The Management of Co-Morbidities in Patients with Heart Failure – Iron Deficiency

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Abstract
Co-morbidities have been recognised as playing a crucial role in the progress of the older patient with HF in particular. The 2016 ESC/HFA HF guidelines stress the significance of co-morbidities more than any previous guidelines have. Iron deficiency is a co-morbidity, that has received very little attention until the last decade, as evidence has accumulated both for the significance of this co-morbidity and the emergence of safe effective therapies that appear to offer significant benefits to the HF population who suffer this co-morbidity.

Keywords: Heart Failure; Cardiology; Guidelines; Iron Deficiency; Anaemia

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Background
Co-morbidities have been recognised as playing a crucial role in the progress of the older patient with HF in particular. The 2016 ESC/HFA HF guidelines stress the significance of co-morbidities more than any previous guidelines have.¹ Fig 1 lists the reasons for the importance of directing attention to co-morbidities frequent in the HF patient. Iron deficiency is one such co-morbidity, that has received very little attention until the last decade, as evidence has accumulated both for the significance of this co-morbidity and the emergence of safe effective therapies that appear to offer significant benefits to the HF population who suffer this co-morbidity.

Iron deficiency (defined as serum ferritin <100 m/L or ferritin between 100 and 299 mg/L with a transferrin saturation <20%) is common in HF, as it is with other chronic illnesses. When present it is associated with a more progressive course of HF, more hospitalisations, worse symptomatology and an impaired prognosis. It can also lead to anaemia (defined as a haemoglobin concentration <13 g/dL in men and <12 g/dL in women) and skeletal muscle dysfunction. It has been a distraction that iron deficiency can cause anaemia because attention has been directed to attempts to correct the anaemia itself, which is also common in HF patients, but transfusions and erythropoietic agents have not been shown to be beneficial in HF patients specially. If anaemia is present a cause should be sought such as the search for a bleeding diathesis or local site of blood loss, along with iron, folate and B12 deficiency. But it is iron deficiency in particular, rather than the anaemia it can cause which has been a success story in our attempts to find and correct a co-morbidity of importance for our HF patients.

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Anaemia is more frequent in women, the elderly, in the presence of kidney impairment and in acutely hospitalised HF patients. In many patients no specific cause is found. When present there appears to be more marked myocardial remodeling, inflammation and volume overload.2 Anaemia is associated with more symptoms, worse functional status, greater risk of HF hospitalization, and reduced survival. The 2016 guidelines warn that erythropoietin-stimulating agent darbepoetin alfa did not improve clinical outcomes in HFREF patients with mild-to-moderate anemia but led to an excess of thrombo-embolic events and is therefore not recommended.[1,3]

**Significance of iron deficiency**

Within a HF population iron deficiency (ID) is associated with a worse prognosis.[4] In a large cohort of CHF patients ID was identified in nearly 50%.[5] Although anaemic patients were more often iron deficient than those without anaemia, the difference was surprisingly small (61.2% vs 45.6%, P < .001). Other independent predictors of ID were worse symptoms, N-terminal pro-BNP and female gender. Functional ID is described as impaired mobilization of iron from iron stores which remain normal (such as is seen in the anaemia of chronic disorders). Hepcidin and soluble transferrin receptor (sTfR) are also of importance if HF as they regulate of iron homeostasis, usage
and uptake. Circulating levels of hepcidin are regulated by iron stores, whereas sTfR levels reflect tissue iron demand increasing to facilitate intracellular iron transfer. Absolute ID (often with very low hepcidin levels) is the predominant form of ID seen in HF, both acute and chronic.

Iron has several crucial roles in the body; haemopoiesis, oxygen transport and storage, cardiac and skeletal muscle metabolism, and mitochondrial function.[7] Myocardial iron stores are also important determinants of myocardial function. Transferin receptor-1 (TTR1) mRNA expression is reduced in the failing heart. [8] and was impaired by aldosterone and norepinephrine. These interactions might suggest broader benefits for iron therapy in HF.

Treatment options for iron deficiency
Therapeutic I.V. iron has been studied in HF both with and without anaemia. Anaemia does not appear to be needed for the therapeutic benefit of IV Iron. I.V. ferric carboxymaltose (FMC) has been shown to improve self-reported patient global assessment and NYHA class (over six months). The FAIR-HF trial [9] enrolled 459 class II or III, HFrEF randomly assigned 2:1 to 200mg of IV FCM or placebo. Self-reported patient global assessment and NYHA class were both significantly improved, regardless of anaemia status. 6-minute walk test and quality-of-life assessments were also improved, with similar rates of death, adverse events, and serious adverse events. The CONFIRM-HF trial [10] using IV FCM showed a significant improvement in functional capacity in HFrEF patients (6 minute CWT +33±11 m, p=0.002) over 52 weeks. The beneficial effect was consistent in all subgroups and there was an associated improvement in NYHA class, PGA, QoL, and Fatigue Scores with a significant reduction in the risk of hospitalizations for worsening HF [hazard ratio (95% confidence interval): 0.39 (0.19–0.82), P = 0.009]. The number of deaths (FCM: 12, placebo: 14 deaths) and the incidence of adverse events were comparable between both groups. Overall these studies show that iron-deficient HF patients treated with IV FCM over a 1-year period resulted in prolonged improved functional capacity, symptoms, and QoL and may be associated with risk reduction of hospitalization for worsening HF. A meta-analysis of IV FCM in HFrEF patients with iron deficiency showed reduced hospitalization rates and improved HF symptoms, exercise capacity and quality of life.[11] 5 (n=907) reporting the clinical impact of iron therapy in patients with HF with ID compared with no iron treatment were analysed. Iron therapy was seen to be associated with a significantly reduced rate of hospitalization for HF (odds ratio [OR], 0.28; 95% confidence interval [CI], 0.16–0.49), and although all-cause mortality was not significantly different (OR, 0.81; 95% CI, 0.42–1.57) in trended in the same direction.

The incidence of hospitalization for HF and death was lowered in the iron supplementation group (OR, 0.47; 95% CI, 0.29–0.76) and there was no increase in adverse event risk. Three of these studies (including the 3 largest)[9,10,12] used IV FCM and two used IV Iron sucrose.[13,14] It is fair to conclude that the proven beneficial effects of IV Iron are only reliably established for IV FCM preparation at present and not other forms of IV iron or oral iron. There are insufficient trial data to show any benefit of oral iron therapy in HF, especially given the severely depleted iron stores in HF. A second meta-analysis consisting of an aggregate data meta-analysis (random effects model) of randomized controlled trials that evaluated the effects of i.v. iron therapy in iron-deficient patients with systolic HF showed that IV iron reduces the risk of the combined endpoint of all-cause death or cardiovascular hospitalization [odds ratio (OR) 0.44, 95% confidence interval (CI) 0.30–0.64, P < 0.0001], and the combined endpoint of cardiovascular death or hospitalization for worsening HF (OR 0.39, 95% CI 0.24–0.63, P = 0.0001), along with improved NYHA class, quality of life and Patient Global Assessment (PGA).[15] The effect of treating iron deficiency in HFrEF remains unproven, but it is under active study.

Conclusions
Based on the evidence reviewed in this chapter and especially the two recent meta-analyses the reason for a strong new recommendation in the 2016 ESC/HFA guidelines on HF management are made clear. For the first time this important co-morbidity is given a clear tabular recommendation, that of a class IIA, A recommendation that “Intravenous FCM should be considered in symptomatic patients with HFREF and iron deficiency (serum ferritin <100m/L or ferritin between 100 and 299mg/L with a transferrin saturation <20%) in order to alleviate HF symptoms, and to improve exercise capacity and quality of life.” Furthermore, they suggest screening HF patients for ID by measuring Ferritin and TSAT. Evidence that it may well improve major outcomes is tantalisingly close. The evidence is, however, strong enough to suggest that all HFREF patients should be screened for iron deficiency and when found IV FCM should be a standard part of what the HF physician can offer to improve the lives of the patients of HFREF.

Declaration of Interest
The authors declare consultancy income from Vifor.

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