Iron Deficiency in Heart Failure – the Relevance for the Patient
Proceedings of a satellite symposium held at the ESC Congress 2014 on 1 September 2014 in Barcelona
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Abstract

A satellite symposium at the 2014 European Society of Cardiology (ESC) congress discussed the importance of iron deficiency (ID) in heart failure (HF). ID is the main cause of anaemia and is observed in almost 50 % of HF patients in Europe and up to 80 % of patients in Asia. ID is an independent factor associated with reduced exercise capacity, reduced quality of life (QoL) and poor outcomes in HF. The importance of ID in HF is reflected in the fact that the current ESC Guidelines for HF recognise ID as a co-morbidity in HF for the first time, and recommend routine diagnosis and monitoring for ID based on iron parameters. Intravenous (i.v) administration of ferric carboxymaltose (FCM) was considered as a possible treatment option according to the findings of the Ferric Carboxymaltose Assessment in Patients With IRon Deficiency and Chronic Heart Failure (FAIR-HF) clinical study, which showed that treatment with FCM in HF patients with ID improves symptoms, exercise capacity and QoL. These findings were confirmed by the recent Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure (CONFIRM-HF) study, which demonstrated that, in symptomatic patients with chronic HF and ID treatment with i.v. FCM over one year resulted in sustainable improvements in exercise capacity, symptoms and QoL, and was associated with a reduced risk of hospitalisations due to worsening HF.

Keywords
Ferric carboxymaltose, heart failure, iron deficiency

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Iron Deficiency in Heart Failure
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HF has a significant impact on QoL that is worse than the impact of other chronic diseases, particularly in terms of physical function.1 HF is characterised by exercise intolerance, fatigue and dyspnoea, and is classified according to severity in New York Heart Association (NYHA) classes I–IV, where Class I is no limitation of physical activity and Class IV is the inability to undertake any physical activity without discomfort.2 An emerging problem in HF is ID. ID is prevalent among patients with HF; in a recent international pooled cohort study (n=1,506), ID (defined as serum ferritin <100 µg/L or <299 µg/L if transferrin saturation [TSAT] <20 %) was found in 50 % of the total patient population. ID is the commonest cause of anaemia, but even in the absence of anaemia, ID was present in 45.6 % of patients (see Figure 1).3 Disease severity, assessed by NYHA class and N-terminal of pro-brain natriuretic peptide (NT-proBNP) levels, proved to be powerful and independent predictors of a disordered iron status. Furthermore, ID has been found to be an independent factor associated with reduced exercise capacity,4 reduced QoL4,5 and poor outcome.3

In 2012, the ESC Guidelines for the diagnosis and treatment of acute and chronic HF recognised ID as a co-morbidity in HF for the first time and recommended diagnosis of ID based on iron parameters in all patients suspected of having HF.2,7 Furthermore, the guidelines now detail the mechanism of action of iron in muscle function (and therefore the explanation for deficiency-related pathology and onset of symptoms in HF independent of the pro-erythropoietic function of iron); the need for routine monitoring for ID; and the beneficial effects on symptoms, physical performance and QoL of treating ID with intravenous (i.v) ferric carboxymaltose (FCM). Based on the findings of the Ferric Carboxymaltose Assessment in Patients With Iron Deficiency and Chronic Heart Failure (FAIR-HF) study, which found that treatment with i.v. FCM in iron deficient patients with chronic HF improves symptoms, exercise capacity and QoL irrespective of whether anaemia was present or not. FCM is now considered as a possible treatment option in the current ESC Guidelines for HF.3 Further investigation.

Iron Deficiency, a Common Neglected Burden in Heart Failure
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Dr Carolyn Lam began by discussing data from the recent prevalence study of ID in HF;8 for which the study cohort was from European countries only. A study of ID in Asian patients with HF (n=751) found a higher prevalence of ID (61 %).3 The prevalence was particularly high in women (71 % versus 59 % in men) and in South Asian Indian populations (a prevalence of 82 %).3 South Asians tend to be vegetarian and also drink black tea, which has been shown to decrease iron absorption by 80 % when taken with food.4

Genetic factors are also important in determining ID; a number of studies have investigated TMPRSS6, which encodes a transmembrane serine protease produced by the liver that regulates the expression of the systemic iron-regulatory hormone hepcidin. Germline mutations in TMPRSS6 have been found in extended families where more than one member had ID.13 Variants in TMPRSS6 have also been found to be risk factors for ID and iron deficiency anaemia (IDA) in 2,139 unrelated elderly Chinese women.15

In order to evaluate the impact of ID in HF, it is important to understand iron metabolism. Dietary iron is utilised not only in circulating erythrocytes, but also in muscle myoglobin and other iron containing enzymes.15 Patients with HF may be iron deficient as a result of reduced iron storage (absolute ID), which may be caused by malnutrition, malabsorption and gastrointestinal (GI) oedema and blood losses (due to use of anticoagulants, non-steroidal anti-inflammatory drugs [NSAIDs] and loss of mucosal integrity).13 Another important cause of ID in HF is impaired iron mobilisation (functional ID), resulting from the inflammatory processes that characterise chronic HF. Activation of pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1) and tumour necrosis factor alpha (TNF-α) causes over-expression of hepcidin by the liver. This blocks the intestinal absorption of iron and diverts iron from the circulation into the reticuloendothelial system (RES), causing reticuloendothelial block, as well as blunting responses to erythropoietin (EPO) and causing apoptosis of erythroid progenitors.15-16 At the cellular level, ID reduces the delivery of oxygen to the mitochondria but also directly decreases the activity of key enzymes of the citric acid cycle and of the respiratory chain of the mitochondria, resulting in reduced oxygen utilisation (which is, in the clinical setting, observed as reduced peak oxygen consumption [pVO2]).16

ID reduces work capacity and energy efficiency in HF17,18 and iron status correlates to NYHA status.3 The fact that ID but not anaemia
is associated with reduced exercise capacity in HF and can be explained by the non-haematopoietic effects of iron, including its role in mitochondrial function in cells with high energy requirements, such as cardiomyocytes and skeletal myocytes. In patients with chronic HF, ID but not anaemia has also been associated with reduced QoL (assessed using the Minnesota Living with Heart Failure [MLWHF] questionnaire), mostly due to physical factors. Furthermore, ID is a stronger negative prognostic indicator for all-cause mortality than anaemia (see Figure 2). A recent study in Singapore assessed the impact of ID in Asian patients with HF. Functional ID was found in the majority (64%) of patients with HF. Patients with ID were more symptomatic with higher NYHA class and MLWHF score, regardless of ejection fraction (EF). Patients with concurrent ID and anaemia had the poorest prognosis regardless of EF.

In the 2012 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, the ESC recommended ID testing in HF patients based on the assessments of ferritin and TSAT. This raises the question of which iron indices are the most useful. Two are currently used: ferritin (a measure of stored iron) and TSAT (a measure of circulating iron for functional utilisation). However, ferritin is also an acute phase protein and can be falsely elevated if inflammation or subclinical infection is present, but a low ferritin level is a clear indication of ID (absolute). If ferritin is increased TSAT (<20%) can be used for the diagnosis of ID (functional). The only limitation of TSAT is the circadian differences since the calculated value is dependent on the serum iron. Due to their intrinsic limitations, the combination of thresholds of these two parameters is suggested, as for the FAIR-HF study (ferritin <100 ng/mL or ferritin 100–299 ng/mL when TSAT <20%). The ideal marker would probably be the soluble transferrin receptor (sTfR); however, this is not widely available or used in clinical practice. Based on the ESC recommendations and data from the FAIR-HF clinical trial, a suggested algorithm for diagnosis on ID in HF is proposed (see Figure 3). Recommendations worldwide are being changed to incorporate the need to assess and treat ID in patients with chronic HF.

In conclusion, ID is present in half of all HF patients in Europe and in up to 80% of Asian patients. While it is the main cause of anaemia in HF, ID occurs in over 45% of non-anaemic patients and is independently associated with reduced exercise capacity, reduced QoL and poor outcomes.
Iron Deficiency in Heart Failure – the Relevance for the Patient

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CONFIRM-HF – Targeting for Improvement in Exercise Capacity in Heart Failure

ID is a frequent co-morbidity in stable HF and in patients admitted to hospital due to HF worsening. Its association with impaired exercise capacity, poor QoL and increased mortality, irrespective of anaemia, make it an attractive therapeutic target – a hypothesis that has recently been tested in clinical studies. Several options are available for the correction of ID. Blood transfusion is generally not recommended since it is associated with high mortality and a lengthy stay in hospital; its use should be reserved for life-threatening emergency situations. Erythropoiesis-stimulating agents (ESA) are used mainly to correct anaemia. In the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) study, a randomised, double-blind trial on anaemic patients with chronic HF (n=2,278), correcting anaemia with darbepoetin alpha did not lead to improvement in survival nor clinically meaningful change in QoL. Furthermore, patients treated with darbepoetin alpha had an increased risk for thromboembolic adverse effects. One potential explanation of the neutral treatment effects on the outcomes could be due to the fact that ESA therapy can further exacerbate ID by stimulating the production of red blood cells, which requires a large amount of iron. Therefore, there could be a subpopulation of patients included in the RED-HF study with underlying untreated ID based on the current definition of ID in the ESC Guidelines for HF. Post hoc sub-analysis investigating the association between ID and the outcomes in the RED-HF trial is undergoing.

Another option for correcting ID is iron therapy, which may be administered by oral or i.v. routes. There is no evidence for the clinical benefits of oral iron supplementation – studies comparing oral iron with ESA in patients with HF and anaemia found no clinically meaningful benefits associated with such combination. A recent pilot study (n=18) suggested that i.v. and not oral iron improves exercise capacity in HF patients. Early clinical studies have also demonstrated the efficacy of i.v. therapy but were either single-arm, open-label studies with a short-term follow-up or small sample size. A larger, randomised, double-blind, placebo-controlled trial was therefore needed. Therefore, the FAIR-HF (n=459) trial was performed and showed that treatment of HF patients with i.v FCM in patients with chronic HF and ID, with or without anaemia, improved symptoms, exercise capacity and QoL at six months, including significant improvements in self-reported patient global assessment (PGA), NYHA functional class, six-minute walk test (6MWT), Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score and EQ-5D visual analogue scale (VAS) score. Improvements were seen from week 4 onwards irrespective of whether or not the patients were anaemic.

In order to broaden the evidence in support to treat ID with i.v. iron in HF, it was necessary to replicate these findings in a further study, and also to evaluate different, more robust and objective endpoints, including safety endpoints as well as a longer follow-up. In addition, the FAIR-HF study employed repeated 200 mg doses, therefore an evaluation of higher single-dose (up to 1,000 mg) was needed. To address these questions, the CONFIRM-HF clinical trial was designed.

CONFIRM-HF was a multicentre, randomised (1:1) double-blind, placebo-controlled trial of stable, ambulatory HF patients. The main inclusion criteria were:

- NYHA class II/III with left ventricle ejection fraction (LVEF) ≤45 %;
- Brain natriuretic peptide (BNP) >100 pg/mL or the prohormone NT-proBNP >400 pg/mL;
- ID, defined as serum ferritin <100 ng/mL or 100–300 ng/mL if TSAT <20 %; and
- haemoglobin (Hb) <15 g/dL and no lower Hb cut-off level.

Patients who needed a blood transfusion were excluded from the study. The methodology involved blinded and unblinded personnel and
Figure 6: Suggested Treatment Algorithm for Iron Deficiency in Heart Failure, Based on Evidence from Clinical Trials

Summary and Take-home Messages

ID remains under-recognised among cardiologists – an audience survey revealed that a significant minority regularly monitor ID in their HF patients. The take-home messages of the symposium were:

- ID is the main cause of anaemia, but also highly prevalent in non-anaemic patients; it is observed in almost 50 % of HF patients in Europe and the prevalence is even higher in Asia.
- ID but not anaemia is associated with:
  - reduced exercise capacity;
  - reduced QoL; and
  - poor outcome.

- Treatment with FCM in iron deficient chronic HF patients (FAIR-HF/CONFIRM-HF studies) improves:
  - symptoms;
  - exercise capacity; and
  - QoL.

These results were seen in both anaemic and non-anaemic patients, and the risk of hospitalisation due to worsening HF may be reduced.

- The ESC Guidelines have given a Class I recommendation for ID testing in all HF patients.

The link for the webcast of the presentations is now available: http://congress365.escardio.org/Session/1418#.VFuk2zFbDIW

The CONFIRM-HF results were also discussed at the Expert on the Spot session and webcast is also available by this link: http://congress365.escardio.org/Session/14134#.VFulWLFbDIW
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CARDIAC FAILURE REVIEW


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