Managing a fateful alliance: anaemia and cardiovascular outcomes

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Abstract
Cardiovascular disease (CVD) is a significant complication in chronic kidney disease (CKD) and a major cause of death in dialysis patients. Clinical studies have shown that anaemia is associated with reduced survival in patients with renal disease, heart failure or both. There is also evidence that, even in otherwise healthy individuals, anaemia is independently associated with an increased risk of CVD. The body adapts to anaemia by increasing cardiac output, which may result in cardiac remodelling and progression of left ventricular (LV) growth. Indeed, low haemoglobin (Hb) has been identified as an independent risk factor for LV growth in CKD patients, suggesting that there is a direct link between anaemia and adverse cardiac outcomes. This suggests that correction of anaemia with recombinant human erythropoietin (rhEPO; epoetin) may improve prognosis. Partial correction of anaemia produces partial regression of LV hypertrophy, while complete correction of anaemia can help to prevent LV dilatation in haemodialysis patients with normal LV volumes. Moreover, in non-dialysis patients with advanced CVD, pilot studies showed that a moderate increase in Hb improved cardiac function and reduced hospitalization rates. In addition, consistent epoetin treatment before the start of dialysis was associated with a reduced risk of developing cardiac disease in CKD patients. In contrast, in dialysis patients with advanced cardiac disease, Hb normalization increased mortality risk. Therefore, early correction of anaemia appears important. The Cardiovascular risk Reduction by Early Anaemia Treatment with Epoetin (CREATE) study is investigating whether this approach is associated with a measurable reduction in cardiovascular risk.

Keywords: anaemia; chronic kidney disease; congestive heart failure; haemoglobin

Introduction
Cardiovascular complications, such as coronary artery disease, left ventricular hypertrophy (LVH) and congestive heart failure (CHF), are highly prevalent in patients with chronic kidney disease (CKD). In the USA, cardiovascular disease (CVD) is the leading cause of mortality in dialysis patients, accounting for approximately half of all deaths [1,2]. Anaemia is a common feature in patients with CKD, inducing fatigue, impairing physical functioning and quality of life and starting to develop at even a modest degree of renal failure [3]. In addition, there appears to be a complex association between a reduction in haemoglobin (Hb) level and cardiovascular outcome [4]. This article summarizes the evidence supporting the existence of a relationship between anaemia, CVD and poor patient outcomes. It also discusses the potential to improve survival in patients with renal disease by early anaemia treatment to increase Hb levels.

Association between Hb and outcome
There is increasing evidence from epidemiological studies of an association between low Hb levels and cardiovascular mortality. A retrospective study [5] of >75 000 US Medicare patients on haemodialysis (CKD stage 5 [6]) investigated the association between haematocrit (Hct) levels and mortality. After adjusting for patient demographics, co-morbidities and severity of disease, the results showed that patients with Hct levels <27 to <30% had higher risks of all-cause (12–33%), cardiac (11–25%) and infectious (13–53%) death, compared with patients who had Hct levels of 30 to <33%. Furthermore, Hct levels of 33 to <36% reduced the risk of death from all causes by an additional 4%. Overall, these findings suggest that improved patient survival is associated with sustained increases in Hct levels. An association between anaemia and adverse cardiovascular outcomes has also been observed in...
patients with earlier stages of CKD not yet requiring dialysis. A recent Canadian study, which included 328 patients with CKD stages 2–4 [6], demonstrated a highly significant ($P = 0.0001$) relationship between Hb level and survival, with an overall risk ratio of 0.754 (0.65–0.85) per 1 g/dl of Hb [7]. In addition, a retrospective study of almost 90,000 Medicare patients with end-stage renal disease showed that those who received consistent epoetin treatment in the 2 year period before the start of dialysis had a lower risk of cardiac disease and death compared with patients who received infrequent epoetin therapy [8]. An association between anaemia and poor prognosis has also been reported recently in transplantation patients. A study of 638 renal transplant recipients identified anaemia as a dominant risk factor in the development of CHF in this patient population [9].

Until recently, many cardiologists did not consider that a significant percentage of their patients had anaemia, and having a low Hb was frequently considered preferable to a high Hb; however, several recently published studies have shown that the prevalence of anaemia in patients with CHF can be as high as 30%, depending on the severity of the condition, and that it is associated with an increased risk of mortality. For example, Ezekowitz et al. [10] reported that among ~12,000 patients with CHF, 17% were anaemic, and the hazard ratio for mortality in this subgroup was 1.34 [95% confidence interval (CI) 1.24–1.46] compared with patients without anaemia. Furthermore, the 50% survival rate was ~1 year less in patients with anaemia compared with patients without the condition (Figure 1). Another study of >1 million Medicare patients with CKD found that over a 2 year period, 34.6% of patients with CHF and anaemia died compared with 26.1% of patients with CHF alone [11]. Importantly, in patients with CHF, the relationship between Hb and mortality has been shown to be fairly linear, suggesting that there is not an optimal Hb level below normal at which the risk of death can be stabilized (Figure 2) [12]. Similar findings have been reported in a number of other studies [13–16].

The most impressive data for an association between Hb levels and prognosis come from the Atherosclerosis Risk In Communities (ARIC) study, which followed >14,000 individuals without evidence of CVD enrolled between 1986 and 1989. Individuals with anaemia (Hb: males <13 g/dl; women <12 g/dl) had a worse prognosis than those with a normal Hb level and no evidence of CVD at the time of enrolment. The results from this study showed that anaemia was independently associated with an increased risk of CVD [hazard ratio 1.41 (95% CI 1.01–1.95)] [17].

Potential explanations

There are several possible, though not mutually exclusive, reasons for the relationship between low Hb and adverse cardiac outcomes. Firstly, anaemia may be a marker of poor cardiac function [13]. Secondly, a low Hb level may be associated with other, as yet unidentified, risk factors that influence a patient’s prognosis. It should be noted, however, that the association between Hb and survival is independent of renal function, as measured by serum creatinine levels [13]. Thirdly, anaemia is a causative risk factor for cardiac ischaemia [18], particularly since coronary artery disease limits the ability to increase oxygen extraction from Hb. Finally, low Hb may cause cardiac remodelling, leading to LVH [19].

Evidence for a causal link

Physiological adaptations to anaemia

When considering the evidence for a possible causal link between low Hb and adverse outcomes, it is important to understand how the body adapts physiologically to low Hb. In general, the body is able to tolerate relatively low Hb levels for a short time without any major problems. For example, a study conducted in healthy individuals who were phlebotomized to reduce Hb levels from 13.1 to 5.0 g/dl illustrated that there are two main components to the physiological response to anaemia [20]. Firstly, an increased amount of oxygen was extracted from Hb, measured as a
progressive reduction in mixed venous oxygen saturation with declining Hb; and, secondly, there was a concomitant increase in cardiac output as the Hb concentration fell (Figure 3). These two mechanisms thereby enable patients to survive with Hb concentrations as low as 4 g/dl, suggesting that the adaptation process is extremely efficient.

Cardiac ischaemia

There are, however, limitations and problems with these adaptation mechanisms. In the myocardium, the ability to increase oxygen extraction under anaemic conditions is limited since baseline oxygen desaturation is already very high. Coronary artery disease increases oxygen extraction further and thus limits the potential for oxygen desaturation of Hb in anaemia. This observation explains why low Hb may increase cardiac ischaemia and why patients with coronary artery disease are at increased risk when they become anaemic. A retrospective study of nearly 79 000 Medicare patients with myocardial infarction (MI) demonstrated that survival was directly associated with Hct level [21]. In patients with an Hct ≤33% (Hb level of ~11 g/dl), receiving a blood transfusion lowered the short-term mortality rate in the period after their MI.

Left ventricular growth

The benefit from increased cardiac output as an adaptive mechanism is also limited by cardiac pathology because, if it is a chronic adaptation to anaemia, it may increase LV growth in response to increased myocardial workload. Indeed, studies have shown that low Hb is an independent risk factor for LV growth in patients receiving dialysis [22], pre-dialysis patients [23] and, more recently, renal transplant recipients [24]. In a retrospective analysis of electrocardiography (ECG) data, Rigatto et al. [24] found that LVH was present in ~14% of renal transplant recipients. Due to a lower sensitivity of ECG for demonstrating LVH, this value is significantly lower than prevalence data determined on the basis of echocardiography. Nevertheless, the presence of LVH in this study was associated with poor patient outcome, both 1 and 5 years after transplantation (Figure 4). Over 5 years, diastolic blood pressure and anaemia were the two major risk factors for LV growth. These results are consistent with a causal link between anaemia, CVD and mortality, suggesting it may be possible to improve prognosis by correcting anaemia with recombinant human erythropoietin (rhEPO, epoetin).

Potential to improve outcome by increasing Hb

Normalization studies

Data from 15 trials have clearly demonstrated that partial correction of anaemia with epoetin results in an 18% decrease in LVH within 1 year in patients receiving dialysis [25]. Another study in 146 haemodialysis patients with either concentric LVH or LV dilatation compared partial (Hb level 10.0 g/dl) and complete (Hb level 13.5 g/dl) correction of anaemia with epoetin and demonstrated that, while complete correction did not reverse overt LV dilatation or concentric LVH, it did help to prevent LV dilatation in patients with normal LV volumes [26]. Smaller studies involving CKD patients not on dialysis have also indicated that epoetin therapy improves cardiac function and leads to regression of LVH [27,28]. Together with data from other investigations [8,29], these findings suggest that a more complete correction of anaemia might result in further regression of LVH and improve patient outcomes.

The US Normalization of Hematocrit Study [30] evaluated the potential benefits of complete correction of anaemia in 1233 haemodialysis patients receiving epoetin therapy, all of whom had a history of CHF or ischaemic heart disease and two-thirds of whom also had diabetes. Although there was an improvement in quality of life in patients in the high Hb target (12–14 g/dl) group, there was also a higher incidence

![Fig. 3. Physiological adaptations to anaemia in healthy volunteers (Weiskopf et al. [20] with permission).](https://academic.oup.com/ndt/article-abstract/20/suppl_6/vi16/1889610/1889610)
of death or non-fatal MI in these individuals (32.7%) compared with patients in the low Hb target (10 g/dl) group (26.7%). The authors concluded that complete correction of anaemia could not be recommended for dialysis patients with clinically evident heart disease. In contrast, two Israeli studies, one uncontrolled \((n=142)\) and one randomized controlled \((n=32)\), in patients with severe CHF and CKD found that increases in Hb concentration from 10 to 12 g/dl and from 10.0–11.5 to \(\geq 12.5\) g/dl, respectively, were associated with improvements in cardiac and renal function and reduced hospitalization rates \([31,32]\). One important aspect that may be responsible for the differences in results between the study by Besarab et al. \([30]\) and those by Silverberg et al. \([31,32]\) is that optimal Hb is dependent upon the overall clinical situation and patients’ co-morbidity. In this context, the capacity of the vasculature to respond to changes in whole blood viscosity may be particularly important.

**Vascular reactivity**

The potential importance of vascular reactivity for the tolerance to increased Hb levels has been illustrated by a Swiss study in transgenic mice that over-express the human erythropoietin gene \([33]\). The mice were severely polyglobulic and had a mean Hb level of 23 g/dl compared with a normal mouse Hb level of 14 g/dl. Despite the higher Hb concentration, the transgenic mice had a normal cardiovascular physiology: heart rate, blood pressure and cardiac output were all unchanged. Moreover, histological analysis of these mice revealed no evidence of MI, stroke or thromboembolism. Circulating and vascular tissue levels of the vasodilator nitric oxide (NO) and NO-mediated endothelium-dependent relaxation were markedly elevated in these transgenic mice. Western blot analysis revealed a 6-fold increase in the levels of endothelial NO synthase in the transgenic mice compared with the wild-type animals. Administration of the NO synthase inhibitor \(\text{N}^\text{G}\)-nitro-L-arginine methyl ester (l-NAME) led to rapid death from left- and right-sided ventricular failure. In contrast, the survival of wild-type mice given l-NAME was unaffected, demonstrating that increased NO synthesis was essential for the survival of the transgenic animals. Increasing the synthesis of NO compensated for the elevated Hb levels that resulted from over-expression of erythropoietin. The findings from this study highlight the need to consider a balance between vascular reactivity and Hb level when treating patients with anaemia. Patients with advanced renal disease, diabetes and cardiovascular complications do not have normal vascular reactivity; indeed, it may be severely impaired as a result of endothelial dysfunction.

**Early vs late correction**

Clinical data suggest that the potential of epoetin treatment to reverse the changes in LV geometry may be limited in patients with advanced renal and cardiac disease. As the US Normalization of Hematocrit Study demonstrated, complete ‘late’ correction of anaemia may even increase the risk of mortality. Therefore, early correction of anaemia may be important in improving patient outcomes, but it is not known whether starting anaemia correction at an earlier stage, when cardiovascular complications are less advanced, can prevent LVH and reduce cardiovascular risk, or if doing so may be associated with other health benefits or risks. Several studies are currently investigating this question. Of these, the Cardiovascular risk Reduction by Early Anaemia Treatment with Epoetin \(\beta\) (CREATE) study is currently the largest, measuring sequential changes of LV mass and geometry by echocardiography and testing the effect of early, complete anaemia correction on a combined end-point of cardiovascular morbidity in patients with CKD.

The CREATE trial is a prospective, randomized, controlled, international study designed to investigate the effects of early anaemia correction on cardiovascular risk reduction in patients with moderate anaemia (Hb level 11–12.5 g/dl) and CKD (creatinine clearances 15–35 ml/min) and who do not yet require renal replacement therapy. Patients have been randomized to either a rapid and early anaemia correction group (target Hb 13–15 g/dl) or a late anaemia correction group, starting treatment once Hb has declined to <10.5 g/dl (target Hb 10.5–11.5 g/dl), which reflects current treatment guidelines. The primary efficacy outcome is the effect of early anaemia correction on the time to first cardiovascular event. Secondary outcomes include progression of CKD and quality of life \([34]\).

**Conclusions**

There is strong evidence for an association between anaemia and an increased risk of adverse cardiovascular outcomes in patients with CKD. Similarly, anaemia increases the risk of mortality in patients with CHF. Even in apparently healthy individuals, moderate anaemia is associated with poor outcomes.

The relationship between anaemia and adverse outcomes is complex. While it is likely to be indirect to some extent, evidence also suggests that there may be a causal link between low Hb levels and the development of CVD. Treatment of anaemia with epoetin has been shown to improve cardiac function and to produce regression of LVH in CKD patients, whether or not they are receiving dialysis. Furthermore, consistent treatment with epoetin before the initiation of dialysis is associated with a reduced risk of developing cardiac disease in patients with CKD. Normalizing Hb levels in patients with advanced CVD has a limited effect on changes in LV geometry, however, and – at least under certain circumstances – may increase their risk of death. The degree of CVD could affect other factors, such as vascular reactivity, which may determine whether partial or
full correction of anaemia is appropriate for a particular individual.

Conflict of interest statement. None declared

References

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