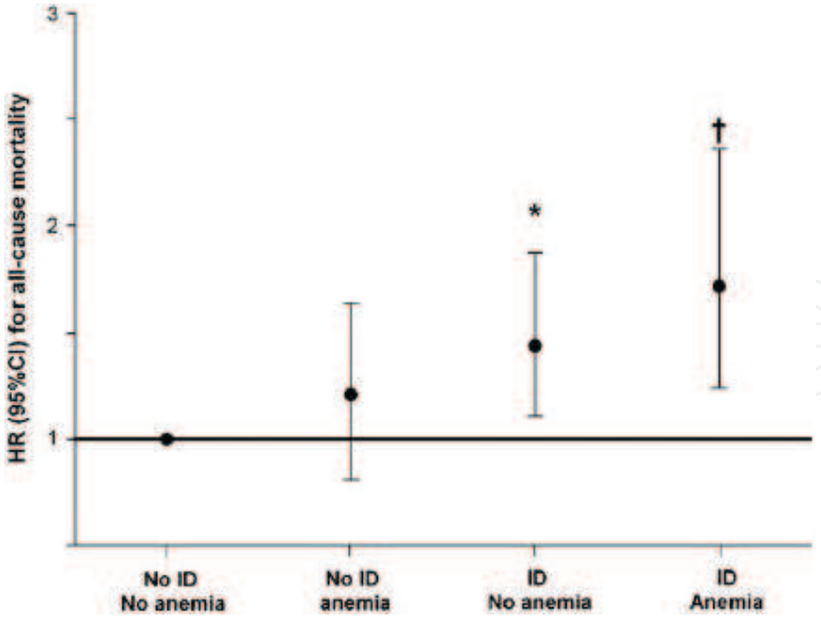

Figure 5. Mortality among groups of ID and/or anemia (* p<0.01; † p<0.001). Modify by Iron deficiency in chronic heart failure: an international pooled analysis.

In addition, iron deficiency in HF patients is severe in the most of the case (on average 1.5–2 g of iron); considering that a tablet has 80 mg of iron (with a bioavailability of 10%), the supplement must be prolonged for months to be effective. As we will see later, the use of iron salt is not supported by clinical trials data.

Intravenous iron may solve these problems and may be more suitable both for physicians and patients [23, 24]. Intravenous iron complex used for ID are ferric gluconate, ferric carboxymaltose, ferric hydroxide sucrose, and ferric hydroxide dextran. A big advantage of intravenous iron is the rapid improvement in iron parameters [25]: it is not influenced by hepcidin absorption blocking mechanisms. Probably it is also cost-effectiveness, because reduce hospitalization and improved quality of life [26].

Comparative data from the different complex are not available. However, ferric carboxymaltose has the advantage of high dose (500 mg) formulation [27]: it seems to be particularly effective in severe ID, that is frequently diagnosed in HF patients, and well tolerated. One or two injections are usually adequate to reach the therapeutic target.

The most of clinical trials on ID correction in HF evaluated the use of ferric carboxymaltose.

2.4. From clinical trials to guidelines

The FAIR-HF study was the first big multicentric, prospective, double-blind, randomized trial [28] published in the contest of iron supplementation in HF, almost 10 years ago. Patients were randomized to receive intravenous ferric carboxymaltose or placebo. Quality of life, symptoms, distance during 6-minute walking test were significantly improved after treatment

with ferric carboxymaltose in patients with chronic HF and ID, with or without anemia. A such strong result was really not expected. The clinical improvement was confirmed in several patient's subgroups, based on hemoglobin level, renal function, gender, ejection fraction. Moreover, intravenous iron improved patient's global assessment and NYHA class in both anemic and non-anemic patients with HF.

Another trial, CONFIRM-HF [11], was performed in heart failure patients with iron deficiency. It was a multicentre, double-blind, placebo-controlled trial that enrolled 304 ambulatory symptomatic HF patients with left ventricular ejection fraction ≤45%, elevated natriuretic peptides, and iron deficiency. The primary endpoint was the exercise capacity. Ferric carboxymaltose significantly improved 6 minutes walking test distance from baseline to week 24. Moreover the treatment may be associated with risk reduction of hospitalization for worsening HF at week 52; although it was a secondary endpoint, it had an amazing relevance.

The EFFECT-HF trial was a multicenter, randomized 1:1, open label, standard of care controlled trial [29]; the primary endpoint was change in peak VO_2 from baseline to week 24. Again, intravenous ferric carboxymaltose significantly improve exercise capacity in heart failure patients. The main limit of this trial was that standard of care not include intravenous iron, but just oral formulation.

So, treatment with intravenous ferric carboxymaltose in patients with HF and iron deficiency improves iron stores.

Whether ferric carboxymaltose seems to be associated with an improved clinical condition and outcome in these high-risk patients, further study are necessary.

In the last few months was performed an individual patient meta-analysis on the topic [30]. Individual patient data were extracted from randomized clinical trials comparing ferric carboxymaltose with placebo in patients with systolic HF and ID. The endpoints were recurrent cardiovascular hospitalizations and cardiovascular mortality. About 839 patients, of whom 504 were randomized to FCM, were included. Ferric carboxymaltose was associated with a reduction in cardiovascular hospitalizations.

The results of this analysis show that treatment of ID with e.v. ferric carboxymaltose in ambulatory systolic HF patients with ID may decrease recurrent cardiovascular hospitalizations.

These findings suggest that intravenous iron therapy may potentially represent a beneficial addition to the standard medical management of HF (**Table 1**).

Although the individual patient meta-analysis is the best type of statistical analysis, a specific randomized clinical trial is needed.

About oral iron therapy, the most relevant trial published is the IRONOUT trial [31]. It was a double-blind, placebo-controlled randomized clinical trial of patients with reduced ejection fraction (<40%). Oral iron polysaccharide (150 mg twice daily) was compared to placebo. Among patients with HF with iron deficiency, high-dose oral iron did not improve exercise capacity over 16 weeks and did not change iron biomarkers. Probably the absorption from

Recurrent event outcomes	FCM (N = 504)	Placebo (N = 335)	p
	NB. Total events (incidence per 100 patient-years of follow-up)		
CV hospitalization and CV death	69 (23.0)	92 (40.9)	0.009
HF hospitalization and CV death	39 (13.0)	60 (26.7)	0.011
CV hospitalization and all-cause death	71 (23.7)	94 (41.8)	0.009
HF hospitalization and all-cause death	41 (13.7)	62 (27.6)	0.011
All-cause hospitalization and all-cause death	108 (36.1)	118 (52.5)	0.060
HF hospitalization	22 (7.3)	43 (19.1)	0.003
CV hospitalization	52 (17.4)	75 (33.3)	0.004
All-cause hospitalization	89 (29.7)	99 (44.0)	0.056

Modify by Effects of ferric carboxymaltose on hospitalizations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis.

Table 1. Results from individual patient meta-analysis by Anker et al.

the gastrointestinal tract is limited by foods, medications, edema of the intestinal mucosa due to venous congestion [32], upregulation of hepcidin [33]. Moreover, each tablet has a dose of iron that is very low (compared with the massive iron deficiency that affects heart failure patients), so the treatment should be prolonged for several months. These results do not support use of oral iron supplementation in patients with HfrEF.

Based on the actual evidence, the current ESC guidelines on diagnosis and treatment of HF [1] recommend very clearly that all patients with HF have to be screened for ID based on serum ferritin and TSAT (Class I, Level C) (**Figure 6**). The dosage of ferritin and TSAT has the same strong of recommendation of the evaluation of hemoglobin and white cells, sodium, potassium, urea, creatinine, glucose, liver function test and other routine analysis. We also have the specific recommendation regarding the treatment: intravenous ferric carboxymaltose should be considered in symptomatic patients with HFrEF and iron deficiency in order to alleviate HF symptoms, and improve exercise capacity and quality of life (**Figure 7**). It is important to note that when the guidelines were published there was not available the results of meta-analysis from Anker that showed the benefits in terms of heart failure hospitalization and cardiovascular death.

Based on the results of FAIR-HF and CONFIRM-HF trials, the 2017 ACC/AHA/HAS guidelines for management of HF [34, 35] also state that IV iron might be reasonable in NYHA Class II to III patients with ID (Class II, Level B) to improve QoL and functional status.

2.5. Real world data

In addition to clinical trials and guidelines, real world data confirm not only the high prevalence and the negative prognostic impact of ID in HF patients, but also the efficacy of i.v. iron, in particular of FCM, to treat this important comorbidity. But, despite this background, real world data show also what is still happening today in clinical practice, that is the poor attention paid to the diagnosis and treatment of ID in HF patients.

Recommendations	Class [a]	Level [b]
The following diagnostic tests are recommended/should be considered for initial assessment of a patient with newly diagnosed HF in order to evaluate the patient's suitability for particular therapies, to detect reversible/treatable causes of HF and co-morbidities interfering with HF:		
- haemoglobin and WBC - sodium, potassium, urea, creatinine (with estimated GFR) - liver function tests (bilirubin, AST, ALT, GGTP) - glucose, HbA1c - lipid profile - TSH - ferritin, TSAT = TIBC	I	C
- natriuretic peptides	IIa	C

Figure 6. Recommendations for diagnostics tests in patients with heart failure. Modify by ESC HF guidelines.

Recommendations	Class [a]	Level [b]	Ref [c]
Iron deficiency			
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	IIa	A	469, 470

Figure 7. Recommendations for the treatment of other comorbidities in patients with heart failure. Modify by ESC HF guidelines.

The PReP prospective Registry [36] show that in a real world setting of 1198 ambulatory patient with HF, ID was present in 42.5% of the study participants, and not previously known in any of them. The prevalence of anemia was 18.9%, and it was known prior to enrolment only in 4.8% of participants. ID, more common in anemic patients, was an independent predictor of reduced exercise tolerance. The authors conclude that despite high prevalence and clinical relevance, ID and anemia are often unappreciated in real world ambulatory HF patients.

Regarding treatment, although several Clinical trials studied FCM use and efficacy, real world evidence is limited. Nunes data [37] show that in 459 HF outpatient with ID treated with FCM therapy, Hb and TSAT increased and FCM was well tolerated; moreover higher doses of FCM (500 mg–1000 mg and 100-3000 mg) showed a significant higher efficacy compared with lower dose (500 mg).

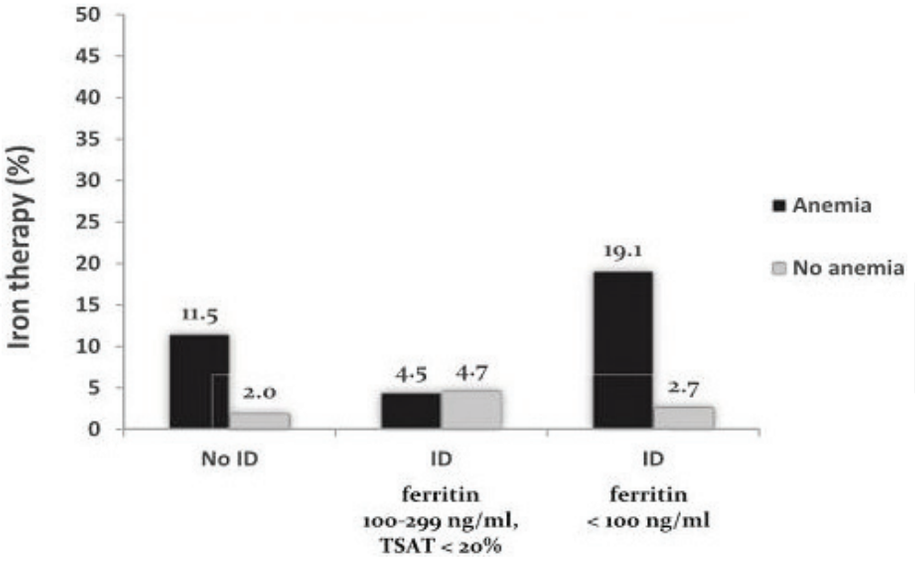

Figure 8. ID is under-treated, especially in non-anemic patients. Modify by RAID-HF registry.

But, despite these data, current guidelines and the results of IRONOUT trial, in real world oral iron is often the first line therapy for ID in HF, that remain an underdiagnosed comorbidity as showed by Wienbergen in the sub-study of the RAID-HF registry [38], aimed to obtain information on ID management in a large real world cohort of HF patients. The results showed that among 1484 participants, iron status was determined only in 62% of them (and 55% had ID), despite it was a registry focusing on ID in HF! Furthermore only 8.5% of ID patients received iron therapy, most of them orally and just 11 of the 13 patients treated with i.v. iron received FCM. Patients on iron therapy had higher NYHA class and were predominantly anemic; physicians analyzed and treated ID only in severe HF or in presence of anemia (**Figure 8**); and it is not evidence based because the efficacy of iron therapy is demonstrated independently of anemia.

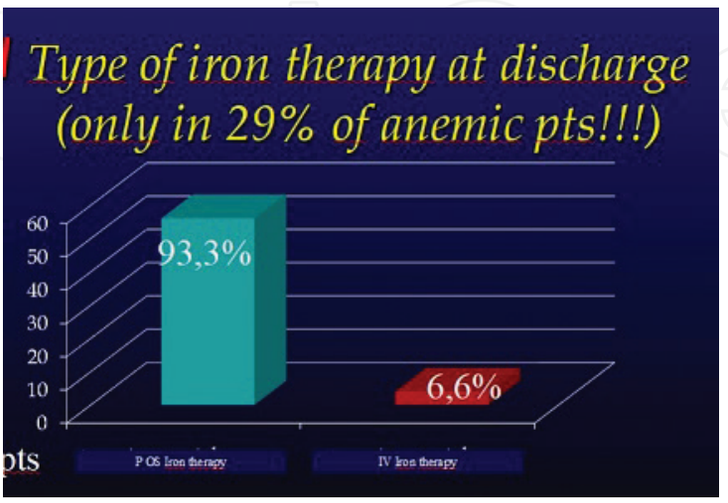

Figure 9. Type of iron therapy at discharge. Modify by Carmes-1 study.

These real word data, that confirm the results of our CARMES 1 study in a cohort of 418 hospitalized HF patients in Italy in which ID was underdiagnosed and undertreated [39] (**Figure 9**), underline that diagnostic and therapeutic efforts on ID management in HF are still low in clinical practice.

3. Conclusion

Iron deficiency, regardless of anemia, is a frequent co-morbidity in HF patients, which impair exercise tolerance, symptoms and quality of life, with a strong negative prognostic impact on hospitalization and mortality rate.

Despite strong evidence of high prevalence of ID in these patients and current guidelines recommendations, the diagnosis of ID and its monitoring over time still have low priority for physicians in clinical practice. Consequently ID is under-treated; furthermore current therapies, in particular i.v. iron as FCM, though effective, turn out to be poorly managed by clinicians.

Therefore ID should be considered more in real world HF healthcare settings to improve patients' quality of life and outcome.

Author details

Francesco Fedele[1]*, Alessandra Cinque[1], Massimo Mancone[1], Viviana Maestrini[1] and Carmen Caira[2]

*Address all correspondence to: francesco.fedele@uniroma1.it

1 Department of Cardiovascular, Respiratory, Nephrologic and Anesthesiologic Sciences, Sapienza University of Rome, Rome, Italy

2 Sacra Famiglia Hospital – Fatebenefratelli. Erba, Como, Italy

References

[1] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2016;**37**:2129-2200

[2] Wong CY, Chaudhry SI, Desai MM, Krumholz HM. Trends in comorbidity, disability, and polypharmacy in heart failure. The American Journal of Medicine. Feb 2011;**124**(2): 136-143

[3] Nakano H, Toshiyuki N, Varum S, Michikazu N, Kunihiro N, Yasuyuki H, Satoshi H, Naotsugu I, Yasuo S, Yasuhide A, Takeshi A, Teruo N, Kengo K, Hiroyuki Y, Hisao O, Satoshi Y, Tashiro C, Toshihisa A, on behalf of the Na DEF Investigators. Impact of iron deficiency on long term clinical outcomes of hospitalized patients with heart failure. International Journal of Cardiology. 2018;**261**:114-118

[4] Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, Lok DJ, Rosentryt P, Torrens A, Polonski L, van Veldhuisen DJ, van der Meer P, Jankowska EA. Iron deficiency in chronic heart failure: An international pooled analysis. American Heart Journal. Apr 2013;**165**(4):575-582

[5] Doehner W, Blankenberg S, Erdmann E, Ertl G, Hasenfuß G, Landmesser U, Pieske B, Schieffer B, Schunkert H, von Haehling S, Zeiher A, Anker SD. Iron deficiency in chronic heart failure: Diagnostic algorithm and present-day therapeutic options. Deutsche Medizinische Wochenschrift. May 2017;**142**(10):752-757

[6] Wish JB. Assessing iron status: Beyond serum ferritin and transferrin saturation. Clinical Journal of the American Society of Nephrology. Sep 2006;**1**(Suppl 1):S4-S8

[7] Dignass A, Farrag K, Stein J. Limitations of serum ferritin in diagnosing Iron deficiency in inflammatory conditions. International Journal of Chronic Diseases. Mar 18, 2018;**2018**:9394060. DOI: 10.1155/2018/9394060 eCollection 2018

[8] Nanas JN, Matsouka C, Karageorgopoulos D, Leonti A, Tsolakis E, Drakos SG, Tsagalou EP, Maroulidis GD, Alexopoulos GP, Kanakakis JE, Anastasiou-Nana MI. Etiology of anemia in patients with advanced heart failure. Journal of the American College of Cardiology. Dec 19, 2006;**48**(12):2485-2489

[9] Solomakhina NI, Nakhodnova ES, Ershov VI, Belenkov YN. The role of hepcidin in formation of anemia of chronic disease and iron deficiency anemia in elderly and old patients with chronic heart failure. Kardiologiia. Mar 2018;**3**:20-27

[10] Cunha GJL, Rocha BML, Menezes Falcão L. Iron deficiency in chronic and acute heart failure: A contemporary review on intertwined conditions. European Journal of Internal Medicine. Jun 2018;**52**:1-7

[11] Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja L, Banasiak W, Polonski L, Filippatos G, McMurray JJ, Anker SD, Ponikowski P. Iron deficiency: An ominous sign in patients with systolic chronic heart failure. European Heart Journal. Aug 2010;**31**(15):1872-1880

[12] Cohen-Solal A, Damy T, Terbah M, Kerebel S, Baguet JP, Hanon O, Zannad F, Laperche T, Leclercq C, Concas V, Duvillié L, Darné B, Anker S, Mebazaa A. High prevalence of iron deficiency in patients with acute decompensated heart failure. European Journal of Heart Failure. Sep 2014;**16**(9):984-991

[13] Nunez J, Comin-Colet J, Minana G, Nunez E, Santas E, Mollar A, Valero E, Garcia-Blas S, Cardells I, Bodi V, Chorro FJ, Sanchis J. Iron deficiency and risk of early readmission following a hospitalization for acute heart failure. European Journal of Heart Failure. Jul 2016;**18**(7):798-802

[14] Nakano H, Nagai T, Sundaram V, Nakai M, Nishimura K, Honda Y, Honda S, Iwakami N, Sugano Y, Asaumi Y, Aiba T, Noguchi T, Kusano K, Yokoyama H, Ogawa H, Yasuda S, Chikamori T, Anzai T, NaDEF Investigators. Impact of iron deficiency on long-term clinical outcomes of hospitalized patients with heart failure. International Journal of Cardiology. Jun 15, 2018;**261**:114-118

[15] Rocha BML, Cunha GJL, Menezes Falcão LF. The Burden of Iron Deficiency in Heart Failure: Therapeutic Approach. Journal of the American College of Cardiology. 2018 Feb 20;**71**(7):782-793

[16] Martens P, Verbrugge FH, Nijst P, Dupont M, Mullens W. Limited contractile reserve contributes to poor peak exercise capacity in iron-deficient heart failure. European Journal of Heart Failure. Apr 2018;**20**(4):806-808

[17] Hoes MF, Grote Beverborg N, Kijlstra JD, Kuipers J, Swinkels DW, Giepmans BNG, Rodenburg RJ, van Veldhuisen DJ, de Boer RA, van der Meer P. Iron deficiency impairs contractility of human cardiomyocytes through decreased mitochondrial function. European Journal of Heart Failure. May 2018;**20**(5):910-919

[18] Jankowska EA, Rozentryt P, Witkowska A. Iron deficiency predicts impaired exercise capacity in patients with systolic chronic heart failure. Journal of Cardiac Failure. 2011;**17**:899-906

[19] Okonko DO, Mandal AKJ, Missouris CG, Poole-Wilson PA. Disordered iron homeostasis in chronic heart failure. Journal of the American College of Cardiology. Sep 2011; **58**(12):1241-1251

[20] Enjuanes C, Klip IT, Bruguera J, Cladellas M, Ponikowski P, Banasiak W, van Veldhuisen DJ, van der Meer P, Jankowska EA, Comín-Colet J. Iron deficiency and health-related quality of life in chronic heart failure: Results from a multicenter European study. International Journal of Cardiology. Jun 15, 2014;**174**(2):268-275

[21] McDonagh T, Macdougall IC. Iron therapy for the treatment of iron deficiency in chronic heart failure: Intravenous or oral? European Journal of Heart Failure. Mar 2015;**17**(3):248-262

[22] Jankowska EA, von Haehling S, Anker SD, Macdougall IC, Ponikowski P. Iron deficiency and heart failure: Diagnostic dilemmas and therapeutic perspectives. European Heart Journal. Mar 2013;**34**(11):816-829

[23] Jankowska EA, Drozd M, Ponikowski P. Iron deficiency treatment in patients with heart failure. Handbook of Experimental Pharmacology. 2017;**243**:561-576

[24] Gstrein C, Meyer M, Anabitarte P. Iron substitution in the treatment of chronic heart failure. Swiss Medical Weekly. Jul 11, 2017;**100**:w14453

[25] Ponikowski P, van Veldhuisen DJ, 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. European Heart Journal. Mar 14, 2015;**36**(11):657-668

[26] Hofmarcher T, Borg S. Cost-effectiveness analysis of ferric carboxymaltose in iron-deficient patients with chronic heart failure in Sweden. Journal of Medical Economics. 2015;**18**(7):492-501

[27] Scott LJ. Ferric carboxymaltose: A review in iron deficiency. Drugs. Mar 2018;**78**(4):479-493

[28] Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Luscher 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. The New England Journal of Medicine. Dec 17, 2009;**361**(25):2436-2448

[29] 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, Cohen-Solal A. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and Iron deficiency. Circulation. Oct 10, 2017;**136**(15):1374-1383

[30] Anker SD, Kirwan BA, van Veldhuisen DJ, Filippatos G, Comin-Colet J, Ruschitzka F, Lüscher TF, Arutyunov GP, Motro M, Mori C, Roubert B, Pocock SJ, Ponikowski P. Effects of ferric carboxymaltose on hospitalizations and mortality rates in iron-deficient heart failure patients: An individual patient data meta-analysis. European Journal of Heart Failure. 2018;**20**:125-133

[31] 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. 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. Journal of the American Medical Association. May 16, 2017;**317**(19):1958-1966

[32] Sandek A, Bjarnason I, Volk HD, Crane R, Meddings JB, Niebauer J, Kalra PR, Buhner S, Herrmann R, Springer J, Doehner W, von Haehling S, Anker SD, Rauchhaus M. Studies on bacterial endotoxin and intestinal absorption function in patients with chronic heart failure. International Journal of Cardiology. 2012;**157**:80-85

[33] Niehaus ED, Malhotra R, Cocca-Spofford D, Semigran M, Lewis GD. Repletion of iron stores with the use of oral iron supplementation in patients with systolic heart failure. Journal of Cardiac Failure. Aug 2015;**21**(8):694-697

[34] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 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. Journal of Cardiac Failure. Aug 2017;**23**(8):628-651

[35] Bozkurt B. What is new in heart failure management in 2017? Update on ACC/AHA heart failure guidelines. Current Cardiology Reports. Apr 17, 2018;**20**(6):39

[36] 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. Clinical Research in Cardiology. Jun 2017;**106**(6):436-443

[37] Nunes AR, Fonseca C, Marques F, Belo A, Brilhante D, Cortez J. Prevalence of anemia and iron deficiency in older Portuguese adults: An EMPIRE substudy. Geriatrics & Gerontology International. 2017;**17**:1814-1822

[38] Wienbergen H, Pfister O, Hochadel M, Michel S, Bruder O, Remppis BA, Maeder MT, Strasser R, von Scheidt W, Pauschinger M, Senges J, Hambrecht R. Usefulness of iron deficiency correction in management of patients with heart failure [from the registry analysis of iron deficiency-heart failure (RAID-HF) registry]. The American Journal of Cardiology. Dec 15, 2016;**118**(12):1875-1880

[39] Caira C, Ansalone G, Mancone M, Canali E, Pagliaro M, Fratarcangeli L, Aznaran CA, Gatto MC, Di Pietro R, Fedele F. Heart failure and iron deficiency anemia in Italy: Results from CARMES-1 registry. Future Cardiology. May 2013;**9**(3):437-444

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