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► **To cite this version:**

Martin Cowie, Rebecca Lucas. Iron replacement therapy in chronic heart failure. *International Journal of Clinical Practice*, 2011, 65 (6), pp.645. 10.1111/j.1742-1241.2011.02636.x . hal-00640467

HAL Id: hal-00640467

<https://hal.science/hal-00640467>

Submitted on 12 Nov 2011

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Iron replacement therapy in chronic heart failure

Journal:	<i>International Journal of Clinical Practice</i>
Manuscript ID:	IJCP-12-10-0657.R1
Wiley - Manuscript type:	Perspective
Date Submitted by the Author:	06-Jan-2011
Complete List of Authors:	Cowie, Martin; Imperial College London, Clinical Cardiology; Royal Brompton Hospital, Clinical Cardiology Lucas, Rebecca; Royal Brompton and Harefield NHS Foundation Trust, Clinical Cardiology
Specialty area:	

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Manuscripts

Clinical Perspective: Iron replacement therapy in chronic heart failure

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3 Anaemia is common in patients with chronic heart failure (HF), particularly if there is
4 concomitant renal dysfunction. It is part of a cardio-renal-anaemia syndrome, in which
5 each component impacts on the other in a vicious cycle.
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9 Prevalence varies according to the definition used but a recent meta-analysis reported
10 anaemia in over one-third of patients with chronic HF (1). The majority of studies in this
11 meta-analysis used the WHO definition of anaemia (haemoglobin <12g/dl in women and
12 <13g/dl in men). Anaemia prevalence increases with age and with HF severity, but
13 averaged 37% in the studies included in the meta-analysis (1).
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16 Anaemia in patients with HF is associated with worse symptoms and decreased exercise
17 capacity (2). It has also been shown to be independently associated with increased risk
18 of hospitalisation and mortality (3), both in patients with left ventricular systolic
19 dysfunction and those with preserved ejection fraction (1).
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22 Outcome studies have not yet established that anaemia is a cause of HF progression
23 rather than simply a marker of disease severity. Nonetheless, evidence is accumulating
24 that there is benefit from correction of anaemia.
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27 The multiple causes of anaemia in HF include haemodilution, chronic inflammation,
28 chronic kidney disease and iron deficiency (for example, from NSAID-induced
29 gastrointestinal bleeding). ACE inhibitors and angiotensin receptor blockers might also
30 play a part by reducing erythropoietin (EPO) activity.
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33 When other causes of anaemia have been excluded, HF anaemia is generally labelled as
34 anaemia of chronic disease. Renal dysfunction and pro-inflammatory cytokine activation
35 appear to contribute to this anaemia in the majority of patients (4), resulting in reduced
36 EPO production or EPO resistance and defective iron utilisation, the latter via increased
37 hepatic production of hepcidin protein (Figure).
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40 Iron deficiency appears to be more important than previously thought as a contributor
41 to anaemia in HF. Although absolute iron deficiency is reported in a minority of cases
42 (<30%) (3) functional iron deficiency may be more common. Poor utilisation of
43 seemingly adequate iron stores was identified in one study as an important factor
44 associated with anaemia in HF (5).
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50 Over the past decade several studies have been undertaken to assess the benefit of
51 correcting anaemia in HF (Table). Initial small single-centre studies reported some
52 improvement in functional capacity and quality of life with use of EPO or its analogues
53 together with supplementary iron (6,7) although a small multicentre study showed no
54 significant effect on exercise tolerance (8) and the larger STAMINA-HeFT randomised
55 trial of 319 patients found no significant clinical benefits from darbepoetin (9).
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4 A meta-analysis of seven randomised trials of erythropoiesis-stimulating agents (ESAs) in
5 HF (10) reported reduced risk of HF hospitalisation. However, no HF trial has yet shown
6 ESA benefit on mortality. Furthermore, the long-term safety of treatment is not proven.
7 This is important in view of adverse cardiovascular effects (thrombotic risk and
8 hypertension) associated with high haemoglobin levels after ESA treatment in chronic
9 kidney disease (CKD) patients. Most recently, the TREAT trial in CKD patients with
10 diabetes reported that treatment with darbepoetin (target haemoglobin 13g/dl) was
11 associated with increased risk of stroke (11). The risk of cardiovascular side effects has
12 led to guideline recommendations not to aim for normalisation of haemoglobin levels
13 when using ESAs in CKD (12, 13).
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17 Meta-analysis of the HF trials reported no increased mortality or adverse events with
18 ESAs (10) but the experience in CKD has led to caution among cardiologists and use of
19 ESAs in HF anaemia (an unlicensed indication in Europe) has declined. Ongoing trials,
20 including the large RED-HF trial of darbepoetin, which has all-cause mortality or HF
21 hospitalisation as its primary endpoint, should provide useful data.
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25 Meanwhile, the evidence base is moving on and there is increasing interest in the idea
26 of iron replacement on its own for correcting anaemia in HF, with data suggesting that
27 using IV iron alone to increase haemoglobin levels can improve cardiac and renal
28 function. Some HF studies have also investigated iron replacement in patients with iron
29 deficiency in the absence of anaemia.
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32 The iron replacement studies in HF anaemia have used IV iron. Oral iron is often poorly
33 tolerated and so may not be taken reliably; in addition, it may not increase iron stores
34 because of hepcidin-induced reduction in duodenal iron absorption (4) as well as
35 malabsorption associated with gut oedema. IV iron is more effective and there are no
36 compliance issues.
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40 Several small studies assessing this new strategy in HF anaemia suggested that
41 treatment can increase haemoglobin, improve exercise capacity and symptoms (14),
42 reduce NTproBNP level and inflammatory status (C-reactive protein level) and reduce
43 hospitalisations (15). In the FERRIC-HF trial (16), in which IV iron was given to HF
44 patients with iron deficiency with or without anaemia, treatment was associated with
45 improved exercise capacity (mean of 60s greater treadmill duration, $P=0.08$, and
46 2.2ml/kg/min of peak oxygen consumption, $P=0.01$) and was well tolerated.
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50 The largest iron study to date is the FAIR-HF trial (17) in which 459 patients with HF due
51 to LV systolic dysfunction and iron deficiency (with or without anaemia) received IV iron
52 or placebo. Active treatment was associated with improvement at week 24 in the
53 Patient Global Assessment (odds ratio for improvement 2.5) and in the New York Heart
54 Association functional class (odds ratio for improvement by one class 2.4).
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3 A new FAIR-HF subanalysis suggests that treatment might also improve renal function
4 (Ponikowski P. et al, reported at the 2010 Annual Scientific Meeting of the Heart Failure
5 Association of the European Society of Cardiology, Berlin).
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8 As with the ESA trials, none of the iron studies so far has had hard endpoints and further
9 randomised studies are needed. IRON-HF is one ongoing trial of iron therapy that
10 includes HF hospitalisations and mortality among the secondary endpoints (18).
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13 There has in the past been concern about use of IV iron because of the history of
14 anaphylaxis with iron dextran. The HF trials used newer non-dextran-containing
15 formulations (iron sucrose or ferric carboxymaltose) with reduced risk of producing
16 hypersensitivity reactions. Ferric carboxymaltose has the additional advantage that
17 higher doses can be given: the total iron requirement can be given in one dose, avoiding
18 the need for patients to make repeated visits for treatment. Also, unlike the other IV
19 iron products, it does not require an initial test dose.
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23 At our centre we have audited our use of IV iron (ferric carboxymaltose) in patients with
24 heart failure and anaemia. In a 12 month period we have given single dose IV iron
25 replacement in 30 patients, without any adverse effect. The patients had moderate to
26 severe symptoms (mostly NYHA Class III) despite optimal medical management with ACE
27 inhibitors, beta-blockers, and aldosterone antagonists and 40% had cardiac
28 resynchronisation therapy also. Median Hb prior to IV iron therapy was 10.5 g/dl, with
29 median estimated GFR of 44 ml/min/m², serum iron 6.8 µmol/l (normal range: 12.6-26),
30 ferritin 46 µg/l (normal range: 32-284), and transferrin saturation 9.5% (normal range:
31 20-45%). The change in mean Hb was 1g/dl after IV iron therapy, with no change in
32 estimated GFR. Serum iron rose to 11.3 µmol/l, ferritin to 274 µg/l and transferrin
33 saturation to 22%.
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38 Correction of anaemia is not yet established as routine therapy in HF guidelines (19, 20)
39 but anaemia is common in HF and its cause and correction should be considered.
40 Specific causes should be investigated and iron status checked. In many cases anaemia is
41 likely to be related to the cardio-renal-anaemia syndrome and treatment with IV iron
42 can be considered. Clinical trials to date and practical experience indicate that with the
43 modern formulations IV iron replacement is useful and well tolerated. However, we
44 need trial data on clinical outcomes to assess the true value of treating HF anaemia, and
45 further investigation of iron replacement in patients who are iron deficient but do not
46 have anaemia.
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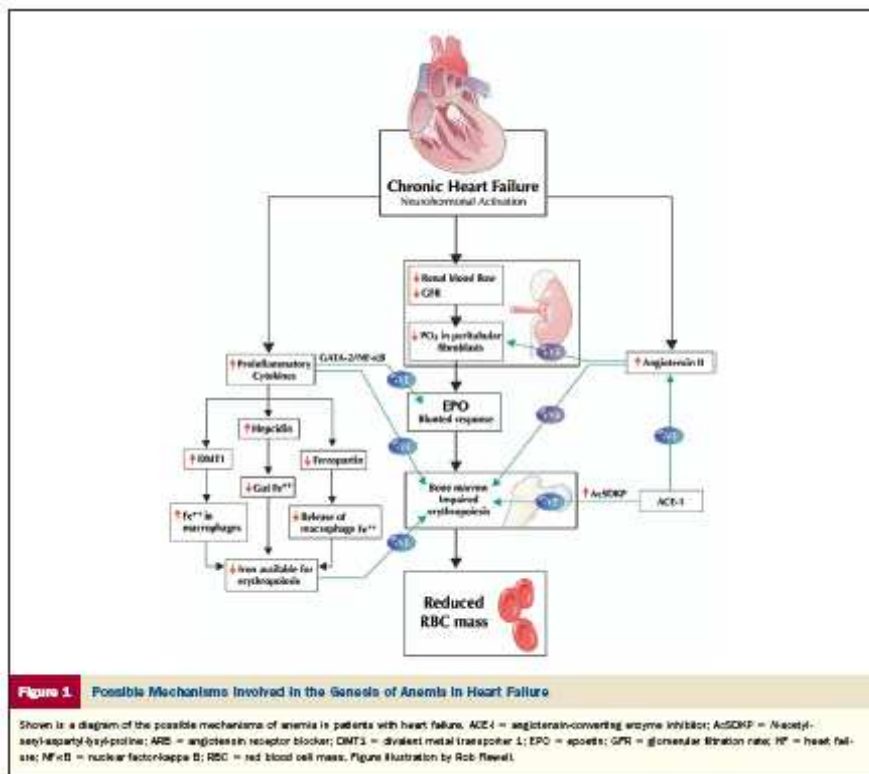
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Disclosures: None

Funding: None

Acknowledgements: None

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Author	No.	NYHA Class	EF at entry	Entry Hb	Treatment	Duration of follow up	Effect on Hb (difference in mean changes between groups)	Outcomes
Silverberg et al. (2001) ⁶	32	III or IV	≤40%	10-11.5 g/dl	EPO (+IV iron) or no treatment	Mean 8.2 months	2.7 g/dl P<0.0001	Multiple endpoints reported, including some comparisons with time period before study. Mean NYHA Class improved in EPO group and deteriorated in control group (P<0.0001), and mean EF increased by 5.5% in EPO group, and deteriorated by 5.4% in control group (P<0.0001).
Mancini et al. (2003) ⁷	26	III or IV	Not entry criterion (mean 23%)	Hct < 35%	EPO (+ oral iron) or placebo	3 months	2.7g/dl P<0.0001	Multiple endpoints. Increase in peak V _O ₂ (1.7 ml/min/kg; P<0.05) and six minute walk test exercise duration (67 seconds; P<0.004) reported in active group.
Ponikowski et al.(2007) ⁸	41	II-IV	≤40%	9-12g/dl	EPO or placebo (all given oral iron unless baseline ferritin > 800ng/ml)	26 weeks	1.5g/dl P=0.005	Primary endpoint: Peak V _O ₂ . NS increase of 0.5 ml/kg/min (P=0.40). Multiple other endpoints reported.
Ghali et al.(2008) ⁹	319	II-IV	≤40%	9-12.5g/dl	EPO or placebo	52 weeks	1.5g/dl (median) P<0.001	Primary: treadmill exercise time (NS change between groups). Secondary: NYHA Class, and health related quality of life.(NS difference between groups) Other: Time to death or first HF hospitalisation (Trend: RRR 32% P=0.10)
Bolger et al.(2006) ¹⁴	16	II or III	Not entry criterion (mean 26%)	Hb≤ 12g/dl male Hb≤11.5g/dl female	IV iron sucrose (all patients) over 12 days	Mean 3 months	N/A	No comparator group, but significant improvement in disease-specific quality of life (P=0.02) and six minute walk tests distance (44m; P=0.01)
Toblli et al.(2007) ¹⁵	40	II-IV	≤35%	Hb<12.5g/dl	IV iron sucrose or saline over 5 weeks	6 months	1.9g/dl P<0.01	Multiple endpoints. Significant increase in EF (6.9%), disease-specific quality of life, and six minute walk test distance (48 m)(All P<0.01) reported for iron group. No hospitalisations in iron group versus 5 in saline group (P<0.01) reported.

Okonko et al.(2008) ¹⁶	35	II or III	≤45%	Hb<12/5g/dl (anaemic group)(N=18) 12.5-14.5g/dl (non-anaemic group)(N=17)	IV iron sucrose or no treatment over 16 weeks	16 weeks	0.1g/dl (P>0.20)	Primary: peak absolute V02. 96 ml/min increase in iron group compared with no treatment (P=0.08), but 204ml/min (P=0.02) for anaemic group. Multiple other endpoints reported, including greater improvement in NYHA Class in iron group (P=0.007).
Anker et al.(2009) ¹⁷	459	II or III	≤40%(NYHAII) ≤45%(NYHA III)	Hb 9-5-13.5g/dl	IV ferric carboxymaltose or saline over 24 weeks	24 weeks	0.59 g/dl (P<0.001)	Primary: patient global assessment, NYHA class (Improved more in iron therapy group P<0.001) Secondary: 6 minute walk test distance, and health related quality of life (improved more in iron therapy group P<0.001) Other: Trend in Time to death or first HF hospitalisation: RRR 39% P=0.08.

Key: NYHA: New York Association Functional Class; EF: Ejection fraction; Hb: plasma haemoglobin concentration; Hct: haematocrit; EPO: erythropoietin; IV: intravenous; N/A: not applicable; RRR: relative risk reduction; VO₂ max: maximal oxygen uptake.