Relative risk of death in UK haemodialysis patients in relation to achieved haemoglobin from 1999 to 2005: an observational study using UK Renal Registry data incorporating 30,040 patient-years of follow-up

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Abstract

Background. Much controversy has been generated in recent years regarding the optimal haemoglobin to target in chronic kidney disease patients receiving erythropoiesis-stimulating agent therapy. This has arisen from the paradoxical conclusions obtained from large retrospective or epidemiological studies versus interventional randomized controlled trials.

Methods. Data from haemodialysis patients in the UK Renal Registry from 1999 to 2005 were analysed year by year for the relative risk of death at different haemoglobin concentrations, compared with a reference of 10–11 g/dl. The population size varied from 2291 in 1999 to 8209 in 2005. The data were analysed by chi-square tests, and a multivariate analysis was performed.

Results. Across the years 1999 to 2005, there was a consistent relationship between the haemoglobin achieved and the risk of death (P < 0.0001). In 2005, the relative risk (RR) of death = 1.32 for a haemoglobin (Hb) of 9–10 g/dl; RR = 0.44 for Hb > 13 g/dl. The relationship between Hb and the RR of death is nevertheless remarkably consistent across the 7 years of study, with an S-shaped correlation (polynomial) between an Hb range of <9 g/dl and an Hb range of >13 g/dl (P < 0.0001). Multivariate analysis also showed age, time on dialysis and diabetes to be strongly predictive of death across all 7 years analysed (P < 0.0001 in all cases).

Conclusion. There is a significant relationship between achieved haemoglobin and mortality across the 7 years analysed, with no increase in risk seen with higher Hb levels.

Keywords: Anaemia; haemoglobin; mortality; haemodialysis; UK

Introduction

Much controversy has arisen in recent years regarding the optimal haemoglobin to target in chronic kidney disease (CKD) patients receiving erythropoiesis-stimulating agent (ESA) therapy. Even before the publication of the CRE-ATE [1] and CHOIR [2] studies, this was a hot topic of debate [3], but the results from these two randomized controlled studies published in the ‘New England Journal of Medicine’ in September 2006 fuelled this debate even further. Commentaries appeared on the limitations of these randomized controlled trials (RCTs) [4,5], but the one indisputable fact remained, namely that all the RCTs tended to show worse outcomes at a higher haemoglobin concentration.

Despite the scientific rigour of the RCTs, there remained some discomfort that the conclusions were at variance with data from a plethora of observational studies [6–9]. The latter have consistently shown better outcomes at haemoglobin concentrations >13 g/dl and worse outcomes at concentrations <9 or 10 g/dl. Patients not receiving ESA therapy but who have haemoglobin concentrations of around 13–14 g/dl usually show the best outcomes in such analyses [7–9].

This has led to the realization that it may not be a high haemoglobin itself that is harmful, but the means by which the higher haemoglobin is achieved, including the use of ESA therapy and/or iron. Another large retrospective analysis suggested that the dose of epoetin required to achieve a given haemoglobin was an independent predictor of mortality at all haemoglobin levels. Thus, Zhang et al. [10], and the post hoc analyses from both the US Normal Hematocrit Trial [11] and the CHOIR study [12] have also raised the hypothesis that high doses of ESA therapy in ESA-resistant patients may be harmful.

The aim of the present study was to report the relationship between haemoglobin concentration and mortality in the UK haemodialysis population, analysed year by year from 1999 to 2005, using UK Renal Registry (UKRR) data. Although similar analyses have been performed elsewhere, the majority have been in US patient populations, and European data are sparse. Differences in practice patterns and outcomes between haemodialysis populations in the US and Europe are well recognized. Furthermore, most of the published studies have looked at a single time period and have not examined possible changes in this relationship over time. The UK Renal Registry database has been in operation since 1997, and data are uploaded from al-
most every dialysis unit in the UK on a yearly basis. The data capture includes demographic characteristics and clinical practice patterns as well as a wide range of laboratory parameters. Robust data on mortality are also collected. The study reported here examines seven yearly time points from 1999 to 2005 and incorporates 30 040 patient-years of follow-up. Over the course of this time period and similar to many other countries, the UK has seen a large increase in the proportion of patients with a haemoglobin >13 g/dl and a concomitant fall in the percentage of patients with a haemoglobin <10 g/dl. Given this large shift in practice over time in the UK renal population, it was of interest to see if this altered the hazard of death for a given achieved haemoglobin. The relative risk of death in relation to different haemoglobin concentrations over this 7-year time period was therefore analysed and compared to a reference point of haemoglobin (Hb) 10–11 g/dl. A range of 10–11 g/dl was used as the reference point as this was in keeping with the UK Renal Association recommended standard of achieving a haemoglobin >10 g/dl during the time period 1999–2005 [13,14].

Materials and methods

The UK Renal Registry collects clinical and biochemical data on a quarterly basis from all patients receiving renal replacement therapy (RRT; both dialysis and transplantation). The UKRR data collection methods and validation procedures have been described in detail elsewhere [15]. In brief, renal centres running Registry-compatible renal information technology (IT) systems are able to electronically export data files to send to the UKRR on a quarterly basis. The local software extraction routines search the IT system to identify all patients on dialysis or with a functioning kidney transplant and send data items to the UKRR from a predefined dataset which includes socio-demographic data, diagnosis, modality changes during the current period, date of death, transfers to other centres and 3-monthly recordings of blood pressure and biochemical and haematological tests. During the study period, UK coverage increased year on year, and by the end of 2007, all UK centres were running UKRR-compatible renal IT systems. Several centres were not sending patient-level haemoglobin data, and these were excluded from the analysis. In the period from 1999 to 2005, haemoglobin data were missing for 7.1%, 6.5%, 7.6%, 6.3%, 6.6%, 7.3% and 11.1%, respectively, of all England and Wales haemodialysis patients at centres sending data to the UKRR.

Patient selection

The numbers of patients included and the demographics of the patient populations are shown in Table 1. All prevalent haemodialysis patients (peritoneal dialysis patients were excluded) monitored by the UKRR and alive on 1 January in each of the years 1999 to 2005 were included in the analysis. The study used a prevalent patient cohort rather than an incident cohort as the latter could confound the results due to low haemoglobins related to variance among centres regarding provision of ESAs prior to RRT. Also, 25% of patients present late (within 3 months of starting RRT). Approximately 70% of the late presenting patients have an acute deterioration of renal function secondary to other medical conditions. The mean individual patient haemoglobin concentration from each of the four quarters in the year was included, and the primary outcome was all-cause mortality in the subsequent year. Patients who had not been on RRT for at least 1 year were therefore excluded as they did not have four quarters of data, as were patients who had less than three haemoglobin values recorded. Patients who received a kidney transplant, withdrew from dialysis or recovered renal function were censored. Median ferritin levels were also examined over this time period to ascertain whether there may be any influence of iron status on the results. As there was a large cohort of patients excluded due to lack of four haemoglobin measurements within a year, a secondary analysis was performed including these patients.

Results

The mean haemoglobin concentration for all haemodialysis patients in the UK progressively increased from 10.9 g/dl in 1999 to 11.6 g/dl in 2005, with the percentage of patients with a value below 10 g/dl falling from 27% to 14% (Figure 1). However, in 2005, there was a marked variability in achieved mean haemoglobin in HD patients among individual centres across the UK, the highest values being 12.7 (SD 1.6 g/dl) and the lowest values being 10.6 (SD 1.6 g/dl) (Figure 2).

For each year, the haemoglobin concentration between 10 and 11 g/dl was designated a relative risk of death of 1.0. Throughout the entire period of study, haemoglobin concentrations above this reference range consistently
showed a 35% lower relative risk of death, and a haemoglobin below 10 g/dl had a 28% higher mortality (P < 0.0001) (Table 2; Figure 3). In 1999, the greatest mortality was seen in patients with a haemoglobin <9 g/dl (73% increased risk of death, although due to the small numbers this was not statistically significant), while the lowest death rate was seen in patients with haemoglobin levels between 12 and 13 g/dl (64% reduced mortality; P = 0.015, Table 3). By 2005, the survival advantage associated with a haemoglobin of around 11–12, 12–13 and ≥13 g/dl was maintained and was highly significant (P < 0.0001).

Despite these fluctuations in the risk of death, when the results were collated for the 7 years of analysis and haemoglobin level was compared with the mortality risk, there was nevertheless quite marked concordance of the data (Table 3; Figure 4). Thus, haemoglobin concentrations <10 g/dl were consistently associated with worse survival,
while patients with haemoglobin concentrations >11 g/dl had a lower death rate. From 1999–2001, there was an improvement in median serum ferritin from 320 to 370 to 410 μg/L, respectively, which thereafter remained stable at around 410 μg/L. Multivariate analysis also showed that age, time on renal replacement therapy and diabetes were independent predictors of survival, all at the \( P < 0.0001 \) level for all the 7 years analysed.

Including the 939 patients who had less than four haemoglobin readings within the year resulted in only minor changes of the hazard ratio (Table 4).

**Discussion**

This is the first attempt to examine changes in mortality outcome data in relation to haemoglobin level in the UK and also the first attempt to examine changes in mortality outcome data in relation to haemoglobin level in any haemodialysis population across a time period greater than 2 years. The analysis was performed using data generated from the UK Renal Registry which has emerged as a credible and useful database, allowing trends in clinical practice patterns to be captured. As is shown in Figure 1, achieved haemoglobin levels in UK haemodialysis patients have been gradually increasing over the last 10 years despite financial constraints on high usage of ESA therapy in the UK at this time due to the high cost of these agents and the welfare-funded nature of the UK National Health Service (where reimbursement policies simply do not operate). Both the pharmaceutical industry and the Anaemia guidelines worked on the premise that anaemia is harmful for a number of physiological functions, particularly the heart, and that correction of anaemia should therefore be beneficial.

Although this premise has not changed following the publication of the CREATE [1] and CHOIR [2] studies, it nevertheless suggested that there may be an upper limit

Table 3. Relative hazard of death by 1 g/dl increments in haemoglobin for 1999–2005 in UK haemodialysis patients (compared with a reference of 10–11 g/dl)

<table>
<thead>
<tr>
<th>Year</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;9)</td>
<td>1.43</td>
<td>1.27</td>
<td>1.24</td>
<td>1.24</td>
<td>0.91</td>
<td>1.03</td>
<td>0.88</td>
</tr>
<tr>
<td>9–10</td>
<td>1.40</td>
<td>1.24</td>
<td>1.17</td>
<td>1.24</td>
<td>1.33***</td>
<td>1.14</td>
<td>1.24***</td>
</tr>
<tr>
<td>10–11 (ref)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>11–12</td>
<td>0.73</td>
<td>0.71**</td>
<td>0.71**</td>
<td>0.81**</td>
<td>0.81***</td>
<td>0.66*</td>
<td>0.68*</td>
</tr>
<tr>
<td>12–13</td>
<td>0.34**</td>
<td>0.46**</td>
<td>0.54*</td>
<td>0.50*</td>
<td>0.58*</td>
<td>0.53*</td>
<td>0.50*</td>
</tr>
<tr>
<td>( \geq 13 )</td>
<td>0.46</td>
<td>0.69</td>
<td>0.42**</td>
<td>0.49*</td>
<td>0.51*</td>
<td>0.37*</td>
<td>0.42*</td>
</tr>
</tbody>
</table>

Table 4. Relative hazard of death by 1 g/dl increments in haemoglobin for 2005 in UK haemodialysis patients (compared with a reference of 10–11 g/dl) for patients with only four Hb values compared with all patients

<table>
<thead>
<tr>
<th>Hazard ratios</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9</td>
<td>0.88</td>
<td>0.88</td>
</tr>
<tr>
<td>9–10</td>
<td>1.24</td>
<td>1.27</td>
</tr>
<tr>
<td>10–11 (ref)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>11–12</td>
<td>0.68</td>
<td>0.70</td>
</tr>
<tr>
<td>12–13</td>
<td>0.50</td>
<td>0.52</td>
</tr>
<tr>
<td>( \geq 13 )</td>
<td>0.42</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Hazard ratios without numbering are not statistically significant.

\* \( P < 0.0001 \).

\** \( 0.0001 < P < 0.01 \).

\*** \( 0.01 < P < 0.05 \).
above which the risks may outweigh the benefits. This is in contrast to most of the observational data [6–9] which tend to show a continuum of benefit from haemoglobin values < 9 g/dl up to haemoglobins of > 13 g/dl. The major limitation of the published randomized controlled trials is that they pre-select two different haemoglobin ranges, the lower value being around 10 g/dl with the upper target being around 14 g/dl. Thus, it is not possible to comment on haemoglobin ranges of 11–12 and 12–13 g/dl. The data shown in Figure 4 suggests a lower mortality at both of these haemoglobin ranges, but it must be remembered that these are ‘achieved’ haemoglobins and not ‘target’ haemoglobins, as is the case for the published RCTs. Analysing these data without knowledge of how much ESA the patient was receiving is therefore of limited value. The advantage of Registry data, however, is that they are ‘real-life’ data, and the likelihood is that the supervising nephrologist has gradually increased the haemoglobin concentration in their patients to levels above 10 g/dl by chronic ESA and/or iron usage. This contrasts to what is seen in the randomized controlled trials, in which physicians are forced to push the haemoglobin up to normal levels, as per the study protocol.

In relation to this topic, a controversial editorial comment in the Lancet by Strippoli et al. [16] was entitled ‘Haemoglobin targets: we were wrong; time to move on’. Many scientific purists were unable to see beyond the arguments expressed in this editorial. The KDOQI group reconvened to re-examine the evidence base in the light of CREATE and CHOIR, and the Tufts University Evidence-Rating Group in Boston independently analysed the available scientific literature on this subject [17]. Three updated haemoglobin target guidelines/recommendations appeared, the most relevant of which are the recommendations that CKD patients receiving ESA therapy should generally aim for a haemoglobin between 11 and 12 g/dl, and that haemoglobin levels above 13 g/dl should not be targeted in CKD patients receiving ESA therapy [17].

Part of the reluctance to accept the data from the randomized controlled trials has been the fact that they are at variance with data from a plethora of observational studies [6–9]. The latter have consistently shown better outcomes at haemoglobin concentrations > 13 g/dl and worse outcomes at concentrations < 9 or 10 g/dl. Patients not receiving ESA therapy but who have haemoglobin concentrations of around 13–14 g/dl usually show the best outcomes in such analyses [7–9]. This has led to the realization that it may not be a high haemoglobin itself that is harmful but the means by which the higher haemoglobin is achieved, including the use of ESA therapy and/or iron.

Another large retrospective analysis suggested that the dose of epoetin required to achieve a given haemoglobin was an independent predictor of mortality at all haemoglobin levels. Thus, Zhang et al. [10] and the post hoc analyses from both the US Normal Hematocrit Trial [11] and the CHOIR study [12] have also raised the hypothesis that high doses of ESA therapy in EPO-resistant patients may be harmful. More recently, a further hypothesis has been generated, based on observational data from a cohort of 40 787 US haemodialysis patients [15]. Compared with a haemoglobin of 12–13 g/dl, patients with a haemoglobin of ≥ 13 g/dl had a significantly greater mortality when they had a relative thrombocytosis (platelet count > 300 × 10^9/l), and the suggestion from this study was that high doses of epoetin were associated with iron depletion which, in turn, was associated with a relative thrombocytosis and greater risk of death [18].

There is a current perception that there is a discrepancy between the latest US KDOQI Anaemia Guidelines update (Hb 11–12 g/dl) [17] and the UK NICE target haemoglobin range (Hb 10.5–12.5 g/dl) [19]. This is not in fact the case. Unfortunately, the majority of readers of the US KDOQI guidelines look only at the headline, namely the 11–12 g/dl target range. There is, however, contained within these guidelines a useful commentary, most of which is neither read nor understood. Thus, the difference between ‘target’ haemoglobin and ‘achieved’ haemoglobin is pivotal to any discussion on this issue, as is the use of the word ‘generally’ in the KDOQI clinical recommendation 2.2. The guidelines do not suggest that a haemoglobin in the 9–11 or the 12–13 g/dl range is harmful, nor do they suggest that transient fluctuations in haemoglobin to levels above 13 g/dl are harmful. The randomized controlled trials strongly suggest that sustained target haemoglobin levels above 13 g/dl may be harmful, although it was the opinion of the KDOQI Anemia Work Group that this has not been conclusively proven [17]. Furthermore, three studies by Zhang et al. [10], Kilpatrick et al. [11] and Szczek et al. [12] have yielded data suggesting that the dose of ESA is as important, if not more important. Thus, in the observational cohort studied by Zhang et al. [10], patients who achieved a Hb > 13 g/dl on the lowest quartile of EPO dose had a lower mortality than patients achieving a Hb of 11–12 g/dl on the highest EPO dose quartile. The post hoc analyses of the US Normal Hematocrit Trial [11] and the CHOIR study [12] also both suggest that the primary end points of these studies are being driven by the patients targetted to a higher Hb but who failed to achieve this despite high doses of EPO. The limitations of all these studies [10–12], however, should be appreciated, and, at best, these data are hypothesis generating.

The study reported here is also not without significant limitations. As with all observational studies, it can only examine associations and not causality. Even with a multivariate analysis, it is impossible to exclude all possible confounders, and it was also not possible in this study to adjust for co-morbidity. There is no information on how much ESA or iron therapy was being used to treat anaemia in this population. The data were only obtained from haemodialysis patients and thus are not generalizable to peritoneal dialysis patients and other CKD populations. Nevertheless, the study incorporates 30 040 patient-years of follow-up over a time period spanning seven complete years. It utilizes a robust method of data capture, with quarterly electronic data extraction from the vast majority of renal centres in the UK. A large cohort of patients was excluded from the analysis because they had less than four haemoglobin results reported over the course of the year. This could have caused bias in the analysis; however, re-analysing the data including these patients did not significantly affect the hazard ratios.
In conclusion, we have shown from this analysis of the UK Renal Registry that there is a strong association between haemoglobin and mortality in UK haemodialysis patients. There is also remarkable consistency of this relationship with survival across the time period 1999–2005, and thus changes in clinical practice, such as the use of ACE inhibitors or angiotensin II blockers, or improvements in dialysis dose and laboratory targets of bone and mineral metabolism have shown no obvious impact on this fairly consistent trend. Given the emerging realization that it may not be haemoglobin concentrations that are harmful but rather the means by which these are achieved, further analyses of the UK Renal Registry database should focus on ESA and iron usage.

Conflict of interest statement. None declared.

References

16. Strippoli GF, Tognoni G, Navaneethan SD et al. Hemoglobin targets: we were wrong, time to move on. Lancet 2007; 369: 346–350

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