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Anaemia in chronic heart failure: what constitutes optimal investigation and treatment?

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Introduction

Whilst the prognosis for patients with chronic heart failure (CHF) has improved over the last two decades, many patients suffer with severe limitation from symptoms and adverse prognosis. Heart failure is the most common cause of admission to hospital in people over 65 years in the developed world, and accounts for around 2% of the UK healthcare budget. Low haemoglobin is a common finding in patients with CHF. Although this observation was made several decades ago, the potential of an important pathophysiological link only recently became widely appreciated. While the cause of anaemia is not always easily identified, it is associated with the severity of heart failure, impairment of renal function, and other co-morbidities. Multifactorial aetiology of such anaemia is likely, and although few patients have a deficiency of vitamin B_{12} or folate this should always be excluded. Anaemia is an independent predictor of mortality and of acute hospital admission, and is also associated with exercise limitation.

Correction of anaemia is, therefore, an appealing strategy. Whilst erythropoietin levels may be elevated in CHF, they are often lower than expected when considering the haemoglobin concentration, indicating a relative deficiency. Similarly, iron metabolism is frequently disturbed, with many patients experiencing either an absolute or functional deficiency. Chronic iron deficiency may contribute to breathlessness and reduced exercise capacity, the hallmarks of symptomatic CHF.

This supplement aims to increase awareness of anaemia in CHF and also to provide an overview of recent studies of erythropoiesis-stimulating agents (ESAs) and of intravenous iron therapy. Recent data from trials of ESAs in chronic kidney disease have highlighted potential detrimental effects on cardiovascular end points and reinforce the need for a major outcome study in CHF. We do not yet know whether correction of iron deficiency can favourably improve survival in CHF; however, observed improvements in New York Heart Association functional class, quality of life, exercise capability, and possibly in hospital admissions, suggest that iron replacement warrants further therapeutic investigation.

The round table meeting brought together specialists from a number of key disciplines (cardiology, nephrology, haematology and elderly care). This facilitated a consensus viewpoint for strategies for the investigation and treatment of anaemia in CHF. We believe that the proposed algorithm (see page S15) will allow a platform for further discussion and provide the basis for treating patients who have severe symptoms despite conventional therapy. We acknowledge that large-scale studies are still needed which incorporate hard end points (mortality and hospitalisation).

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Professor Philip Kalra, Consultant Nephrologist, Salford Royal Hospitals NHS Trust

Professor Iain Macdougall, Consultant Nephrologist, King's College Hospital, London

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Conflict of interest statement

Callum Chapman has received honoraria from Vifor Pharma. Andrew Clark has received honoraria for work on advisory boards from Vifor Pharma. Kingsley Hampton has received honoraria from Vifor Pharma. Paul Kalra has received honoraria from Amgen, Pharmacosmos, Servier, Takeda and Vifor Pharma for delivering lectures and for advisory board work. Philip Kalra has received honoraria from Amgen, Pharmacosmos, Roche and Vifor Pharma for delivering lectures and for advisory board work; Amgen and Roche have provided educational grants to support departmental research work. Iain Macdougall has received honoraria, consultancy fees and research support from Affymax, AMAG, Amgen, Ortho Biotech, Roche, Takeda and Vifor Pharma. Theresa McDonagh has received speaker's and advisory board honoraria from Vifor Pharma. Iain Squire is a member of speaker bureaus for Novartis and Vifor UK, and a member of trials steering committees for Janssen and Novartis.

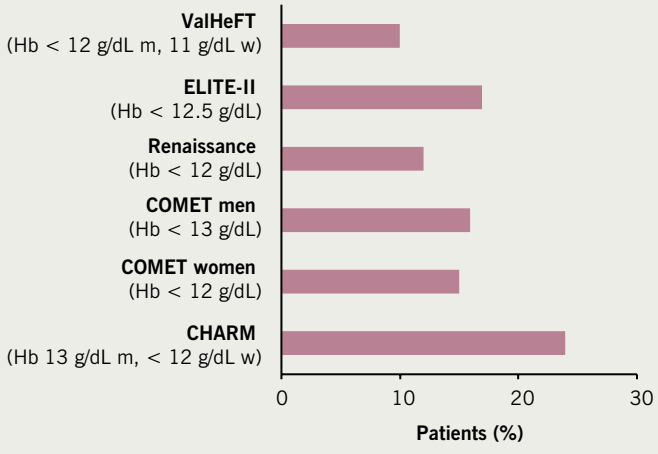
Anaemia in chronic heart failure – how common is it and what does it mean?

Iain Squire

Introduction

Chronic heart failure (CHF) is one of the major health challenges in the 21st century. As might be expected from a chronic condition, which increases in prevalence with age, CHF is often accompanied by one or more co-morbid conditions. Many of these add to the patient's symptom burden and to the complexity of managing the CHF. In addition, a few common co-morbid conditions are related intimately to the CHF disease process itself and may be, at least in part, the consequence of the heart failure syndrome. They may also contribute to its progression. Renal impairment and anaemia are the best-recognised conditions in this context and are frequently found together in the presence of CHF. There are multiple mechanisms by which anaemia may arise in the CHF population. Iron deficiency anaemia is relatively common in CHF and, given the potential for its correction, this type of anaemia has been the focus of a great deal of clinical and research interest. The aim of this article is to consider the prevalence of anaemia – iron deficiency or otherwise – in CHF, and its impact on morbidity and mortality.

Figure 1. The prevalence of anaemia in chronic heart failure in clinical trials. (The definition of anaemia is given in brackets)



Adapted from data from ValHeft (*N Engl J Med* 2001;**345**:1667–75 and *Circulation* 2005;**112**:1121–7); ELITE-II (*Eur Heart J* 2004;**25**:1021–8); Renaissance (*Circulation* 2004;**110**:149–54); COMET (*Eur Heart J* 2006;**27**:1440–6); CHARM (*Circulation* 2006;**113**:986–94)

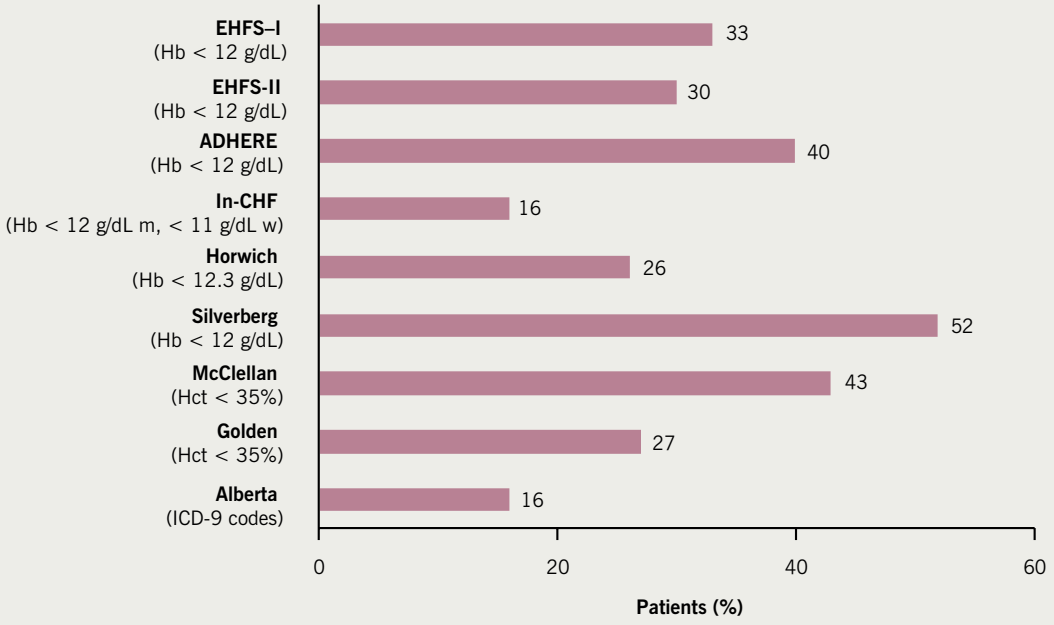
Key: CHARM = Candesartan in Heart Failure – Assessment of Reduction of Mortality and Morbidity; COMET = Carvedilol and Metoprolol European Trial; ELITE-II = Losartan Heart Failure Survival Study; Hb = haemoglobin; m = men; Renaissance = Randomized Etanercept North American Strategy to Study Antagonism of Cytokines; ValHeft = Valsartan Heart Failure Trial; w = women

Prevalence

In published reports of patients with heart failure, the prevalence of anaemia varies markedly, reflecting the very varied characteristics of the studied populations. In reports based upon clinical trials, the reported prevalence ranges from 10–25% (**figure 1**), while in cohorts of patients in observational or registry-based studies, it appears to be higher, from 15–50% (**figure 2**). This variation is unsurprising given the relatively selected nature of patients recruited to clinical trials in CHF. A reasonable overall estimate can be gleaned from a large systematic review of 34 studies, including more than 150,000 patients, in which anaemia prevalence was approximately 37%.[1] Anaemia is more often seen in women with CHF. It is very uncommon in patients with asymptomatic left ventricular impairment, but becomes increasingly common as symptoms become more severe – 20% of patients with New York Heart Association (NYHA) class II CHF are anaemic, rising to more than 50% of patients with NYHA class III and IV CHF.

It is interesting to note that the prevalence of anaemia increases with time in cohorts of

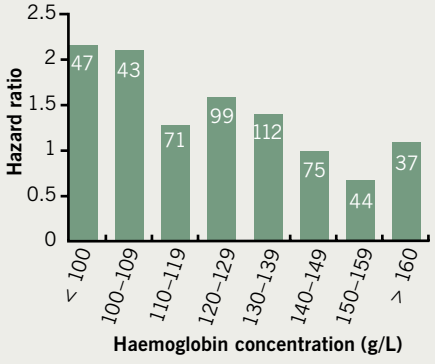
Figure 2. The prevalence of anaemia in CHF in observational and registry studies. (The study definitions are given in brackets)



Adapted from data from EHFS (EHFS-1 *Eur Heart J* 2003;**24**:442–63; EHFS-II *Eur Heart J* 2003;**24**:464–74); ADHERE (*Am Heart J* 2005;**149**:209–16); In-CHF study (*J Card Fail*;**11**:9108); Horwich study (*J Am Coll Cardiol* 2002;**39**:1780–6); Silverberg study (*J Am Coll Cardiol* 2000;**35**:1737–44); McClellan study (*Curr Med Res Opin* 2004;**20**:1501–10); Golden study (*Neth J Med* 2001;**59**:270–9); Alberta study (*Circulation* 2003;**107**:223–5)

Key: ADHERE = Acute Decompensated Heart Failure National Registry; EHFS = Euro Heart Failure Study; Hb = haemoglobin; Hct = haematocrit; ICD = International Classification of Diseases

Figure 3. Hazard ratio for death during follow-up according to admission haemoglobin concentration in 528 patients with a first hospital admission for heart failure



Adapted from Newton JD, Squire IB. *Heart* 2006;**92**:1441–6

Key messages

- Anaemia in CHF is common
- It negatively impacts on quality of life and survival

patients with CHF: in other words, there is an incidence of new-onset anaemia. In SOLVD (Studies of Left Ventricular Dysfunction),[2] approximately 9% of patients developed anaemia within the first year of follow-up. In COMET (the Carvedilol and Metoprolol European Trial),[3] anaemia increased in prevalence from 14% at one year of follow-up to over 25% at five years. Importantly, the development of anaemia is an important indicator of adverse outcome, which will be discussed below.

Impact on quality of life

As already discussed, anaemia is a common co-morbidity in CHF and shows a clear adverse association with quality of life. Haemoglobin shows graded, inverse association with objective measures of exercise capacity, such as maximum oxygen uptake. Data from the CHARM (Candesartan in Heart Failure – Assessment of Reduction of Mortality and Morbidity) studies show that both cardiovascular and non-cardiovascular hospital admissions are more common in patients with CHF and anaemia.[4] The *change* in haemoglobin over time is also related to change in quality of life. For example, quality of life falls in those patients in whom haemoglobin falls, and improves in proportion to

the increase in haemoglobin in those patients in whom this occurs.

Impact on life expectancy

In addition to impacting on quality of life, lower haemoglobin shows a strong, graded association with the risk of death for patients with CHF. In the systematic review and meta-analysis referred to above,[1] anaemia was associated with an approximate doubling of the risk of death and was an independent marker of the likelihood of death over six months' follow-up. In the CHARM studies,[4] anaemia was associated with increased risk of death both in patients with reduced left ventricular ejection fraction and in those with preserved left ventricular function.

In a cohort of 528 consecutive patients admitted to hospital for the first time with the diagnosis of heart failure,[5] anaemia was seen in 39% of men and 43% of women. Any reduction in haemoglobin below the normal reference range was associated with approximately 40% increase in mortality risk, with a very clear, graded relationship with the risk of death during follow-up (**figure 3**).

Conclusion

Anaemia is common in patients with CHF and is associated with adverse impact on quality of life and survival

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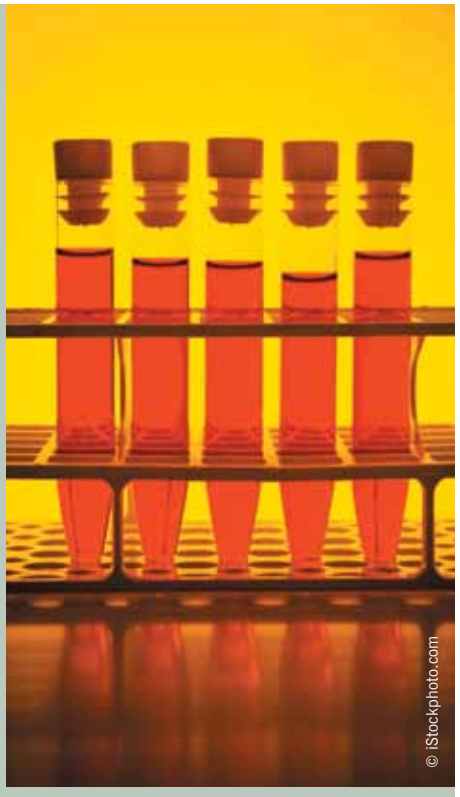
Round table discussion

How do we define anaemia?

The panel considered it important to agree a definition of anaemia. Many investigators use the World Health Organization (WHO) criteria, initially proposed in 1968, in which the threshold for anaemia in men over 15 years is a haemoglobin concentration <13.0 g/dL; and for non-pregnant women <12.0 g/dL. Debate continues as to whether these values are appropriate in the elderly, whether there should be sex differences, and whether they are appropriate in CHF.

The group agreed that the level decided upon should ideally be evidence-based and should be the level "which impacts on prognosis". Data from the ELITE II study[1] showed a haemoglobin level of around 14.5 g/dL was associated with best prognosis, whereas below this level, there was "quite a marked step down in the likelihood of survival". Other findings from the literature suggest there may be a level (around 12.5 g/dL) at which we might "dichotomise the association with adverse outcomes" (in other words, there is a major association with increased mortality below this value).

Caution is required when discussing anaemia, iron deficiency anaemia and iron deficiency with normal haemoglobin levels as they are not the same entity. Patients may exhibit iron deficiency yet have 'normal' haemoglobin values. Indeed iron deficiency *per se* is an independent predictor of mortality in CHF. Furthermore, we do not have ideal markers of iron deficiency, and those commonly used, such as ferritin, may have a very wide 'normal' range e.g. 12–200 μg/L. A low ferritin level within the normal range may not be biologically ideal. Although it is key to have a definition to 'prompt' physicians, patients with CHF are different from healthy subjects and even patients with gastrointestinal disease. In summary, the optimal haemoglobin level in CHF is not known. Patients with a haemoglobin level below WHO or local laboratory quoted normal ranges, such as 12 or 13 g/dL (with some debate on whether there is a sex-specific difference) should be the focus for further investigation and consideration for treatment. Some patients with haemoglobin in the normal range who remain symptomatic may also have iron deficiency which might warrant attention.



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The origins of anaemia in patients with chronic heart failure

Andrew L Clark

Introduction

We have already seen how anaemia is common in patients with chronic heart failure (CHF) and how it impacts on symptoms and prognosis. Increasingly, anaemia is being thought of as a possible target for treatment, and so an understanding of the possible causes of anaemia in CHF is vital for developing appropriate therapy (**figure 1**). Unfortunately, apart from unusual patients with specific pathologies underlying their anaemia, the origin of anaemia is multifactorial in most patients (**table 1**).

Haematinic deficiency

The commonest single haematinic deficiency related to anaemia in patients with CHF is iron deficiency. Around half of all patients with anaemia have evidence of iron deficiency on the basis of abnormal results for serum iron, iron binding capacity and ferritin.[1,2] Folate or vitamin B_{12} deficiency is relatively uncommon. Iron is used by the body not only for haemoglobin production but in a variety of enzyme systems, which may be affected by iron deficiency.

There are many possible reasons for iron deficiency in patients with CHF. Dietary intake may be poor in the elderly population, and blood loss, too, is common. Although it is difficult to be prescriptive, the finding of iron deficiency should prompt gastroenterological investigations for possible underlying pathology. Gastrointestinal malignancy may be seen in patients with CHF as both conditions become more common with increasing age. If a patient has multiple haematinic deficiencies, such as iron and folate together, it should prompt a search for possible malabsorption, particularly coeliac disease.

The behaviour of erythropoietin (epo) in CHF is not completely clear. In some studies, epo has been found to be raised in proportion to the severity of heart failure, with increasing epo related to adverse outcome.[3] Other investigators have found that the level of epo is lower than might be expected for the level of haemoglobin in some anaemic patients with CHF.[4] The disparity might be related to the different assays used: some forms of epo are inactive, yet still measured in some assays.

Renal impairment

Renal impairment is extraordinarily common in patients with CHF, with more than half having a glomerular filtration rate less than 60 ml/min. Anaemia and iron deficiency are both more common in those with renal impairment.[2] The outlook is worse for patients with both anaemia and renal dysfunction than with either alone.

The effects of CHF treatment

An irony of CHF treatment is that some of the successful treatments which improve prognosis are associated with anaemia. Angiotensin-converting enzyme (ACE) inhibitors, in particular, cause anaemia.[5] The reason is not clear. A tetrapeptide, N-acetyl-seryl-aspartyl-lysyl-proline, is an endogenous inhibitor of erythropoiesis. It is broken down by ACE, so ACE inhibitors may prolong its effects, causing anaemia.[6] In addition, angiotensin II tends to increase renal epo production via a reduction in renal blood flow: inhibiting angiotensin II therefore may contribute to a reduction in epo production.

It is worth noting that in COMET (the Carvedilol and Metoprolol European Trial), the more effective of the two beta blockers tested (carvedilol) was associated with a lower haemoglobin,[7] suggesting that there may be some consequences of successful heart failure treatment in general that induce anaemia.

Aspirin can, of course, contribute to anaemia by its effects on blood loss and potentially via its renal effects. There is no good evidence that aspirin is beneficial in patients with CHF and so stopping it may be the correct approach in the patient with CHF and anaemia.

Haemodilution

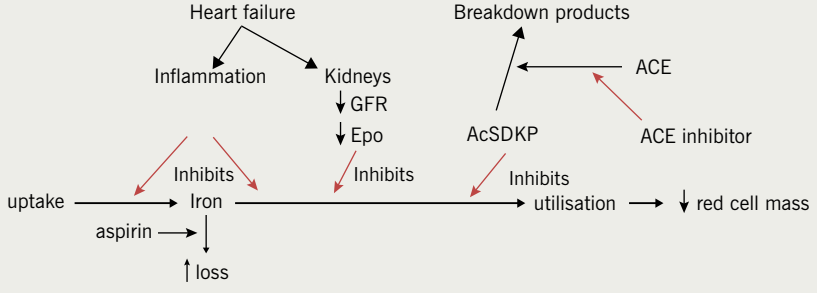
It is difficult to measure fluid status precisely although it is undoubtedly the case that some patients with CHF are anaemic not because their red cell mass is low, but because their plasma volume is high and the red cells are diluted, giving

Table 1. Origins of anaemia

• Haematinic deficiency	
• Renal impairment	
• Treatment	- beta blocker - ACE inhibitor, angiotensin receptor blocker
• Haemodilution	
• 'Anaemia of chronic disease'	- related to inflammation - related to impairment of iron utilisation - related to blunted erythropoietin production

Key: ACE = angiotensin-converting enzyme

Figure 1. Some possible pathways for the development of anaemia in patients with chronic heart failure



Key: ACE = angiotensin-converting enzyme; AcSDKP = N-acetyl-seryl-aspartyl-lysyl-proline; epo = erythropoietin; GFR = glomerular filtration rate. Red lines indicate inhibition. The possible effect of haemodilution is not included

the factitious impression of anaemia. In one study, two thirds of patients who were apparently clinically euvolaemic were in fact hypervolaemic.[8]

In a very careful study of 37 patients with heart failure and anaemia, around a half had dilutional anaemia and half had true anaemia – that is, a reduced red cell mass.[9] However, this was a population of severely affected patients being assessed for possible heart transplantation, so it is difficult to know how generally applicable the results are.

Key messages

- The origins of anaemia in heart failure are multifactorial
- Its pathways are complex and not well understood
- There is no single treatment that will suit all patients
- Treatment must be based on an understanding of the causes of anaemia in each patient

The anaemia of chronic disease

Many chronic illnesses cause anaemia, and CHF is no exception. What all these conditions have in common is an association with systemic inflammation. The anaemia seems to be related to a primitive physiological response to inflammation (usually, in evolutionary terms at least, associated with infection): sequestering iron is a defence against invading bacteria, which are dependent upon its supply to multiply.

CHF is, of course, an inflammatory disease.[10] Characteristic features of the anaemia of chronic disease are that iron is potentially available to the bone marrow, but is not being used. In association, epo may be reduced more than is expected for the haemoglobin level. Some studies have suggested that in patients with anaemia and CHF, up to 60% may have the anaemia of chronic disease, as suggested by low serum iron and iron-binding capacity but normal (or increased) ferritin.[11]

There has been much interest in hepcidin, a molecule produced by the liver in inflammatory states. Hepcidin reduces intestinal iron absorption and mobilisation from reticulo-endothelial stores, and might thereby contribute to iron deficiency and anaemia. However, more recent investigations have suggested that hepcidin may not be as important as first thought.[12]

Conclusion

Anaemia is common in patients with CHF but its origin is complex and imperfectly understood. In any individual patient, there may be more than one cause of anaemia, and in each patient anaemia should be investigated before embarking on treatment. It is only by understanding the origin of anaemia that appropriate treatment can be given: using a single treatment in every patient may cause harm

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Round table discussion

It seems surprising that treatments associated with improved outcomes in CHF such as ACE inhibitors (as discussed) and beta blockers can exacerbate anaemia. Why beta blockers are associated with anaemia is less clear. Aspirin can also cause blood loss and make patients iron deficient as well as exacerbating renal dysfunction. All agreed that the benefits of ACE inhibitors and beta blockers greatly outweigh this minor impact on haemoglobin.

Testing for iron deficiency

What is the best test to determine iron deficiency in CHF? In healthy individuals, ferritin levels are directly correlated with the total amount of body iron stored. Reduced levels suggest iron deficiency but different cut-off points are used to prompt intervention in patients with gastroenterological or gynaecological pathology compared to those with CHF. Because ferritin is an acute phase protein, its level may be affected by any inflammation. A transferrin saturation (TSAT) [reference range 15–50% in men; 12–45% in women] provides a measure of how much serum iron is actually bound and thereby available for use. A number of other variables may suggest iron deficiency, including low mean corpuscular volume (MCV), % hypochromic red cells, increased total iron binding capacity [TIBC] and increased soluble serum transferrin receptors. Not all of these tests are available in every haematology laboratory.

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Anaemia treatment in chronic heart failure

Iain C Macdougall

Introduction

The treatment of anaemia in chronic heart failure (CHF) has many parallels with the treatment of anaemia in chronic kidney disease. Two major therapies are available, namely erythropoietin replacement therapy and intravenous iron supplementation, and both have been widely used in nephrology for the last 20 years. Indeed, both have become standards of care for treating anaemia in chronic dialysis patients, the majority of whom have inappropriately low circulating erythropoietin levels and negative iron balance. Erythropoiesis-stimulating agents (ESAs) are required to boost the production of red cells in the bone marrow, whilst intravenous iron will correct any iron deficiency and also lower the dosage requirements of ESA therapy.

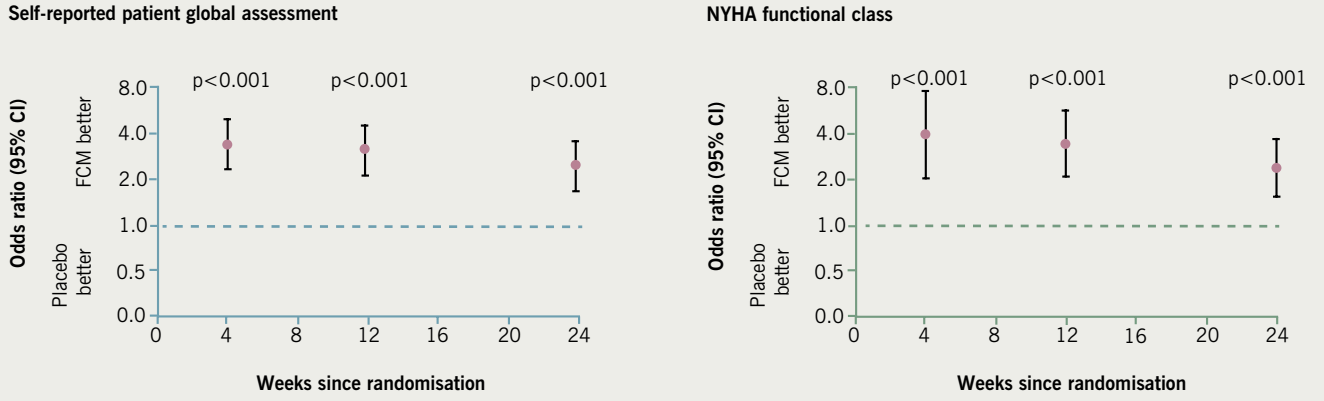
The situation in the anaemia of CHF is less advanced, but in recent years there has been increasing interest in the use of both of these treatment strategies. A few small clinical trials have suggested some potential benefits of stimulating erythropoiesis with ESA therapy in heart failure anaemia, whilst the administration of IV iron has shown similar benefits even in the absence of ESA therapy. Indeed, the recently published FAIR-HF (Ferinject® Assessment in patients with Iron deficiency and chronic Heart Failure) trial[1] has opened the eyes of cardiologists to the potential for this latter treatment strategy to improve the symptoms and signs of heart failure.

ESA therapy

The first report of the use of ESA therapy in treating patients with heart failure appeared in 2000 by Silverberg *et al.*[2] This was a retrospective analysis of 142 patients with anaemia and CHF, of whom 26 were treated with subcutaneous erythropoietin and intravenous iron for more than six months. The mean haemoglobin level increased significantly, and this was associated with an increase in ejection fraction and New York Heart Association (NYHA) functional class. Lower doses of diuretics were needed during the study period, and there were fewer patients hospitalised than before. In a subsequent small, randomised controlled trial of 32 patients, Silverberg *et al.*[3] confirmed these favourable findings on the same clinical end points. Mancini *et al.*[4] then showed that in 26 anaemic patients with CHF, ESA therapy increased the haemoglobin concentration, and there was a concomitant increase in peak oxygen consumption (VO_2) and exercise duration. Similar small studies from Italy[5] and Greece[6] provided additional evidence for the possible beneficial effect of ESAs in CHF, while Ponikowski *et al.*[7] in 41 patients showed that darbepoetin alfa was able to increase and maintain haemoglobin levels, with a trend to improved exercise capacity.

Two large studies were then initiated.[8,9] Van Veldhuisen *et al.*[8] found a significant increase in several quality of life measures with ESA treatment over a six-month study period, while the effect on six-minute walking distance showed a borderline statistically significant increase (p=0.074). In the STAMINA-HeFT (Study of Anemia in Heart Failure – Heart Failure Trial), 319 patients were treated with darbepoetin alfa or placebo for 12 months,[9] and there was a non-significant favourable trend (HR 0.68 [95% CI 0.43,1.08]; p=0.10) with regard to its effect on the composite end point of all-cause mortality or first hospitalisation for CHF. A meta-analysis of 650 patients, of whom 363 had been treated with erythropoietin,[10] showed that ESA treatment resulted in a lower risk of hospitalisation for CHF (risk ratio [RR] 0.59, 95% CI 0.41–0.86, p=0.006) while there was no significant effect on mortality (RR 0.69, 95% CI 0.39–1.23, p=0.21). These cautiously optimistic outcomes led to the design of the RED-HF (Reduction of Events with Darbepoetin alfa in Heart Failure) Trial.[11] The RED-HF trial is targeted to enrol 2,600 patients with CHF and anaemia; the study was initiated in 2006 and has, to date, recruited more than

Figure 1. Improvements in self-reported patient global assessment and NYHA functional class in the FAIR-HF study



Adapted from Anker *et al.*[1]

Key: FCM = ferric carboxymaltose; NYHA = New York Heart Association

2,000 patients out of the projected 2,600, although recent recruitment has been slow.

Two randomised controlled studies of ESA therapy in the chronic kidney disease anaemia literature raised causes for concern in the entire study population,[12,13] although curiously, the increased cardiovascular risk was not seen in patients with heart failure at baseline compared to those without heart failure. In TREAT (Trial to Reduce Cardiovascular Events with Arenesp® Therapy),[13] patients with a history of CHF (n=1,347) seemed to fare better with darbepoetin alfa compared to those without CHF at baseline.[14] Similarly, in a substudy of CHOIR (Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease),[12] the increased risk associated with targeting the higher haemoglobin level was not observed in patients with HF at baseline (hazard ratio 0.99), while in those without HF at baseline it was markedly increased (hazard ratio 1.86, p=0.004).[15] Clearly there are limitations of both of these analyses, and the definitive answer regarding the benefits (or otherwise) of ESA therapy will hopefully come from the analysis of the RED-HF study.

Intravenous iron supplementation

Several studies have examined the efficacy and safety of intravenous iron supplementation alone in patients with CHF. Bolger *et al.*[16] studied 16 patients with anaemia and mild-to-moderate CHF. In an uncontrolled study they showed that after intravenous administration of 1,000 mg iron sucrose during a two-week period, the haemoglobin concentration increased significantly after three months, while NYHA functional class, quality of life and walking distance improved.

The first controlled study was conducted by Toblli *et al.*[17] Forty patients with mild anaemia (haemoglobin ≤12.5 g/dL) and iron deficiency (ferritin <100 μg/L, transferrin saturation [TSAT] <20%) were randomised to receive 200 mg intravenous iron sucrose or a saline control once weekly. At the end of the six-month study, patients who had received intravenous iron (n=20) had a mean increase in haemoglobin from 10.3 to 11.8 g/dL, and this was associated with improved renal function and lower NT-proBNP levels, while their left ventricular function, quality of life and six-minute walking distance all significantly improved. Interestingly, there were five hospitalisations for CHF in the control group, and none in the intravenous iron group.

The second European study (FERRIC-HF) by Okonko *et al.*[18] randomised both anaemic and non-anaemic patients, all of whom had iron deficiency (ferritin level <100 μg/L, or a ferritin between 100–300 μg/L in combination with a transferrin saturation <20%). Of the 35 patients in this study, 18 were anaemic and 17 were non-anaemic. Twenty-four were randomised to initially receive weekly intravenous iron, with additional iron supplementation as required per protocol during the maintenance phase. Intravenous iron use was greater in anaemic than in non-anaemic patients (1,051 *vs.* 781 mg). Intravenous iron improved exercise capacity and symptoms of CHF, and the benefits were more evident in anaemic patients. Treatment was overall well tolerated and the clinical event rate was also similar.

The third and largest study by far in this field is the FAIR-HF study, published in November 2009.[1] In this double-blind, placebo-controlled

Key messages

- There is a suggestion that intravenous iron therapy may be of benefit in patients with CHF and iron deficiency. The FAIR-HF study showed benefits in patient-reported outcomes, in NYHA functional class and exercise capacity in patients with iron deficiency irrespective of haemoglobin level
- Several small studies have suggested that ESA therapy in CHF may be of benefit. Results from the RED-HF study should further elucidate its potential role

study, 459 HF patients with iron deficiency (ferritin level <100 μg/L, or a ferritin between 100–300 μg/L in combination with a TSAT <20%), with or without anaemia, were randomised to 2:1 treatment with weekly intravenous iron (ferric carboxymaltose, n=304) or saline (placebo, n=155) for a total period of 24 weeks. The primary end points of the study were patients' global assessment and NYHA functional class (**figure 1**). Weekly iron therapy rapidly increased iron levels, and there was a modest increase in haemoglobin levels in those with anaemia at baseline (+0.9 g/dL, p<0.001 *vs.* controls), with no change in those who did not have anaemia at baseline (+0.2, p=0.21). Intravenous iron improved both primary end points: patients' global assessment and NYHA functional class (both p<0.001). Interestingly, this beneficial effect was similar in patients with and without anaemia. Improvements were also seen for six-minute walking distance and quality of life measures. Intranevous iron was generally well tolerated, and there were no obvious differences in hard end points such as all-cause death (3.4% *vs.* 5.5%, for intravenous iron *vs.* control, respectively) and first hospitalisation (17.7% *vs.* 24.8%, respectively) between the two groups. A *post hoc* analysis of FAIR-HF has also suggested a possible improvement in renal function in the patients receiving intravenous iron compared to placebo.

Thus, there is now enough evidence for cautious optimism in the use of intravenous iron in patients with CHF. One of the particularly interesting findings in the FAIR-HF study was the fact that improvements were seen in both the anaemic and the non-anaemic groups, raising a hypothesis that perhaps iron replacement may initiate positive effects outwith the bone marrow, possibly on the cardiac myocyte.[19] Further studies are required to confirm these findings, and to elucidate their aetiology.

Conclusion

Both ESA therapy and intravenous iron supplementation have been the subject of careful study in patients with CHF over the last few years. The definitive study of the use of ESA therapy in patients with CHF is the RED-HF trial,[11] which is ongoing, and which will unquestionably provide valuable data to address this topic. The FAIR-HF trial[1] generated encouraging data, albeit with 'soft' but meaningful end points, and there is certainly enough optimism from this study to justify further research in the potential role of intravenous iron in improving symptoms and outcomes in patients with CHF

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Round table discussion

The round table discussion on anaemia treatment in chronic heart failure has been combined with the discussion on anaemia management in chronic kidney disease (see pages S13–S14).

Lessons to be learned from recent studies of anaemia management in chronic kidney disease

Philip A Kalra

Introduction

Anaemia is extremely common in patients with chronic kidney disease (CKD). Causes are multifactorial but erythropoietin deficiency, iron deficiency or diminished availability and chronic inflammation are pre-eminent. For over two decades it has been possible to correct the anaemia of patients with CKD with combinations of iron therapy and erythropoiesis-stimulating agents (ESA) with relative ease. Results of recent studies, however, have indicated that haemoglobin targets need to be revised and that more consideration should be directed to individualised treatment dependent upon the patient's haemoglobin response, ESA dosage and level of co-morbidity.

Epidemiology of anaemia in CKD

The likelihood of anaemia occurring in CKD increases as renal function declines. All patients receiving haemodialysis therapy will require treatment for anaemia, and so too will almost all of those receiving peritoneal dialysis (the difference accounted for by haemodialysis exposing the patient to a greater inflammatory state, and also regular minor blood losses). Below a glomerular filtration rate (GFR) of 45 ml/min, erythropoietin secretion by the kidney declines and when patients enter stage 4 CKD (eGFR < 30 ml/min), around 30–40% will be anaemic.

Aetiology of anaemia in CKD

Figure 1 summarises the factors contributing to anaemia in CKD. As already mentioned, erythropoietin secretion declines with decreasing GFR, and this is the predominant cause. Iron deficiency (either absolute or 'functional' – the latter referring to a situation where ferritin levels are within target, but transferrin saturation is decreased [< 20%], usually indicative of poor iron bio-availability) is very common, and many patients have an inflammatory state accompanied by high hepcidin levels. Other contributors are severe hyperparathyroidism (which can affect bone marrow responsiveness), blood loss on dialysis, the bone marrow effects of uraemia and the effects of certain medications (e.g. angiotensin-converting enzyme [ACE] inhibitors).

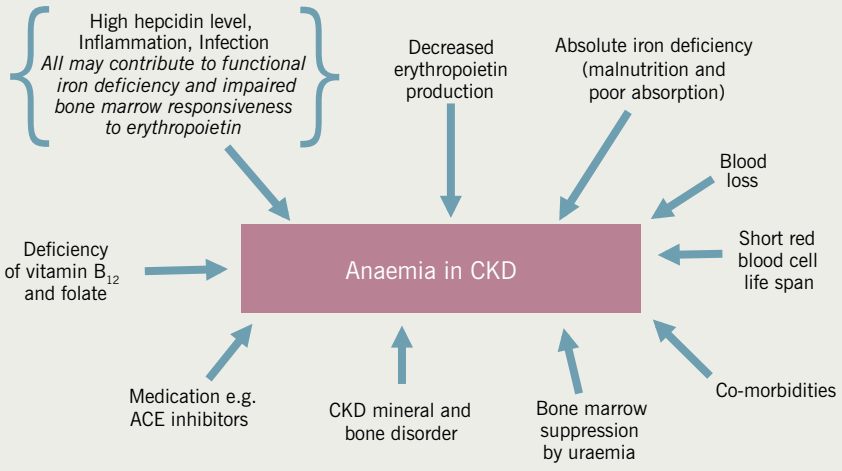
Benefits of correction

ESA became available in the late 1980s as recombinant human hormone preparations. There followed a surge in use, with large numbers of patients being able to benefit. Before the advent of ESA therapy, dialysis patients regularly ran mean haemoglobin levels of 7–9 g/dL, with accompanying profound malaise, lethargy and risk of increased co-morbidity. These patients often received regular top-up blood transfusions, with attendant increases in allo-antigenicity, decreasing their chances of receiving a suitable renal transplant. Over the years, small studies have showed that benefits in anaemia correction were translated into clinical improvements, including quality of life, cognition and sexual function (see **table 1**). In the mid 1990s it became clear that success of ESA therapy for patients with advanced CKD necessitated repletion and maintenance of iron stores, and hence came the dawn of intravenous iron therapy for patients.

Table 1. Potential benefits of correction of anaemia in chronic kidney disease

↑	quality of life
↑	exercise capacity
↓	cardiac output (from high output)
↓	angina
↓	left ventricular hypertrophy
↓	bleeding tendency
↑	brain/cognitive function
↓	depression
↑	sleep patterns
↑	sexual function
↑	endocrine function
↑	immune function
↑	muscle metabolism
↓	hospitalisations
↓	transfusions
↑	nutrition

Figure 1. Factors contributing to anaemia in chronic kidney disease (CKD)



Adapted from Agarwal AK. *J A Med Dir Assoc* 2006;**7**:S7–S12

Iron treatment

The definitions of iron deficiency in CKD patients are different from those used in the general population. Absolute iron deficiency is considered present if the serum ferritin is <100 μg/L, whereas functional iron deficiency has been defined earlier in the article. Patients with advanced CKD are at risk of both; the patient with CKD has poor iron absorption and a likelihood of chronic or repeated acute inflammation. Although oral iron therapy is suitable and effective for many iron deficient patients with earlier stage CKD, the effectiveness and patient tolerance decline with decreasing eGFR, and the majority of patients requiring iron therapy at stage 4 CKD or worse are most appropriately treated with intravenous iron.

ESA therapy

Human recombinant erythropoietins have traditionally been available as one of three main products: epoetin alpha, epoetin beta or darbopoetin. The development of many biosimilar ESAs has brought swathes of new compounds to the marketplace. ESAs tend to be administered as an intravenous bolus to haemodialysis patients, but non-dialysis CKD and peritoneal dialysis patients are treated with weekly, fortnightly or monthly subcutaneous injections.

Target haemoglobin – results of recent trials

Since the advent of ESA therapy, questions have been raised about the optimal haemoglobin target for patients with CKD. With the increasing need for evidence-based medicine, there were calls for trials which could clearly demonstrate the benefits of ESA to patients with CKD. The first large randomised control trial (RCT) of ESA therapy in dialysis patients, which assessed the benefits of normalising haemoglobin (i.e. to 14 g/dL and above), was worryingly stopped early by the trial safety committee because more patients in the higher haemoglobin arm had developed major cardiovascular events.[1]

Interest has more recently turned to ESA therapy for non-dialysis CKD, and in particular, the benefit to patients of elevating haemoglobin to levels above the previous European target of 12.5 g/dL. Three large RCTs have used one of the three main ESAs in non-dialysis CKD.

The CHOIR (Correction of Haemoglobin and Outcomes In Renal insufficiency) study enrolled 1,432 patients with an estimated glomerular filtration rate (eGFR) 15–50 ml/min and haemoglobin < 11 g/dL. Patients were randomised to one of two groups, one with a target haemoglobin > 13 g/dL, the other a haemoglobin > 11.3 g/dL – epoietin alpha was given subcutaneously to both groups.[2] The primary end point was a composite of death, myocardial infarction, stroke and hospitalisation for heart failure. The trial was stopped early by the data monitoring committee because of a significant increase in events occurring in the higher haemoglobin group. A quality of life questionnaire revealed no improvement in the higher haemoglobin group.

The CREATE (Cardiovascular risk Reduction by Early Anaemia Treatment with Epoetin Beta) study randomised 605 patients with eGFR 15–35 ml/min and haemoglobin 11–12.5 g/dL to one of two groups.[3] The higher target haemoglobin group (13–15 g/dL) were treated with epoetin beta. The lower target group (10.5–11.5 g/dL) only received this ESA when triggered by the haemoglobin falling below 10.5 g/dL. There was no difference in the time to first cardiovascular event, or the frequency of cardiovascular death, in the two groups.

TREAT (The Trial to Reduce cardiovascular Events with Aranesp Therapy) randomised 4,038 patients with diabetes with an eGFR 20–60 ml/min between two arms, the first having darbopoetin to achieve a target haemoglobin of 13 g/dL, the other arm receiving placebo unless the haemoglobin fell below 9 g/dL, in which case darbopoetin was administered.[4] The primary end point was a composite of time to death from any cause or first major cardiovascular event, and this was no different between the arms. There was major concern in that the stroke incidence was significantly greater in the higher haemoglobin arm. A separate subanalysis of 1,872 TREAT patients separated them according to whether they were poor or good responders to initial darbepoetin therapy.[5] Poor responders had lower haemoglobin despite higher ESA dose (darbepoetin 232 *vs.* 167 μg) at 12 weeks, and a higher risk of cardiovascular events (RR 1.31) and mortality (RR 1.41).

Subgroup analyses of patients in these studies who had heart failure have been discussed on page S9.

Interpretation and NICE guidance

In the light of recent evidence, the National Institute for Health and Clinical Excellence (NICE) guidance for the management of anaemia in CKD has now been updated[6] and emphasises the following:

1. Target haemoglobin should usually be 10–12 g/dL when using ESA therapy
2. Accept a lower aspirational haemoglobin target when the response to ESA is poor (i.e. avoid using very high ESA doses)
3. Allow a higher aspirational haemoglobin than 12 g/dL in selected patients with limited co-morbidity and very good response to ESA
4. Early and optimal use of iron therapy, which usually will entail intravenous administration, is recognised to be highly important. In many instances, the response to iron therapy should be assessed before a decision is made regarding the need for ESA

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Key messages

- The use of iron and ESA therapy to correct anaemia in CKD has been associated with many clinical benefits
- In CKD, the effectiveness of oral iron therapy and patient tolerance decline with decreasing eGFR
- Clinical trials with ESA therapies have suggested a lower target haemoglobin level for patients with CKD
- A trial of IV iron therapy is appropriate in many CKD patients before considering ESA commencement

Round table discussion

What lower levels of haemoglobin and markers of iron deficiency should we consider that "set alarm bells ringing"?

A pathologically low haemoglobin in a patient with CHF might identify a higher risk individual, prompt investigation for co-morbid pathology or be considered a treatment target. Available study data primarily relate to patients with CHF and left ventricular systolic dysfunction. The majority of these studies defined anaemia according to WHO criteria (< 13 g/dL men, < 12 g/dL women) and consistently showed its presence to be an adverse prognostic marker. Subgroup analysis from the FAIR-HF study suggests that patients with a haemoglobin level above 12 g/dL and associated iron deficiency still respond to intravenous iron (accepting the limitations of trial subanalyses). As already discussed, it is not clear what the optimal number is to define anaemia in patients with CHF, but it appears it should be above 12 g/dL.

Similarly, standard ferritin cut-off values are probably flawed since inflammation, an integral component of advanced heart failure, is a major stimulus for ferritin. Patients can still have a normal ferritin level even when there is iron deficiency.

Iron has multiple actions in addition to promoting erythropoiesis. It is needed for numerous catalytic enzyme systems and in muscle metabolism, while mitochondria need iron to generate energy. This may explain some of the benefits with iron repletion in FAIR-HF, the hypothesis being that iron repletion has benefits in addition to increasing haemoglobin levels. Studies in animal models suggest that iron deficiency is harmful and that iron repletion helps; this needs to be confirmed in human studies, where we already know that lower haemoglobin levels are associated with adverse outcomes.

A recent study of patients with CHF (n=546) has shown that iron deficiency as defined in the FAIR-HF study (serum ferritin < 100 μg/L or < 300 μg/L, if transferrin saturation [TSAT] < 20%) was present in 37%.[1] It was an independent predictor of adverse outcome. Iron deficiency was common in both anaemic (57%) and non-anaemic (32%) patients (anaemia being defined according to WHO criteria).

It may also be of value, where possible, to take into account previous haemoglobin level and markers of iron deficiency. For example, a progressive drop in haemoglobin over several months suggests that early investigation would be appropriate.

What constitutes best practice for investigations of aetiology of anaemia in patients with CHF?

A detailed patient history and clinical examination is fundamental and may direct

further investigation. Basic tests, such as urea and electrolytes (U&Es), thyroid function tests (TFTs), liver function tests (LFTs) and C-reactive protein (CRP), should be performed for all patients. Whilst deficiencies of vitamin B_{12} and folate are relatively uncommon, they are amenable to safe correction and should be excluded. Accepting the difficulties already highlighted regarding definition and assessment of iron deficiency, the panel thought it reasonable to measure serum ferritin and TSAT, and to consider iron treatment for those patients with absolute (ferritin < 100 μg/L) or functional (ferritin > 100 μg/L but TSAT < 20%) iron deficiency.

The panel developed a pragmatic algorithm (see page S15) to help guide investigation and potential treatment. The algorithm focuses on symptomatic patients with low haemoglobin according to local normal ranges. For a very small group of patients with normal haemoglobin levels, investigation may be appropriate (e.g. consistent drop in haemoglobin within normal range over time and/or microcytosis).

Some patients will require more detailed investigation by either a gastroenterologist or haematologist. The decision to investigate further will be driven by an individual patient's clinical characteristics such as co-morbidities, including renal dysfunction. The precise value of ferritin which reflects absolute iron deficiency is uncertain in individuals with inflammatory diseases such as CKD, which will influence local pathways in deciding, for example, who to refer for gastroenterological evaluation. In general, patients who have very low ferritin values (below the normal local lab range) or who have a greater than anticipated drop in ferritin following correction with iron therapy (suggesting ongoing iron loss) should have a gastroenterological opinion.

Who should be considered for iron therapy ?

The data from FAIR-HF, using intravenous iron, provide the best guidance we have available at present. Intravenous iron was associated with improvements in well-being, heart failure class, and an increase in six-minute walk distance in patients with heart failure and iron deficiency, with and without anaemia.

Further studies with hard end points and long-term safety data are required. In the interim, consideration should be given to the following issues:

Symptomatic versus asymptomatic individuals

- Correction of iron deficiency is currently linked to improvements in symptoms and quality of life. It seems reasonable to focus on symptomatic subjects.

Oral versus intravenous iron

- The available data described relate to the use of intravenous iron. However, the availability of intravenous iron to those looking after patients with CHF may be limited. It is therefore important to develop local pathways to streamline the investigation and treatment of patients.
- Whether oral iron is effective in patients with CHF is unknown. Associated inflammation and gut oedema may contribute to iron malabsorption. Since oral iron often causes side effects there "is a world of difference between prescribing oral iron and a patient taking oral iron". The majority of patients with symptomatic CHF will be on at least four cardiovascular drugs, which again may influence compliance with new drugs. Oral iron is rarely used in patients with more advanced chronic renal disease, and almost never in dialysis patients.
- Pragmatism is important. In some circumstances or localities (driven by access to intravenous iron and day case units) it may be sensible to give a trial of oral iron replacement in symptomatic patients with CHF (this is not in conflict with NICE anaemia guidelines).
- In FAIR-HF, iron therapy was given repeatedly every two to four weeks. Yet single dose total iron replenishment

is far more attractive from a health economic perspective and patient's point of view. Modern formulations of intravenous iron therapy are safer and much more tolerable to the patient, and quicker and more straightforward to administer. Many clinicians believe the pendulum is swinging away from oral iron. Intravenous iron can be given safely over a relatively short period of time on a day case unit.

- Around 70% of patients with heart failure have this diagnosis made during a hospital admission, and anaemia is often detected in very symptomatic patients at the same time. Giving intravenous iron in this situation is relatively straightforward (in the absence of infection and when the patient is stabilised and euvolemic).

What is the current role for ESAs in CHF treatment?

The RED-HF study looking at darbepoetin alfa in CHF should answer the question. Recent data from studies in patients with CKD have highlighted some concerns about ESAs, especially when they are used in high dose. The consensus view was that at present there is not strong enough evidence to recommend routine ESA therapy in heart failure.

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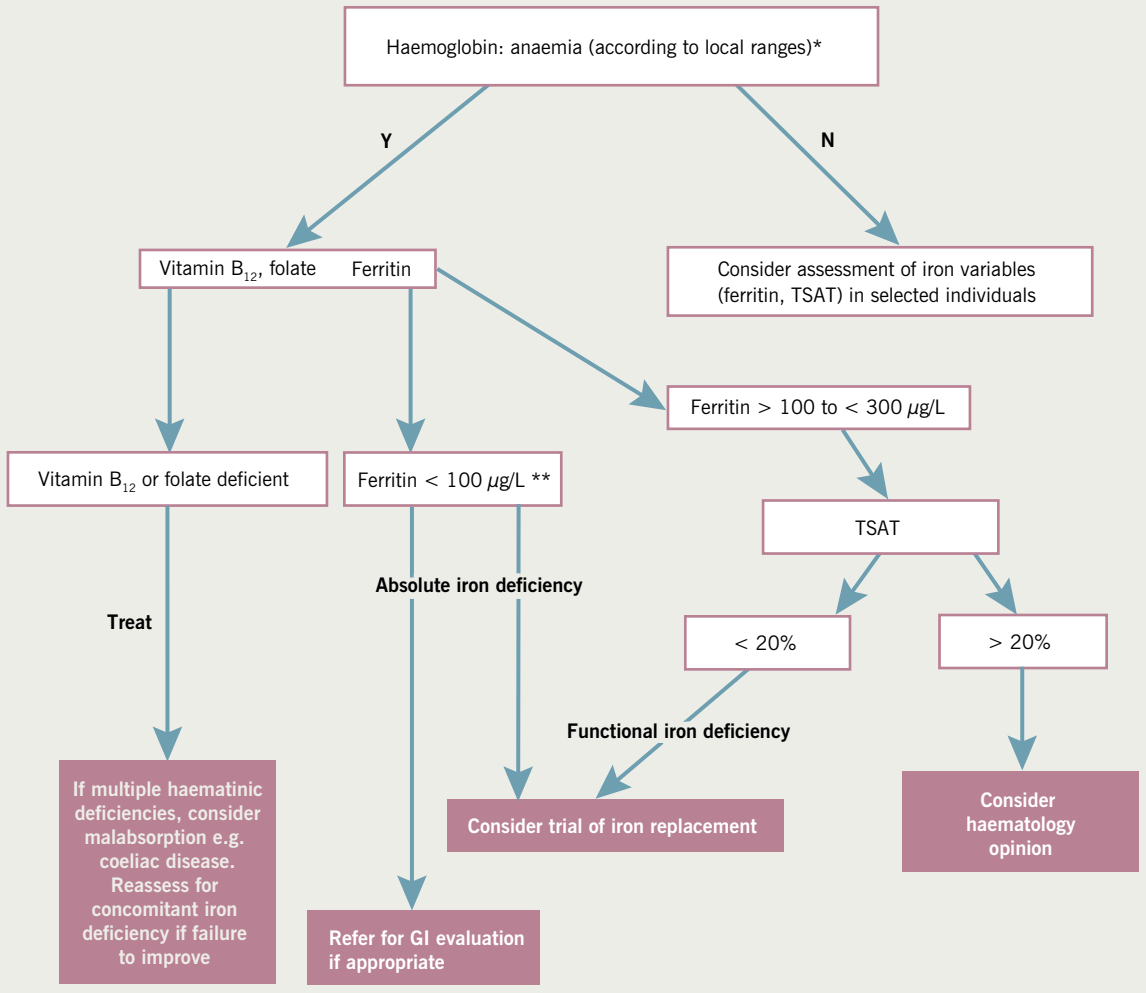
Final summary

Low haemoglobin and iron deficiency are common in patients with chronic heart failure. Recent studies suggest that treatment with intravenous iron is associated with improvements in symptoms and quality of life. Data on mortality and hospitalisation are lacking and should be a key focus over the next few years. Bringing together expertise from a number of specialties is essential to ensure that patients receive optimal investigation and treatment in timely fashion.

Algorithm for the investigation of anaemia



* If all red cell indices are within normal range, it is unusual to find a specific haematinic deficiency. Patients with normal haemoglobin but abnormal red cell indices should be investigated further

*The decision to investigate further will be driven by an individual patient's clinical characteristics such as co-morbidity, including renal dysfunction

** The precise value of ferritin which reflects absolute iron deficiency is uncertain in individuals with co-morbid inflammatory diseases such as chronic kidney disease and/or chronic heart failure. This may influence local pathways in deciding who to refer for GI evaluation. In general, patients who have very low ferritin values (below normal local lab range) or who exhibit a subsequent drop in ferritin following correction with iron therapy (suggesting ongoing iron loss) should be considered. Patients with functional iron deficiency may be managed as those with absolute iron deficiency if they have a dramatic response to intravenous iron

Key: GI = gastrointestinal; N = no; TSAT = transferrin saturation; Y = yes

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