Anaemia in chronic renal disease: lessons learned since Seville 1994

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Abstract
Cardiovascular disease is the major cause of death among patients with end-stage renal disease, accounting for almost half of all fatalities. In recent years much progress has been made in understanding the pathogenesis of cardiovascular disease in the uraemic population. Anaemia is a consistent finding in chronic renal disease, affecting up to 90% of patients, and the central role of anaemia in the development of cardiovascular dysfunction is now well established. A significant proportion of patients have established cardiovascular complications on initiation of dialysis, raising the possibility of early correction of anaemia as a strategy for preventing cardiovascular co-morbidities among renal patients. Randomized, controlled trials have shown that normalization of haemoglobin (Hb) with recombinant erythropoietin (rh-Epo) is of no cardiovascular benefit in haemodialysis patients with symptomatic heart failure, ischaemic heart disease, or severe left ventricular dilatation, although suggestive evidence exists for benefits at earlier stages of cardiac disease. Results from large-scale clinical trials are required to clarify the effects of early anaemia correction on mortality and cardiovascular function, as well as appropriate treatment targets in different patient populations. The potential exists for higher Hb levels to extend patient survival through cardioprotective effects.

Keywords: anaemia; cardiovascular disease; early intervention; target haemoglobin

Introduction
The incidence of morbidity and mortality associated with end-stage renal disease (ESRD) remains high, and is related to several different factors including age, adequacy of dialysis, anaemia and the development of cardiovascular complications. The prognosis for patients with ESRD is poor, with 5-year survival rates estimated to be approximately 20%; this is lower than the survival rates for breast and colon cancer [1] (Figure 1).

The European Dialysis and Transplantation Association (EDTA) Registry maintains the details of more than 500 000 renal patients and shows that cardiovascular disease (CVD) is the major cause of death among dialysis patients, accounting for almost half of all deaths [2]. More recent data from the US Renal Data System (USRDS) has demonstrated that cardiovascular mortality is 10–20 times higher in patients on dialysis than in the general population [1]. A detailed evaluation of co-morbidities among 822 patients about to commence dialysis revealed that heart failure was present in more than a third of the cohort, and that the presence of heart failure was predictive of premature death [3]. The severity of heart failure also correlated with the risk of early death. In a further study, the prevalence of CVD in 432 Canadian dialysis patients was investigated by annual echocardiography following initiation of dialysis, with mean follow-up of 41 months. At the start of dialysis, only 16% of patients displayed normal echocardiographs, 16% had systolic dysfunction, 23% left ventricular (LV) dilatation and 42% had concentric left ventricular hypertrophy (LVH) [4]. These findings demonstrate that patients with ESRD often begin dialysis with advanced cardiovascular dysfunction, which is likely to impact on their prospects for long-term survival on renal replacement therapy. Indeed, the presence of heart failure at the onset of dialysis is associated with a 93% increase in the risk of death compared with patients entering dialysis without heart failure [5]. Further, de novo development of heart failure during renal replacement therapy has been shown to increase the risk of death 5-fold compared with dialysis patients who do not develop heart failure [6].

Given the extent of cardiovascular mortality among patients with ESRD, the implementation of strategies to reduce the cardiovascular burden in the pre-dialysis phase would seem appropriate. This paper will review data from the last 7 years, and focus on the role of anaemia as a risk factor for cardiovascular dysfunction.
in renal disease. The potential benefits of anaemia correction therapy in decreasing cardiovascular morbidity and mortality will also be discussed. In addition, lessons learnt from clinical practice during the intervening time will be explored.

**Anaemia as a risk factor for cardiovascular dysfunction**

Anaemia is a consistent finding in chronic renal disease, affecting up to 90% of patients [7]. The relationship between anaemia and CVD is now firmly established, and results from alterations in LV structure and function. These alterations lead to adaptive LVH, then maladaptive cardiomyopathy, which predisposes to heart failure or ischaemic heart disease and ultimately premature death.

Recent analysis of data from the Canadian Organ Replacement Registry highlights the correlation between anaemia and mortality in dialysis patients. For both haemodialysis (HD) and peritoneal dialysis (PD) patients, decreasing levels of haemoglobin (Hb) were associated with increasing mortality [8,9] (Table 1). A decreased level of Hb has been identified as an independent risk factor for congestive heart failure in dialysis patients [10]. Also, anaemia is associated with the presence of LV dilatation on starting dialysis and subsequent LV growth (LVG) [11,12] (Figure 2). This is an important finding with respect to the long-term prognosis for ESRD, as patients with LV abnormalities at initiation of dialysis are less likely to survive compared with those in whom the echocardiographic profile is normal [4] (Figure 3).

Anaemia has also been identified as a risk factor for LVG in patients with mild-to-moderate renal insufficiency [13]. A prospective multicentre Canadian study of 446 patients with estimated creatinine clearance rates in the range 25–75 ml/min found that 34% of the

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**Table 1. Relationship between anaemia and mortality in Canadian dialysis patients (Murphy et al. [8,9])**

<table>
<thead>
<tr>
<th>Hb (g/dl)</th>
<th>HD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8</td>
<td>4.6</td>
<td>22.8</td>
</tr>
<tr>
<td>8–8.9</td>
<td>3.9</td>
<td>4.2</td>
</tr>
<tr>
<td>9–9.9</td>
<td>2.3</td>
<td>1.5</td>
</tr>
<tr>
<td>10–10.9</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td>11–11.9*</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>12–12.9</td>
<td>0.09</td>
<td>4.5</td>
</tr>
<tr>
<td>&gt;13</td>
<td>1.0</td>
<td>3.0</td>
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</table>

*Figures represent risk of mortality relative to patients with Hb level in the range 11–11.9 g/dl.
cohort had LVH on enrolment into the study, with highest prevalence among those with poorest renal function (Figure 4). Of the patients enrolled, 318 completed 12 months of follow-up, and serial echocardiograms (at baseline and at 12 months) were available for 246. Of these, 25% demonstrated significant LVG, and multivariate logistic analysis revealed that this growth was predicted by a decrease in Hb level \( \text{Hb} \). Hb levels have also been found to be predictive of de novo cardiac failure among renal transplant recipients [14]. A total of 429 patients with no cardiac disease at the time of transplantation were followed up for a median of 7.4 years, in which time 101 cardiac events were recorded. Analysis of risk factors for this de novo cardiac failure identified decreased Hb levels, along with advanced age and elevated systolic blood pressure [14].

**Effects of anaemia correction on mortality, cardiovascular function and quality of life**

Randomized, controlled trials have shown that normalization of Hb with epoetin does not improve outcomes in HD patients at the later phases of cardiac disease, when severe LV dilatation has developed or cardiac symptoms are present. The US Normal Haematocrit Trial compared the effects of full (target haematocrit 42%) vs partial (target haematocrit 30%) correction of anaemia in HD patients with asymptomatic heart failure or ischaemic heart disease [15]. Patients in the high target haematocrit group had a higher rate of vascular access thrombosis and a trend towards greater mortality than those in the low target haematocrit group.

Suggestive evidence exists that normalization of Hb is beneficial when initiated at earlier phases of cardiac disease. For example, a study of 146 HD patients with asymptomatic cardiomyopathy compared the benefits of partial (target Hb 10 g/dl) and complete (target Hb 13.5 g/dl) correction of anaemia on LV mass index in those patients with concentric LVH, and on LV volume index in those with LV dilatation [16]. The study found that Hb normalization does not appear to induce regression of overt LV dilatation or concentric LVH, but may be beneficial in preventing LV dilatation in patients with normal LV volumes. This study also compared quality of life parameters in the partial and complete correction groups using the Kidney Disease Questionnaire.
Using repeated-measures analysis of variance, there were greater improvements in fatigue, depression and relationships with others in the group with target Hb 13.5 g\text{dl}, while physical symptoms and frustration were similar in both groups. Data from a prospective, randomized double-blind crossover study in 14 HD patients who were otherwise well, also suggest that full correction of anaemia has benefits over partial correction in terms of quality of life, as assessed by the Sickness Impact Profile (SIP) [17]. The SIP score was significantly less among patients treated for full reversal of anaemia (target Hb 14 g\text{dl}) compared with those treated for partial reversal (target Hb 10 g\text{dl}) for both total score ($P<0.02$) and psychosocial dimension score ($P<0.01$). In addition, the work category score at target Hb 14 g\text{dl}, but not at target Hb 10 g\text{dl}, was significantly reduced in comparison with baseline ($P<0.01$), indicating that health limitations might have less influence on the capacity for employment at a physiological Hb concentration.

Lessons learnt since Seville 1994

In the last 7 years much progress has been made in understanding the pathogenesis of CVD in the uraemic population. It is now apparent that the changes in cardiac structure and function that predispose to heart failure and ischaemic heart disease can occur early in

Fig. 4. Relationship between prevalence of LVH and renal function in pre-dialysis patients (adapted from Levin et al. [13]).

(a)

Fig. 5. Changes in clinical practice among renal physicians in 1994 and 2001: (a) target Hb implemented in their clinic and (b) optimal target Hb.
Anaemia in CRD

the progression of renal disease, such that many patients initiating dialysis already have cardiovascular dysfunction. The central role of anaemia in the development of cardiovascular complications at all phases of renal disease has also been established, raising the possibility of early correction of anaemia as a strategy for preventing cardiovascular co-morbidities among renal disease patients.

The progress that has been made in understanding the development of CVD in uraemic patients appears to be reflected by changes in clinical practice and perceptions among renal physicians over the last 7 years. At the meeting in Seville in 1994, renal physicians were surveyed to determine the target Hb in their clinic, what they thought the optimal Hb target should be, and the most important reason for increasing Hb in dialysis patients. Sixty-eight per cent of physicians recorded a target Hb of 10–11 g/dl in their clinic, and 55% thought the target Hb should be 12–13 g/dl. The need to improve quality of life was identified as the most important reason for increasing Hb by 40% of physicians, while cardioprotective effects and longer patient survival were identified as the main reason by only 18% and 10% of those questioned. When the same questions were put to physicians attending the current meeting, the responses were strikingly different (Figure 5). The majority of physicians (69%) recorded a target Hb of 11–12 g/dl in their clinic, and 77% thought the target Hb should be 12–13 g/dl. Further, 52% of respondents identified cardioprotective effects (28%) or longer patient survival (24%) as the most important reason for increasing Hb in dialysis patients, with only 18% identifying improved quality of life.

Conclusion

Although the importance of anaemia in the development of the cardiovascular complications associated with renal disease has been well established, the role of anaemia correction in reversing or preventing these complications is less clear. Large-scale clinical trials indicate that there is no cardiovascular benefit in full correction of anaemia in patients who already have symptomatic cardiac disease or severe LV dilatation [15,16]. However, there is evidence to suggest that earlier intervention can prevent the development of LV dilatation, as well as improving quality of life [16,17]. The results of several on-going studies should help to clarify the benefits of early treatment of anaemia in both dialysis and pre-dialysis patients. Large-scale studies are also required to establish the benefits of anaemia prevention in chronic renal insufficiency and renal transplant patients, and the effects of Hb normalization in both HD and PD patients.

References