ISSN 2321 – 7359 EISSN 2321 – 7367

discovery

Medical Science

The International Weekly Journal for Medicine

Iron Deficiency – A new paradigm in Heart Failure

Mark Abela[1], Caroline J Magri[1,2], Andrew Cassar[1,2]

1.Department of Cardiology, Mater Dei Hospital, Tal-Qroqq, Msida MSD 2090, Malta
2.University of Malta Medical School, University of Malta, Tal-Qroqq, Msida MSD 2090, Malta

Publication History
Received: 28 August 2014
Accepted: 11 October 2014
Published: 15 October 2014

Citation
Mark Abela, Caroline J Magri, Andrew Cassar. Iron Deficiency – A new paradigm in Heart Failure. *Medical Science*, 2014, 13(51), 64-69

ABSTRACT

Iron deficiency (ID) is one of the most prevalent conditions in chronic heart failure (CHF) patients. Similar to the pathophysiology of anaemia of chronic disease in chronic inflammatory diseases, the inflammatory status in such patients as evidenced by increasing levels of inflammatory cytokines with worsening CHF, impairs functional mobilisation of iron from body stores, eventually resulting in a relative ID, ineffective erythropoiesis and anaemia. ID independent of haemoglobin status has been shown to be a very strong mortality and re-hospitalisation predictor. Evidence regarding the potential therapeutic implications is rather limited, mostly based on small scaled randomised controlled trials. Results are however similar, showing that iron supplementation may help improve iron stores, haemoglobin levels, quality of life, functional status and exercise tolerance. With the updated European Society of Cardiology (ESC) heart failure guidelines recommending screening for iron deficiency (Evidence Ic), the ongoing management debate of whether to treat or not to treat patients diagnosed with iron deficiency will certainly be a hot topic for discussion in the coming months.

Keywords: Iron Deficiency, Haemoglobin, Anaemia, Chronic heart failure, Prognosis

1. INTRODUCTION

Chronic Heart Failure (CHF) is a common cause of morbidity, accounting for greater than one million patients needing hospitalisation in the United States (US), exceeding 17 billion in expenses (Desai et al., 2012). The trend towards a more cost effective healthcare has prompted the research sector to focus on new aspects into the pathophysiology of CHF, hoping to identify a new way of improving patient prognosis whilst also identify those with the highest risk of

© 2014 discovery publication. All rights reserved

mortality. Iron deficiency has emerged as an important prognostic marker in CHF. It is also highly predictive of reduced exercise capacity, low quality of life, mortality and increased re-hospitalisation rates, even in non-anaemic patients (Horwich et al., 2002; Dec, 2009;, Stewart et al., 2010), keeping in mind that iron deficiency (ID) occurs in approximately 33% of non-anaemic individuals (Jankowska et al., 2010).

2. PHYSIOLOGICAL ROLE OF IRON

Iron is an important intracellular metabolically active element, playing several roles in a number of physiological pathways, governed mostly by its ability to oxidize to its ferric and ferrous forms. This capability has made it an important cofactor in a number of metalloproteins, responsible for oxygen transport (haemoglobin) and storage (myoglobin), oxidative phosphorylation (electron transport chain), protein synthesis (ribonucleotide reductase), neurotransmission (monoamine oxidase) and inflammation (cyclooxygenase) (Jankowska et al., 2010; Okonko et al., 2011). ID may thus contribute to significant cellular dysfunction. Depletion also drives the cell to G1/S phase mitotic arrest and apoptosis. The shortened cell cycle brings about ineffective cellular function, with ventricular hypertrophy and increased catecholamine secretion. The unfavourable effects of these physiological mechanisms might be the reasons behind the adverse effects in ID CHF patients (Okonko et al., 2011).

3. DEFINING IRON DEFICIENCY

In the 2012 European Society of Cardiology (ESC) Heart Failure (HF) guidelines, authors recommended routine screening for ID in all HF patients. The definition implemented in this guideline was based on the same criteria used in most randomised controlled trials (RCTs) tackling the topic. A patient was deemed to be ID based on a ferritin level of <100ug/L (absolute iron deficiency) or a ferritin level of 100-299ug/L with a transferrin saturation (TSAT) of less than 20% (functional iron deficiency) (Task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European society of cardiology, 2012; Klip et al., 2013; Lipsic & Van der Meer., 2012; Cohen-Solal et al., 2014). As ferritin is an acute phase reactant, baseline levels in CHF patients may be higher than controls because of the chronic inflammatory state. Other authors even recommend using just TSAT as the main biochemical marker of ID, with a cut off of 20% (Okonko et al., 2011). Authors concur that ID is probably under-estimated, with ferritin potentially unreliable as a biochemical marker of iron stores. In a study by Nanas et al. (2006), bone marrow aspiration of advanced CHF patients revealed ID to be present in 73% of the population, much higher when compared to a biochemical assessment of iron stores (Nanas et al., 2006).

4. PREVALENCE OF IRON DEFICIENCY

Despite the rich abundance of iron content obtained in the diet, ID is still the commonest nutritional deficiency, present in 2% and 9% of adult males and females in the US (Hegde et al., 2006). ID itself even in the absence of anaemia has been recognized as an important player in chronic inflammatory diseases (Weiss & Goodnough, 2005). Its role and management implications in CHF has only recently been recognized, with a large study of 546 patients revealing that 37% had ID, irrespective of their haemoglobin (Hb) levels (Jankowsk et al., 2010). Untreated ID can eventually result in anaemia, and ID is actually considered as the commonest cause of anaemia in the US (Hegde et al., 2006). In a study of 959 hospitalised patients with HF, 15.5% of the 369 anaemic individuals had a haematenemic deficiency, with iron deficiency being the commonest (6.2%). In a separate international pooled cohort consisting of 1,506 patient with HF, 753 (50%) of the cohort (anaemic and non-anaemic) were ID (Klip et al., 2013). Haematenemic deficiencies must not be under-estimated in the non-anaemic patients, with a maximum of 27% reported to be suffering from such deficiencies (Gonzalez-Costello & Comin-Colet, 2010).

5. IRON DEFICIENCY AS A PROGNOSTIC MARKER

Worse survival in non-anaemic and anaemic iron depleted individuals has been demonstrated in numerous studies, with one study recording a 3 year survival rate of 59% compared to 71% in iron replete individuals. This latter cohort also identified a 2 fold risk of mortality in non-anaemic iron depleted patients (compared to a 3-fold risk in anaemic individuals), suggesting that anaemia is a less reliable prognostic marker than ID; similar results were obtained in a separate cohort (Stewart et al., 2010; Jankowska et al., 2010). In another study, ID anaemic patients had a 2-fold greater risk of death than non-anaemic iron deficient patients, with the risk rising to 4-fold when compared to iron replete individuals, again highlighting that the iron pool rather than anaemic status itself is the stronger prognostic marker (Okonko et al., 2011). Besides mortality, ID independent of anaemia is predictive of higher New York Heart Association (NYHA) functional class, decreased aerobic performance, poorer exercise tolerance and lower quality of life, along with an increased risk of heart transplantation, irrespective of the presence of anaemia (Jankowska et al., 2010; Okonko et al., 2011; Klip et al., 2013; Aung et al., 2013).

Mark Abela et al.
Iron Deficiency – A new paradigm in Heart Failure,
Medical Science, 2014, 13(51), 64-69,
http://www.discovery.org.in/md.htm

© 2014 discovery publication. All rights reserved

6. PREDICTORS OF IRON DEFICIENCY

Many cohorts have identified a number of predictors which can be used to assess dysregulation in iron homeostasis. NYHA functional class has been a consistent independent predictor, whilst non-Caucasian ethnicity, higher CRP, female gender, lower mean corpuscular volume, higher red cell distribution width (RDW), higher natriuretic peptide levels, renal insufficiency, anaemia and lower beta-blocker have all been implicated (Horwich et al., 2002; Stewart et al., 2010; Okonko et al., 2011; Klip et al., 2013; Aung et al., 2013; Pozzo et al., 2011).

7. TYPES OF IRON DEFICIENCY

ID can be absolute or relative. Absolute deficiency encompasses those pathologies which bring about decreased absorption or loss from the gastrointestinal tract (Maeder et al., 2011). Malnutrition, malabsorption (bowel oedema) and drugs (aspirin, oral anticoagulants, omeprazole) are some of the potential culprits (Horwich et al., 2002). A relative deficiency on the other hand reflects normal total body iron stores with defective iron mobilisation from the reticuloendothelial system to the bone marrow. Relative deficiency is postulated to be secondary to activation of macrophages and up-regulation of inflammatory cytokines suppressing erythropoiesis as part of a chronic inflammatory state (Weiss & Goodnough, 2005). With higher inflammatory biomarkers (including soluble TNF-α, IL-6 and GDF-15) along the disease course, a relative deficiency (with or without absolute deficiency) is thought to be one of the main driving forces for ID in CHF (Martinez-Ruiz et al., 2012; Okonko et al., 2013).

8. ANAEMIA IN HEART FAILURE

Anaemia is highly prevalent in heart failure patients, with studies quoting values of 22-37%, sometimes even greater than 50%. ID and anaemia overlap with each other in HF, with both independently worsening quality of life and HF symptomatology. Anaemia itself is a prognostic marker that reflects a 3-fold mortality risk, independent of iron status (Stewart et al., 2010).

The aetiology underlying anaemia in CHF is considered multifactorial, with haemodilution (Westenbrink et al., 2007; Androne et al., 2003; Adlbrecht et al., 2008), hemolysis in patients with artificial valves (Kliger et al., 2013; Kubo et al., 2010), gastrointestinal bleeding in patients with high venous pressures (Holleran et al., 2013), blunted erythropoietin (Epo) response as a result of renal impairment and bone marrow dysfunction (Eschbach, 2002; Westenbrink et al., 2010; Kissel et al., 2007; Van der Meer et al., 2008), all having a contributory role. Haematenemic deficiencies apart from iron are also thought to play major roles (Witte et al., 2004).

Epo resistance plays a major role. Studies have shown that inflammatory cytokines fail to attenuate erythroid marrow activity, resulting in a quantitative exhaustion of erythroid progenitor cells (BFU-E). CHF patients would thus have lower absolute reticulocyte counts and reticulocyte production indices. There is also an inadequate Epo production relative to the degree of anaemia as CHF severity worsens (Okonko et al., 2013). IL-6 and TNF-α are known to directly inhibit renal Epo by activating the GATA binding protein (GATA2) and nuclear factor-κβ (Klip et al., 2013; Anand, 2008). These chronic inflammatory changes together with suboptimal Hb synthesis due to ID are the other main reasons for anaemia of chronic disease in CHF, with or without dysregulation in oxidative metabolism, cellular immune mechanisms and energetics (Anderson & Vulpe, 2009; Cario et al., 2006; Wilson & Reeder, 2008; Beard, 2001).

9. THE PATHOPHYSIOLOGY OF IRON DEFICIENCY

An equilibrium in normal iron homeostasis is maintained thanks to the flow of iron between the storage (reticuloendothelial system), functional (erythroid marrow) and circulatory compartments. ID in CHF is thought to occur in response to pro-inflammatory cytokines which decrease the inter-compartmental mobilisation of iron by down-regulating ferroprotein (Dec, 2009). With worsening NYHA class, persistent hypoferremia impairs iron storage, giving rise to absolute ID (Okonko et al., 2011; Maeder et al., 2011).

At the cellular level, numerous changes take place in response to the ongoing inflammatory processes. Inflammatory provocation activates macrophages in the reticuloendothelial system, giving rise to up-regulation of numerous proteins, including TNF-α, IL-1β and IL-6. IL-6 in particular up-regulates hepcidin, a peptide hormone synthesized primarily in the liver. Overproduction occurs in response to liver congestion in CHF (Beard, 2001). Hepcidin promotes both iron trapping (in macrophages and hepatocytes) and iron malabsorption by directly inhibiting ferroportin (Deicher & Horf, 2006; Van Vekthuisen et al., 2011). This has been confirmed in animal studies (Nicholas et al., 2002).

Myocardial stores are also disturbed in ID, with biopsies showing a 68% reduction in transferrin mRNA, with a consequent lower tissue iron content in failing hearts. Animal studies have proven that lower myocardial iron contributes to progressive cardiac fibrosis, mitochondrial swelling and abnormal sarcomere structure, implying significant repercussions on cardiac function (Maeder et al., 2011; Tobli et al., 2007).

Mark Abela et al.
Iron Deficiency – A new paradigm in Heart Failure,
Medical Science, 2014, 13(51), 64-69,
http://www.discovery.org.in/md.htm

© 2014 discovery publication. All rights reserved

10. LOW VERSUS PRESERVED EJECTION FRACTION HEART FAILURE

Heart failure with preserved EF (HFPEF) accounts for 40% of all HF patients, with incidence on the rise and comparable morbidity and mortality to those with HF reduced EF (HFREF). Biomarker studies have identified extracellular matrix remodelling, oxidation, inflammation, cardiomyocyte stress and fibrosis to all play some role in the pathophysiology of HFPEF (Putko et al., 2014).

Whether ID plays a role in HFPEF is still unclear. On the one hand, cellular changes in myocyctes as a result of ID can have a significant impact on cardiac function. Changes in oxygen metabolism and cellular energetics contribute towards myocardial fibrosis, one of the main driving forces behind diastolic dysfunction. An insufficient energy supply for both LV relaxation and filling may in turn lead to a worse quality of life and cardiac function in those with preserved EF. On the other hand, transferrin receptors in myocytes are actually not down-regulated, as occurs in low EF HF, but rather up-regulated suggesting a preserved compensatory mechanism. It has been suggested that ID is at least a risk factor in preserved EF HF, having the potential as a prognostic predictor independent of the pathophysiological processes in diastolic dysfunction (Kasner et al., 2013). Undoubtedly, further studies are needed.

11. SHOULD WE TREAT?

Whilst anaemia in CHF might reflect end stage cardiac disease, early identification of non-anaemic iron depleted patients is very important. The perception of anaemia itself might also need to change. A mild drop in Hb of <11.6g/dL (females) and <12.6g/dL (males) might not be significant in clinical practice, not prompting physicians to screen for haematenemic deficiencies. However, a minimal decline in Hb has been shown to be significantly associated with impaired survival. Furthermore, ID (irrespective of haemoglobin) decreases work capacity by 10% to 50%, proportional to the severity of the deficiency (Darlington et al., 2008).

Studies have shown that treating ID in CHF patients reduces re-hospitalisation risk whilst also improving quality of life and exercise tolerance (Tobbli et al., 2007; Darlington et al., 2008; Kai-Hu et al., 2013; Bolger et al., 2006; Silverberg et al., 2011; Anker et al., 2009; Usmanov & Silverberg, 2011). Left sided chambers decrease in size, immediately noting improved cardiac contractility (Georgieva & Georgieva, 1997). However, some argue that iron therapy may not be an option. With the negligible physiological excretion of iron, excess iron triggers free radical generation, notably in coronary atherosclerotic plaques. So rather than treating CHF, iron itself may really worsen ischaemia or potentially end up giving iron-overload cardiomyopathy (Lippi et al., 2013). HF guidelines have at this point established that screening for ID is very important. There is however no consensus regarding established treatment. Blood transfusion is not recommended as a maintenance therapy (Mak et al., 2008).

Iron therapy is one potential strategy which is being explored in numerous trials which only included patients with HFREF, with no trials pertaining to HFPEF currently available. With oral iron noted to be ineffective because of poor absorption due to bowel oedema and gastrointestinal intolerance (Silverberg et al., 2011; Palazzuoli et al., 2006), therapy with intravenous (IV) iron (mainly iron sucrose and iron carboxymaltose) looks promising to say the least. IV iron is given by slow injections or by infusions, usually well tolerated. In general, iron carboxymaltose improves Hb levels much faster than iron sucrose, and is known to replenish iron stores in non-HF patients with IDA, including those with chronic kidney disease (Peraira-Moral & Nunez-Gil, 2012). Numerous trials like FERRIC-HF (35 patients) (Darlington et al., 2008), FAIR-HF (459 patients) (Anker et al., 2009), IRON-HF (23 patients) (Beck-da-Silva et al., 2013), and CONFIRM-HF (304 patients) (Ponikowski et al., 2014) all provided evidence that patients treated with intravenous iron have improved functional capacity (NYHA class), better symptom control, improved exercise tolerance, decreased hospital re-admission rates and improved quality of life. In a separate cohort of patients N-terminal pro-brain natriuretic peptide (NT-pro-BNP) at 6 months following treatment with IV iron was found to improve, correlating with the previously mentioned benefits (Beck-da-Silva et al., 2013).

It was previously thought that supplementation with erythropoietin (Epo) might help to tackle the blunted endogenous Epo response. This approach has however taken much lower priority after the poor results in the RED-HF trial, a randomized double-blinded trial that consisted of 2278 patients with HFREF exposed to darbepoetin alfa or placebo (Swedberg et al., 2013). Increased plasma Epo levels in CHF patients have actually been associated with a worse prognosis, irrespective of Hb levels (Beck-da-Silva et al., 2013). Its routine use in CHF cannot, therefore, be recommended.

12. CONCLUSION

Whilst studies have shown that iron deficiency in CHF is highly prevalent and is a poor prognosticator, the question of whether to treat or not to treat (especially in non-anaemic individuals) is highly debatable (Gozalez-Costello & Comin-Colet, 2010). Whether iron therapy is more beneficial in a sub-cohort of CHF patients is as yet unknown. It is still debatable whether IV iron is better than the oral formulation, though current data is in favour of intravenous treatment. A large placebo-controlled mortality-driven trial is needed to confirm the long-term effects of IV iron in

Mark Abela et al.
Iron Deficiency – A new paradigm in Heart Failure,
Medical Science, 2014, 13(51), 64-69,
http://www.discovery.org.in/md.htm

© 2014 discovery publication. All rights reserved

CHF (Peraira-Moral & Nunez-Gil, 2012). Further studies are also needed to assess whether a preventive strategy of iron supplementation to avoid the onset of ID anaemia in CHF might have prognostic benefit (Martinez-Ruiz et al., 2012). Until such studies are performed, it is reasonable to screen CHF patients for ID and possibly treat patients on an individual basis after standard optimised medical treatment has been provided without significant benefit.

REFERENCES

1. Adlbrecht C, Kommata S, Hülsmann M, Szekeres T, Bieglmayer C, Strunk G, Karanikas G, Berger R, Mörtl D, Kletter K, Maurer G, Lang IM, Pacher R. Chronic heart failure leads to an expanded plasma volume and pseudoanaemia, but does not lead to a reduction in the body's red cell volume. *Eur Heart J,* 2008, 29, 2343e50
2. Anand I. Anemia and chronic heart failure implications and treatment options. *J Am Coll Cardiol,* 2008, 52, 501-511
3. Anderson G, Vulpe C. Mammalian iron transport. *Cell Mol Life Sci,* 2009, 66, 3241-3261
4. Androne AS, Katz SD, Lund L, LaManca J, Hudaihed A, Hryniewicz K, Mancini DM. Hemodilution is common in patients with advanced heart failure. *Circulation,* 2003, 107, 226e9
5. 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(25), 2436-48
6. Aung N, Ling HZ, Cheng AS, Aggarwal S, Flint J, Mendonca M, Rashid M, Kang S, Weissert S, Coats CJ, Richards T, Thomas M, Woldman S, Okonko DO. Expansion of the red cell distribution width and evolving iron deficiency as predictors of poor outcome in chronic heart failure. *Int J Cardiol,* 2013, 168, 1997-2002
7. Beard J. Iron biology in immune function, muscle metabolism and neuronal functioning. *J Nutr,* 2001, 131(2), 5685-5795
8. 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 patients with anemia. *Int J Cardiol,* 2013, 168, 3439-3442
9. Beck-da-Silva L, Rohde LE, Pereira-Barretto AC, de Albuquerque D, Bocchi E, Vilas-Boas F, Moura LZ, Montera MW, Rassi S, Clausell N. Rationale and Design of the IRON-HF study: A randomized trial to assess the effects of iron supplements in Heart Failure patients with anemia. *J Card Fail,* 2013, 13(1), 14-17
10. Bolger AP, Bartlett FR, Penston HS, O'Leary J, Pollock N, Kaprielian R, Chapman CM. Intravenous iron alone for the treatment of anemia in patients with chronic heart failure. *J Am Coll Cardiol.,* 2006, 48(6), 1225-1227
11. Cario G, Bemuzzi F, Recalcati S. A precious metal: iron, an essential nutrient for all cells. *Genes Nutr,* 2006, 1, 25-39
12. Cohen-Solal A, Leclercq C, Deray G, Lasocki S, Zambrowski JJ, Mebazaa A, Groote P, Damy T, Galinier M. Iron deficiency: an emerging therapeutic target in heart failure. *Heart*, 2014, 100, 1414-1420
13. 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. *J Am Coll Cardiol.,* 2008, 51(2), 103-112
14. Deicher R, Horl W. New insights into the regulation of iron homeostasis. *Eur J Clin Invest,* 2006, 36, 301-309
15. Desai SA, Stevenson WL. Rehospitalization for Heart Failure: Predict or Prevent? *Circulation,* 2012, 126, 501-506
16. Eschbach JW. Anemia management in chronic kidney disease: role of factors affecting epoetin responsiveness. *J Am Soc Nephrol,* 2002, 13, 1412e4
17. Georgieva Z, Georgieva M. Compensatory and adaptive changes in microcirculation and left ventricular function of patients with chronic iron deficiency anaemia. *Clin Hemorheol Microcirc,* 1997, 17, 21-30
18. Gozalez-Costello J, Comin-Colet J. Iron deficiency and anaemia in heart failure: understanding the FAIR-HF trial. *European Journal of Heart Failure,* 2010, 12(11), 1159-1162
19. Hegde N, Rich MW, Gayomali C. The Cardiomyopathy of Iron Deficiency. *Tex Heart Inst J,* 2006, 33, 340-344
20. Holleran G, Hall B, Hussey M, McNamara D. Small bowel angiodysplasia and novel disease associations: a cohort study. *Scand J Gastroenterol,* 2013, 48, 433e8
21. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater functional capacity and a significant increase in mortality in patients with advanced heart failure. *J Am Coll Cardiol.,* 2002, 39(11), 1780-1786
22. Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja 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, 30, 1872-1880
23. Kai-Hu S, Hui T, Jun-Xu W. Iron deficiency as a good potential prediction of chronic heart failure. *Am Heart J* 2013, 166, e31
24. Kasner M, Aleksandrov AS, Westermann D, Lassner D, Gross M, von Haehling S, Anker SD, Schultheiss HP, Tschöpe C. Functional iron deficiency and diastolic function in heart failure with preserved ejection fraction. *Int J Cardiol,* 2013, 168, 4652-4657
25. Kissel CK, Lehmann R, Assmus B, Aicher A, Honold J, Fischer- Rasokat U, et al. Selective functional exhaustion of hematopoietic progenitor cells in the bone marrow of patients with postinfarction heart failure. *J Am Coll Cardiol,* 2007, 49, 2341e9
26. Kliger C, Eiros R, Isasti G, Einhorn B, Jelnin V, Cohen H, Kronzon I, Perk G, Fontana GP, Ruiz CE. Review of surgical prosthetic paravalvular leaks: diagnosis and catheter based closure. *Eur Heart J,* 2013, 34, 638e49
27. 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. *Am Heart J,* 2013, 165, 575-582
28. Kubo T, Kitaoka H, Terauchi Y, Tamura S, Okawa M, Yamasaki N, Yabe T, Doi YL. Hemolytic anemia in a patient with hypertrophic obstructive cardiomyopathy. *J Cardiol,* 2010, 55, 125e9
29. Lippi G, Sanchis-Gomar F, Cervellin G. Intravenous iron therapy in patients with heart failiure: A double-edged sword. *Int J Cardiol,* 2013, 168(5), 4863
30. Lipsic E, Van der Meer P. Erythropoietin, iron, or both in heart failure: FAIR-HF in perspective. *European Journal of Heart Failure,* 2012, 12, 104-105

© 2014 discovery publication. All rights reserved

31. Maeder TM, Khammy O, Remedios CD, Kaye MD. Myocardial and systemic iron depletion in heart failure. *JACC,* 2011, 58(5), 474-480
32. Mak G, Murphy NF, McDonald K. Anemia in Heart Failure: to Treat or not to Treat? *Curr Treat Options Cardiovasc Med,* 2008, 10, 455-464
33. Martínez-Ruiz A, Tornel-Osorio PL, Sánchez-Más J, Pérez-Fornieles J, Vílchez JA, Martínez-Hernández P, Pascual-Figal DA. Soluble TNFa receptor type I and hepcidin as determinants of development of anemia in the long-term follow-up of heart failure patients. *Clin Biochem,* 2012, 45, 1455-1458
34. 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
35. Nicholas G, Bennoun M, Porteu A, et al. Severe iron deficiency anemia in transgenic mice expressing liver hepcidin. *Proc Natl Acad Sci USA,* 2002, 99, 4596-4601
36. Okonko OD, Mandal KA, Missouris GC, Poole-Wilson AP. Disordered iron homeostasis in chronic heart failure. *J Am Coll Cardiol.*, 2011, 58(12), 1241-1251
37. Okonko OD, Marley SB, Anker SD, Poole-Wilson PA, Gordon MY. Suppression of erythropoiesis in patients with chronic heart failure and anaemia of unknown origin: evidence of an immune basis. *Int J Cardiol,* 2013, 166, 664-671
38. Palazzuoli A, Silverberg D, Iovine F, Capobianco S, Giannotti G, Calabrò A, Campagna SM, Nuti R. Erythropoietin improves anemia, exercise tolerance, and renal function and reduced B-type natriuretic peptide and hospitalization in patients with heart failure and anaemia. *Am Ht J,* 2006, 152(6), e9-15
39. Peraira-Moral J. Roberto & Núñez-Gil Ivan J. Anaemia in heart failure: intravenous iron therapy. *E-journal of the ESC council for cardiology practice,* 2012, 10(6)
40. Ponikowski P, J. van Veldhuisen D, 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 deficiency. *Eur. Heart J.,* 2014, pii: ehu385
41. Pozzo J, Fournier P, Lairez O, et al. Iron deficiency in non-anemic heart failure patients. *Archives of Cardiovascular Diseases Supplements,* 2011, 3, 79-86
42. Putko BN, Wang Z, Lo J, Anderson T, Becher H, Dyck JRB, Kassiri Z, Oudit JY, on behalf of the Alberta HEART Investigators. Circulating Levels of Tumor Necrosis Factor-Alpha Receptor 2 Are Increased in Heart Failure with Preserved Ejection Fraction Relative to Heart Failure with Reduced Ejection Fraction: Evidence for a Divergence in Pathophysiology. *PLoS ONE,* 2014, 9(6), e99495
43. Silverberg D, Iaina A, Wexler D, Schwartz D. Iron repletion in heart failure patients. *Hypertension,* 2011, 57, 381-382
44. Stewart T, Freeman J, Stewart J, Sullivan A, Ward C, Tofler GH. Anaemia in Heart Failure: A prospective evaluation of clinical outcome in a community population. *Heart, lung and circulation,* 2010, 19, 730-735
45. Swedberg K, Young JB, Anand IS, Cheng S, Desai AS, Diaz R, Maggioni AP, McMurray JJV, O'Connor C, Pfeffer MA, Solomon SD, Sun Y, Tendera M and J. van Veldhuisen D for the RED-HF Committees and Investigators. Treatment of Anemia with Darbepoetin Alfa in Systolic Heart Failure. *N Eng J Med.,* 2013, 368(13), 1210-19
46. The Task force for the Diagnosis and Treatment of Acute and Chronic Heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (AFA) of the ESC. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J,* 2012, 13, 1787-1847
47. Toblli JE, Lombrana A, Duarte P, Gennaro FD. Intravenous iron reduces NT-pro-Brain Natriuretic Peptide in anemic patients with chronic heart failure and renal insufficiency. *J Am Coll Cardiol.*, 2007, 50(17), 1657-1665
48. Tomoyasu S, Hanawa H, Jiao S, Ohno Y, Hayashi Y, Yoshida K, Kashimura T, Obata H, Minamino T. Inappropriate Expression of Hepcidin by Liver Congestion Contributes to Anemia and Relative Iron Deficiency. *Journal of Cardiac Failure,* 2014, 20(4), 268-277
49. Usmanov RI, Silverberg DS. Intravenous iron without erythropoietin for the treatment of iron deficiency anemia in patients with moderate to severe congestive heart failure and chronic kidney insufficiency. *JNEPHROLOGY,* 2008, 21, 235-242
50. van der Meer P, Lok DJ, Januzzi JL, de la Porte PW, Lipsic E, van Wijngaarden J, Voors AA, van Gilst WH, van Veldhuisen DJ. Adequacy of endogenous erythropoietin levels and mortality in anaemic heart failure patients. *Eur Heart J,* 2008, 29, 1510e5
51. Van Veldhuisen DJ, Anker SD, Ponikowski P, Macdougall IC. Anemia and iron deficiency in heart failure: mechanisms and therapeutic approaches. *Nat Rev Cardio.,* 2011, 8, 485-493
52. Weiss G, Goodnough L. Anemia of chronic disease. *N Eng J Med.,* 2005, 352, 1011-1023
53. Westenbrink BD, Visser FW, Voors AA, Smilde TD, Lipsic E, Navis G, Hillege HL, van Gilst WH, van Veldhuisen DJ. Anaemia in chronic heart failure is not only related to impaired renal perfusion and blunted erythropoietin production, but to fluid retention as well. *Eur Heart J,* 2007, 28, 166e71
54. Westenbrink BD, Voors AA, de Boer RA, Schuringa JJ, Klinkenberg T, van der Harst P, Vellenga E, van Veldhuisen DJ, van Gilst WH. Bone marrow dysfunction in chronic heart failure patients. *Eur J Heart Fail,* 2010, 12, 676e84
55. William Dec G. Anemia and Iron Deficiency - New therapeutic targets in Heart Failure? *N Eng J Med.,* 2009, 10, 1-3
56. Wilson M, Reeder B. Oxygen-binding haem proteins. *Exp Physiol,* 2008, 93, 128-132
57. Witte KK, Desilva R, Chattopadhyay S, Ghosh J, Cleland JG, Clark AL. Are hematinic deficiencies the cause of anemia in chronic heart failure? *Am Heart J,* 2004, 147, 924e30

© 2014 discovery publication. All rights reserved