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INVITED EDITORIAL

Iron deficiency in heart failure—time to redefine

Pieter Martens[1,2]*, Niels Grote Beverborg[3], and Peter van der Meer[3]

[1]Department of Cardiology, Ziekenhuis Oost-Limburg, Schiepse Bos 6, Genk 3600, Belgium; [2]Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; and [3]Department of Cardiology, University Medical Center Groningen, University of Groningen, Hazenplein 1, Groningen, The Netherlands

This editorial refers to 'Prognostic role of transferrin saturation in heart failure patients', by J. Campodonico *et al.*, doi:10.1093/eurjpc/zwaa119

Iron deficiency (ID) is worldwide one of the most common nutritional deficits. The role of ID as a modulator of symptoms and disease severity is well established in several specialties in medicine.[1] Not surprisingly numerous different definitions of ID exist.[1] Even within the field of heart failure, several definitions of ID were used early on in the literature.[2,3] Those definitions of ID could be based on bone marrow iron staining or abnormal levels of serum iron parameters [ferritin, transferrin saturation (TSAT), free iron, soluble transferrin receptors or percentage of hypochromic red blood cells], with different cut-offs being used and sometimes a combination of several parameters.[2,3]

The first major clinical trial, the Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency (FAIR-HF), defined ID as a ferritin <100 μg/L or between 100 and 300 μg/L if TSAT was <20%. Published in 2009, the results of this trial showed us that this definition could identify a patient population with heart failure with a reduced ejection fraction that benefitted (in terms of functional status improvement) from the intravenous (IV) administration of ferric carboxymaltose (FCM).[4] A finding that was later confirmed in several other trials,[5,6] resulting into the recognition of this definition in both European and American heart failure guidelines. This definition is finding its way to clinical practice, although slowly possibly because of relative complexity of the definition. When applied, it can identify a subgroup of heart failure patients with more pronounced symptoms, worse exercise capacity. and higher risk for adverse outcome including heart failure admissions and cardiovascular mortality.[7]

However, this definition is based on its use in early pilot studies with IV iron and the extrapolation of knowledge from the field of nephrology.[8] Indeed, no formal validation of the definition in patients with heart failure has been performed. In their article, Campodonico *et al.*[9] challenge this definition of ID in heart failure. In their cohort of 661 heart failure patients, they assessed the relation between clinical outcome (all-cause mortality) and different definitions of ID (based on haemoglobin, ferritin, and TSAT). Their most important finding is that a TSAT of <20% is associated with a higher risk of all-cause mortality, while other definitions of ID do not show this association.[9] Several important limitations have to be taken into account, including the single-center design, the superficial study population description, the absence of data relating to exercise capacity, and the fact that they used the endpoint of all-cause mortality (instead of cardiovascular mortality with or without heart failure readmission). However, the results are relevant and in line with increasing data in heart failure that the patients with a ferritin of <100 μg/L but with TSAT > 20% exhibit different clinical features and treatment response. In the current definition, these subjects are considered to be iron deficient but maybe better referred to as having 'isolated hypoferritinemia'.

Several studies have indirectly questioned whether we should keep these patients in our definition of ID. First, Grote *et al.* assessed the accuracy of the classic definition of ID (ferritin <100 μg/L or between 100 and 300 μg/L if TSAT was <20%) in comparison to the gold standard being bone marrow iron staining. Interestingly, none of the patients with isolated hypoferritinemia (ferritin <100 μg/L and a TSAT of >20%) had ID on bone marrow staining.[10] Second, most studies that assess the relation between exercise capacity and ID have found a strong correlation between TSAT and exercise capacity, but the correlation with ferritin is often weak or absent if TSAT is >20%.[7] Furthermore, improvement in peakVO_2 after the administration of IV iron is associated with changes in TSAT and less with ferritin.[8] Third, a patient level meta-analysis of several trials looking at IV FCM in heart failure with reduced ejection fraction has found statistical interaction between the treatment effect of FCM on several hard clinical endpoints (composites of recurrent cardiovascular or recurrent heart failure admissions combined with cardiovascular or all-cause mortality).[11] In that meta-analysis, patients with isolated hypoferritinemia did not show benefit with IV FCM. However, it needs to be emphasized that this subgroup analysis is *post hoc* and needs to be interpreted with care. The latter is in line with the current study of Campodonico *et al.*,[9] which shows that patients with isolated

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* Corresponding author. Tel: +32 89 327160, Fax: +32 89 327918, Email: pieter.martens2@zol.be

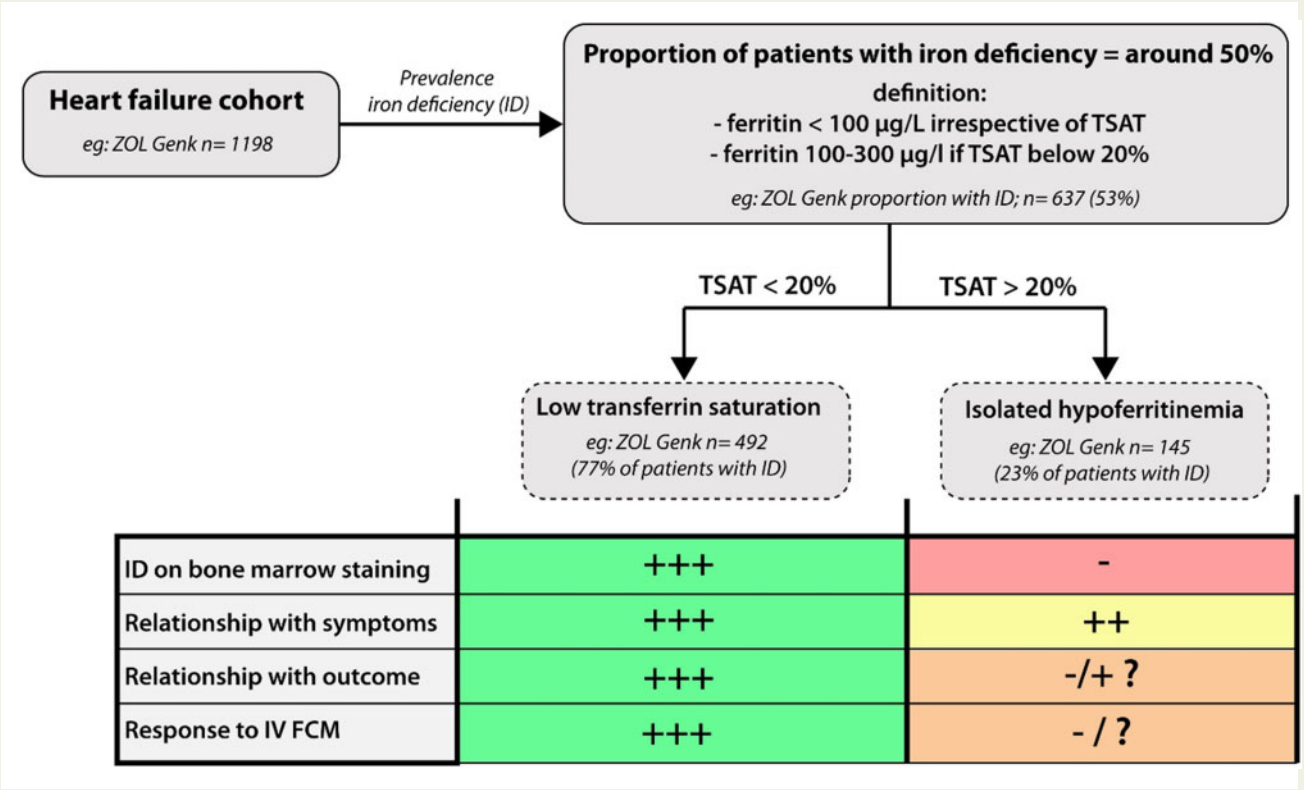

Figure 1 Proportion of patients with isolated hypoferritinemia in comparison to other iron-deficient patients and implications.

hypoferritinemia have a similar prognosis to patients without ID. Ultimately, any intervention to improve prognosis in a subgroup that does not have an impaired prognosis is questionable. Fourth, in a well-designed MRI study, improvements in myocardial iron content after IV iron correlated with TSAT changes and not changes in ferritin.[12]

Collectively, these data underscore the importance of a low TSAT (<20%) in our definition of ID in heart failure (see *Figure 1*), which is not present in patients with isolated hypoferritinemia. In the heart failure cohort of 'ZOL Genk' in Belgium, patients with isolated hypoferritinemia compromised 23% of all patients with ID, which is similar to the 25% in the cohort of Campodonico *et al.* An analysis for sake of this editorial of the 'ZOL Genk' cohort indicates that patients with isolated hypoferritinemia have a significantly higher peakVO_2 than iron-deficient patients with a TSAT of <20% (13.3 ± 4.1 vs. 11.8 ± 3.4, $P = 0.001$), but still lower than controls without ID (16.8 ± 3.4, $P < 0.001$). So clearly a fair proportion of our patients in the current definition of ID seem to behave differently (see *Figure 1*). Ongoing trials with IV iron [FAIR-HF2 (NCT03036462), IRON-MAN (NCT02642562), HEART-FID (NCT03037931), AFFIRM-AHF (NCT02937454), and IRON-CRT (NCT0338052)] will give more information regarding the prevalence of isolated hypoferritinemia in larger cohorts of iron-deficient patients. Furthermore, these trials will determine the response to IV iron therapy and will determine the effect on hard clinical endpoints. As a results, these trials will give additional information whtether we should keep isolated hypoferritinemia in the definition of ID.

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References

1. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet* 2016;**387**:907–916.
2. Opasich C, Cazzola M, Scelsi L, De FS, Bosimini E, Lagioia R, Febo O, Ferrari R, Fucili A, Moratti R, Tramarin R, Tavazzi L. Blunted erythropoietin production and defective iron supply for erythropoiesis as major causes of anaemia in patients with chronic heart failure. *Eur Heart J* 2005;**26**:2232–2237.
3. 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. *J Am Coll Cardiol* 2006; **48**:2485–2489.
4. Anker SD, Comin CJ, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Luscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, von Eisenhart RB, Pocock SJ, Poole-Wilson PA, Ponikowski P. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009;**361**:2436–2448.
5. 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; for the CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiencydagger. *Eur Heart J* 2015;**36**:657–668.
6. van Veldhuisen DJ, Ponikowski P, van der Meer P, Metra M, Bohm 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* 2017;**136**:1374–1383.
7. Martens P, Nijst P, Verbrugge FH, Smeets K, Dupont M, Mullens W. Impact of iron deficiency on exercise capacity and outcome in heart failure with reduced, mid-range and preserved ejection fraction. *Acta Cardiol* 2017;**2**:1–9.
8. Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, Foldes G, Thum T, Majda J, Banasiak W, Missouris CG, Poole-Wilson PA, Anker

SD, Ponikowski P. 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;**51**:103–112.

9. Campodonico J, Nicoli F, Motta I, De Amicis MM, Bonomi A, Cappellini M, Agostoni P. Prognostic role of transferrin saturation in heart failure patients. *Eur J Prevent Cardiol*, doi:10.1093/eurjpc/zwaa119.
10. Grote BN, Klip IT, Meijers WC, Voors AA, Vegter EL, van der Wal HH, Swinkels DW, van PJ, Mulder AB, Bulstra SK, Vellenga E, Mariani MA, de Boer RA, van Veldhuisen DJ, van der Meer P. Definition of iron deficiency based on the gold standard of bone marrow iron staining in heart failure patients. *Circ Heart Fail* 2018;**11**:e004519.
11. Anker SD, Kirwan BA, van Veldhuisen DJ, Filippatos G, Comin-Colet J, Ruschitzka F, Luscher TF, Arutyunov GP, Motro M, Mori C, Roubert B, Pocock SJ, Ponikowski P. 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;**20**:125–133.
12. Nunez J, Minana G, Cardells I, Palau P, Llacer P, Facila L, Almenar L, Lopez-Lereu MP, Monmeneu JV, Amiguet M, Gonzalez J, Serrano A, Montagud V, Lopez-Vilella R, Valero E, Garcia-Blas S, Bodi V, Espriella-Juan R, Lupon J, Navarro J, Gorriz JL, Sanchis J, Chorro FJ, Comin-Colet J, Bayes-Genis A. Noninvasive imaging estimation of myocardial iron repletion following administration of intravenous iron: the myocardial-IRON trial. *J Am Heart Assoc* 2020;**9**:e014254.