Clinical research

Haemoglobin predicts survival in patients with chronic heart failure: a substudy of the ELITE II trial

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Received 18 February 2003; revised 2 March 2004; accepted 2 April 2004

Aims The correction of anaemia in chronic heart failure (CHF) has been suggested to be associated with an improvement in symptoms and cardiac function. We aimed to investigate the relationship between the concentration of haemoglobin and survival in CHF.

Methods and results We analysed haemoglobin concentrations in 3044 patients recruited in the Evaluation of Losartan In The Elderly (ELITE II) trial. Patients of mean age 71.5 ± 6.8 years (±SD) and New York Heart Association (NYHA) class 2.5 ± 0.6 were enrolled from June 1997 to May 1998 and followed-up for survival (range 1–780 days, median 551). In univariate analysis, age, NYHA class, serum creatinine, left ventricular ejection fraction (all P < 0.0001) and sex (P = 0.046) all predicted survival. Haemoglobin as a continuous variable for all patients was not a significant prognostic marker (P = 0.26). However, sub-dividing patients according to 1.0 g/dL increments of haemoglobin revealed that the survival relationship was non-linear. The results from the polynomial regression suggest that the optimal interval is a symmetric one centred around 14.5 g/dL. This was independent of age, sex, NYHA class, left ventricular ejection fraction, creatinine, co-existing chronic obstructive pulmonary disease and treatment allocation (P < 0.001). There was a minor fall in plasma haemoglobin at the 12-month follow-up (mean change for all patients 0.3 ± 2.2 g/dL, P < 0.0001), with no difference between captopril and losartan groups (P > 0.3).

Conclusion Haemoglobin is an independent predictor of mortality in CHF patients, with anaemic and polycythaemic patients having the worst survival.

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KEYWORDS
Haemoglobin; Chronic heart failure; Survival

Introduction

Chronic diseases are often associated with anaemia which can worsen symptoms and lead to a poor quality of life. Anaemia is a relatively common finding in chronic heart failure (CHF),¹ worsening as the severity of heart failure increases.² The principal symptoms of CHF are a limitation of exercise capacity and fatigue, both of which may be exacerbated by a low haemoglobin level. Peak exercise tolerance is related to the blood oxygen carrying capacity in CHF³ and myocardial ischaemia with deficient oxygen delivery is thought to contribute

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to cardiac dysfunction in the majority of CHF cases. Correcting the anaemia associated with heart failure could be expected to have beneficial effects on cardiac function and morbidity in CHF.

Erythropoietin has been approved for the treatment of anaemia secondary to chronic renal failure for over 10 years, resulting in improvements in both the morbidity and mortality associated with this condition.4,5 The most common causes of death among patients with end-stage renal failure are cardiovascular. Partial correction of common causes of death among patients with end-stage renal failure are cardiovascular. Partial correction of anaemia in these patients reduces exercise-related cardiac ischaemia6 and diminishes the degree of left ventricular hypertrophy.7 In a study by Besarab and colleagues,8 patients with CHF or ischaemic heart disease undergoing haemodialysis were randomly assigned to one of two groups. In the first group, erythropoietin was administered to achieve and maintain a haematocrit of 42% (the normal-haematocrit group), whereas the second group received erythropoietin sufficient to maintain a haematocrit of 30% (the low-haematocrit group) throughout the study. Although mortality rates decreased with increasing haematocrit values in both groups, the overall mortality was non-significantly higher in the normal-haematocrit group as compared with the low-haematocrit group (risk ratio 1.3, 95% CI 0.9–1.9). This suggests that increasing the haematocrit value above a certain threshold level with erythropoietin might have an adverse effect on prognosis. This is consistent with the results of large epidemiological studies which have shown that the impact of haemoglobin on survival follows a U-shaped curve.9,10,11 It has not been determined whether being polycythaemic is a risk factor in heart failure.

The relationship between plasma haemoglobin and mortality in patients with CHF is unclear. Although recent reports have suggested that anaemia may be associated with a worse outcome in patients with heart failure,12,13,14 it is not known if changes in haemoglobin relate to prognosis or whether there is an optimal range for survival. The medication used to treat heart failure patients may potentially influence the plasma haemoglobin level, in particular drugs such as ACE-inhibitors, diuretics, aspirin and warfarin. The interaction between drugs and plasma haemoglobin level in CHF has not been previously evaluated in detail.

The main hypothesis of our study is that haemoglobin is an independent predictor of mortality in patients with CHF. We sought to investigate this by studying CHF patients who were recruited in the Evaluation of Losartan In The Elderly (ELITE II) trial.15

### Methods

#### Study patients

We analysed haemoglobin levels taken at baseline in 3044 patients recruited in the ELITE II trial. All patients in the ELITE II trial who had had their haemoglobin level assessed were included in this sub-study (i.e., 97% of all trial patients). Patients were enrolled from June 1997 to May 1998, the entry criteria and design of the trial being discussed in detail elsewhere.15 Of note, chronic obstructive pulmonary disease (COPD) was not specified as an exclusion criterion of the trial, being diagnosed in 260 (8.5%) patients in this study. The mean age of the patients was 71.5 ± 6.8 years (± SD), New York Heart Association (NYHA) class 2.5 ± 0.6, left ventricular ejection fraction (LVEF) 31 ± 7%, haemoglobin 14.0 ± 1.6 g/dL and haematocrit 42 ± 5% (Table 1, Figs. 1(a) and (b)). There was no significant difference between patients with co-existing COPD and those with no COPD in terms of baseline haemoglobin (14.1 ± 1.5 vs 14.0 ± 1.6, P = 0.1) and haematocrit (0.42 ± 0.05 vs 0.42 ± 0.05, P = 0.7). The haemoglobin level was also assessed in 1962 patients at 12 months follow-up. These patients were not significantly different from the overall cohort. The clinical characteristics of patients subgrouped according to plasma haemoglobin concentration are given in Table 2.

#### Statistical analysis

All data are presented as means ± SD. The unpaired Student’s t-test, ANOVA with Fisher’s post hoc test and ANOVA for repeated measures were used as appropriate. A two-tailed t-test was used

### Table 1 Baseline clinical characteristics of 3044 CHF patients from the ELITE II study

<table>
<thead>
<tr>
<th></th>
<th>All CHF patients (n = 3044)</th>
<th>CHF patients with Hb at 1-year follow-up (n = 1962)</th>
<th>Comparison by survival status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.5 ± 6.8</td>
<td>71.6 ± 6.9</td>
<td>73.0 ± 7.2</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>2100/944</td>
<td>1472/490</td>
<td>375/140</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1725/804</td>
</tr>
<tr>
<td><strong>Anthropometry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 ± 10</td>
<td>167 ± 10</td>
<td>166 ± 10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73 ± 15</td>
<td>73 ± 15</td>
<td>70 ± 15</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.2 ± 4.4</td>
<td>26.1 ± 4.4</td>
<td>25.1 ± 4.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>26.4 ± 4.5</td>
</tr>
<tr>
<td><strong>Clinical assessment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.5 ± 0.6</td>
<td>2.4 ± 0.6</td>
<td>2.8 ± 0.6</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>31 ± 7</td>
<td>31 ± 7</td>
<td>30 ± 7</td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>141 ± 4</td>
<td>141 ± 4</td>
<td>140 ± 4</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>104 ± 29</td>
<td>103 ± 30</td>
<td>109 ± 33</td>
</tr>
<tr>
<td>Plasma Hb (g/dL)</td>
<td>14.0 ± 1.6</td>
<td>14.0 ± 1.6</td>
<td>13.9 ± 1.7</td>
</tr>
<tr>
<td>Plasma haematocrit (%)</td>
<td>42 ± 5</td>
<td>42 ± 5</td>
<td>42 ± 5</td>
</tr>
</tbody>
</table>

Data represented are means ± SD. NYHA, New York Heart Association class; LVEF, left ventricular ejection fraction; Hb, haemoglobin. *P < 0.0001 for unpaired t-test of mean of corresponding groups.
and a P-value <0.05 considered significant. The risk of Type I error was therefore 0.05 for each individual comparison. Cox proportional-hazards analysis was performed using baseline values to assess the association between variables and all-cause mortality. The variables selected to obtain the univariate model were those which are generally accepted as being of prognostic value in heart failure such as age, renal function and ejection fraction, together with the parameter of interest, i.e., haemoglobin (both as a continuous and a discrete variable). In order to assess whether haemoglobin was an independent prognosticator, those parameters with significant univariate values were subsequently selected for the multivariate model. The proportional hazard assumption of the model was assessed by inspection of the log time–log hazard plot for all covariates. The significance levels for χ² (likelihood ratio test) were calculated. Kaplan–Meier cumulative survival plots were constructed for display (StatView 5, Abacus Concepts, Berkeley, USA).

To investigate the relationship between haemoglobin levels and survival, patients were initially subdivided according to 1.0 g/dL increments of haemoglobin and the hazard ratios for each group calculated (Fig. 3(a)). At the extremes of Hb, where there were few patients, we made a single group for all patients with a haemoglobin level below 10.5 g/dL, and similarly a single group for patients with a haemoglobin of 17.5 g/dL or greater. This analysis demonstrated that the association between haemoglobin and survival was non-monotonic.

Because the relationship was non-monotonic, polynomial survival regression was performed to determine the optimal haemoglobin range; in view of the shape of Fig. 3, a quadratic model was chosen. To check the validity of this “optimal” haemoglobin range, we calculated the cumulative mortality for each overlapping 1 g/dL interval in the region close to this range and plotted it at the centre of the interval, showing the standard error (Fig. 3(b)). Thus, for example, the point and error bar at 14.5 g/dL represents the mortality of the 852 patients with haemoglobin values between 14.0 and 15.0 inclusive. The adjacent point at 14.6 g/dL represents the 821 patients with haemoglobin values between 14.1 and 15.1, 768 of which are the same as the previous set. Although the patient sets overlap heavily in this graph (unlike Fig. 3(a)), it makes it easier to visualise the shape of the relationship between haemoglobin and risk, without the influence of an arbitrary starting point and without making the assumption of a polynomial relationship.

**Results**

Of the 3044 CHF patients who were followed up (median 551 days [interquartile range, IQR, 184]), 515 died after 1–702 days (median 263 days [IQR 275]). The median follow-up period of the 2529 survivors was 584 days (IQR 162 days). The cumulative survival of all the patients was 94.0% at 6 months, 88.4% at 12 months, 84.3% at 18 months and 83.1% at 24 months.

**Table 2**  Clinical characteristics of 3044 CHF patients sub-divided according to plasma haemoglobin concentration

<table>
<thead>
<tr>
<th></th>
<th>Hb &lt;12.5 g/dL (n = 513)</th>
<th>Hb 12.5–13.9 g/dL (n = 951)</th>
<th>Hb 14.0–15.0 g/dL (n = 852)</th>
<th>Hb &gt;15.0 g/dL (n = 728)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73.7 ± 7.2***</td>
<td>72.0 ± 7.0**</td>
<td>70.9 ± 6.3</td>
<td>70.0 ± 6.6**</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>257/256</td>
<td>569/382</td>
<td>649/203</td>
<td>625/103</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.2 ± 5***</td>
<td>25.9 ± 4.4*</td>
<td>26.4 ± 4.3</td>
<td>26.9 ± 4.1</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.6 ± 0.6**</td>
<td>2.5 ± 0.6</td>
<td>2.5 ± 0.6</td>
<td>2.5 ± 0.6</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>31 ± 7</td>
<td>31 ± 7</td>
<td>31 ± 7</td>
<td>31 ± 7</td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>140 ± 4*</td>
<td>141 ± 4</td>
<td>141 ± 4</td>
<td>141 ± 4</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>108 ± 37*</td>
<td>102 ± 29</td>
<td>104 ± 27</td>
<td>103 ± 25</td>
</tr>
<tr>
<td>Plasma haematocrit (%)</td>
<td>36 ± 3***</td>
<td>40 ± 2***</td>
<td>43 ± 2</td>
<td>48 ± 3***</td>
</tr>
<tr>
<td>No. of COPD patients (%)</td>
<td>33 (6.4)</td>
<td>80 (8.4)</td>
<td>78 (9.2)</td>
<td>69 (9.5)</td>
</tr>
</tbody>
</table>

All values are means ± SD. Hb, plasma haemoglobin; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease.

*P < 0.05.
**P < 0.01.
***P < 0.0001 vs patients with Hb 14.0–15.0 g/dL (ANOVA).
We found there was a significant and strong linear relationship between plasma haemoglobin level and haematocrit \( (r = 0.89, P < 0.0001) \) which holds true for both males \( (r = 0.89, P < 0.0001) \) and females \( (r = 0.88, P < 0.0001) \), Fig. 2. Using the regression formula, a haemoglobin level of 12 g/dL is equivalent to a haematocrit of 37\% in the ELITE II study. This study has demonstrated that in CHF a change of 1 g/dL in haemoglobin is associated with a change of 2.6\% in haematocrit, which holds true for both males and females.

In the univariate analysis, age, NYHA class, serum creatinine, LVEF \( (P < 0.0001 \text{ for each},) \) presence of COPD \( (P = 0.0049) \) and gender \( (P = 0.046) \) all predicted survival (Table 3), whereas treatment allocation did not \( (P = 0.136) \). Plasma haemoglobin at baseline analysed as a continuous variable for all patients was not a significant prognostic marker \( (P = 0.26) \). This is due to the non-linear relationship between haemoglobin and survival. Subdividing patients according to 1.0 g/dL increments of haemoglobin illustrates the U-shaped survival curve for haemoglobin, with the range 14.5–15.4 g/dL appearing to have the best prognosis (Fig. 3(a)).

Applying polynomial survival regression analysis, the best fit was demonstrated for a quadratic model whose co-efficients were \(-1.07 \text{ and } 0.037 \) for the first and second powers of haemoglobin (g/dL), respectively. With both powers of haemoglobin, the likelihood ratio test \( \chi^2 \) value was 11.24, \( P = 0.0036 \). From this model, the de-
rived haemoglobin level giving the lowest risk for mortality was 1.07/2 × 0.037, i.e., 14.5 g/dL. The optimal Hb for survival for males was determined as being 15.0 g/dL and for females as being 13.1 g/dL.

To test the validity of our findings, we performed additional survival analyses. The relationship of mortality at 2 years to haemoglobin was also calculated without making the parametric assumption of a polynomial relationship, by determining the mortality in overlapping 1 g/dL intervals of haemoglobin (Fig. 3(b)). This confirmed that the nadir of mortality appeared to lie just below 15 g/dL. Since this curve is not symmetrical, it is not easy to identify a single unique optimal haemoglobin. Therefore, for practical purposes we have used the range 14.0–15.0 g/dL, which encompasses the optimal haemoglobin in all three analyses (histogram Fig. 3(a), polynomial regression and Fig. 3(b)).

Kaplan–Meier survival analysis was performed by sub-grouping patients according to haemoglobin into four categories (Fig. 4). In this analysis the best survival was found for patients with a baseline haemoglobin level of 14.0–15.0 g/dL (cumulative survival at 2 years 83.0%; 95% CI 79.4–86.6%; Fig. 4). Patients in the low haemoglobin (<12.5 g/dL) and high haemoglobin (>15.0 g/dL) groups had the greatest mortality (cumulative survival at 2 years for low haemoglobin group: 74.8%; 95% CI 69.0–80.6; cumulative survival at 2 years for high haemoglobin group: 78.3%; 95% CI 73.7–82.9). The clinical characteristics of patients in each category are given in Table 2.

Of the 2691 patients alive at 12 months, follow-up haemoglobin measurements were available at that time-point in 1962 (73%). There was no significant difference in age, NYHA class, LVEF or serum creatinine between patients who had had a 12-month haemoglobin assessment and those who had not (all P > 0.3, Table 1). There was a slight fall in mean plasma haemoglobin from 13.9 g/dL at baseline to 13.7 g/dL at 12 months (P < 0.0001). There was no significant difference in the change in haemoglobin between the captopril and losartan groups (P > 0.3).

Of the 3044 patients in our sub-study, 681 (22.4%) patients were taking β-blocker therapy, whereas 2363 (77.6%) were not. We found there was a significant U-shaped relationship between haemoglobin levels and survival in patients not on β-blockers, with the range 14.8–15.3 g/dL being optimal (P = 0.0003). There was no U-shaped relationship present for patients taking this class of medication.

Patients taking loop diuretics (n = 1902, 62.5%) had a marginally lower haemoglobin level (13.9 g/dL) as compared to patients not on this type of medication (Hb 14.1 g/dL, P < 0.001). There were 459 (15.1%) patients taking thiazide diuretics. We found no significant difference in haemoglobin level between patients on thiazides (Hb 14.1 g/dL) and those who were not taking these drugs (Hb 14.0 g/dL, P = 0.10) (Table 4).

Patients taking aspirin (n = 1788, 58.7%) had a slightly lower haemoglobin level as compared to those not on this drug (Hb 13.9 vs 14.1, P = 0.01). However, when patients who were taking aspirin, warfarin or heparin (n = 2196, 72.1%) were compared to patients not on any of these drugs, no difference in haemoglobin level was found (Hb 14.0 g/dL for both groups).

When excluding patients with COPD, the relationship between haemoglobin and survival did not change significantly, with the range of 14.0–15.0 g/dL still being the best predictor of prognosis (data not shown).

Discussion

This study has shown that plasma haemoglobin is a significant predictor of mortality for patients with chronic heart failure. In the population studied here, the

Table 4 Cox proportional hazards analysis of survival in 3044 CHF patients: multivariate analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>χ²-value</th>
<th>P-value (likelihood ratio test)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb 14.0–15.0 g/dL (no)</td>
<td>6.4</td>
<td>0.0117</td>
<td>1.303 (1.061–1.600)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>21.3</td>
<td>&lt;0.0001</td>
<td>1.030 (1.017–1.042)</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>3.9</td>
<td>0.0482</td>
<td>0.815 (0.665–0.998)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>76.0</td>
<td>&lt;0.0001</td>
<td>1.901 (1.646–2.197)</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>6.3</td>
<td>0.0122</td>
<td>1.004 (1.001–1.006)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>10.3</td>
<td>0.001</td>
<td>0.981 (0.969–0.992)</td>
</tr>
<tr>
<td>COPD? (yes)</td>
<td>4.4</td>
<td>0.0354</td>
<td>1.335 (1.020–1.748)</td>
</tr>
</tbody>
</table>

Hb, haemoglobin; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease.
relationship was not linear, and patients who were severely anaemic or polycythaemic had the worst survival. Haematocrit, which is a measure of the ratio of the volume of packed red blood cells to the volume of whole blood, is often used as a surrogate marker for plasma haemoglobin. This study has demonstrated that in CHF a change of 1 g/dL in haemoglobin is associated with a change of 2.6% in haematocrit, which holds true for both males and females (Fig. 2).

The cause of anaemia in CHF is not completely understood but it is likely to be the result of a combination of factors. Chronic inflammatory conditions are often associated with a mild degree of anaemia, termed ‘the anaemia of chronic disease’. This is due to a defective release of iron from cells, a reduction in erythrocyte survival time, and an impairment of erythropoietin secretion.16 Inflammatory cytokines, which are known to be elevated in patients with CHF and relate to many of the systemic manifestations of this syndrome,17,18 interfere with both the effect of erythropoietin at the bone marrow and the release of stored iron in the reticuloendothelial system.19,20

Anaemia is known to contribute to the decreased exercise capacity of CHF patients,21 and may also be involved in the pathogenesis of oedema in this condition.22 A potential mechanism is that the low concentration of haemoglobin in severely anaemic patients causes a reduction in the inhibition of nitric oxide activity thereby leading to generalised vasodilatation. The resulting low blood pressure may provide the stimulus for neuro-hormonal activation and salt and water retention.

In a randomised open study by Silverberg and co-workers,23 the correction of even mild anaemia with subcutaneous erythropoietin and intravenous iron therapy resulted in a marked improvement in patient symptoms and cardiac function. Due to the small number of patients in the study and the short length of follow-up, the prognostic benefits of treating anaemia in CHF could not be assessed and it was not clear whether there was an optimal range for haemoglobin. These results were strengthened by a study from Mancini et al.24 In the Framingham study, the impact of haematocrit on all-cause death as well as morbidity and mortality due to cardiovascular disease was shown to follow a U-shaped curve.9 In keeping with this finding, other prospective epidemiological studies of healthy populations have also shown that the lowest mortality rate appears to correlate with a mid-range haematocrit level in both sexes and at all ages.10,11

In the present study, patients with a plasma haemoglobin level of 14.9 g/dL appear to have the lowest absolute risk of death at 2 years follow-up. Both anaemic and polycythaemic patients tend to have a worse prognosis (Figs. 3(a), (b) and 4). The importance of this finding is that although anaemia in CHF is associated with a poor prognosis, it appears that polycythaemia is also associated with an impaired outcome (Fig. 3(a)).

The frequency and importance of haematological abnormalities in CHF is well established.25 CHF is known to be a prothrombotic state, even in patients who are in sinus rhythm.26 Consequently, CHF patients who are polycythaemic are likely to be particularly at risk of events which have thrombosis as the underlying pathological mechanism, such as strokes and myocardial ischaemia. Furthermore, any increase in blood viscosity requires additional work by the myocardium and also results in a decrease in tissue oxygen delivery.27

Recent evidence suggests that haemoglobin may have a fundamental role in carrying molecules related to nitric oxide.28 A high haemoglobin level may, therefore, promote systemic vasoconstriction by trapping nitric oxide. Another mechanism by which polycythaemia may result in detrimental effects in CHF is through the generation of oxygen-derived free radicals. Iron is known to be an important co-factor in the production of free radicals,29 and there is increasing evidence to suggest that these highly reactive molecules may play a crucial role in the process of cardiac remodelling and apoptosis in CHF.30 Although polycythaemia is not as common as anaemia in CHF (5.9% of the patients in the present study had a haemoglobin >16.5 g/dL as compared to 16.9% of patients with a haemoglobin <12.5 g/dL, Figs. 1(a) and (b)), it is critical to ensure that when correcting mild anaemia patients do not inadvertently become polycythaemic. Our study was not able to establish a clear relationship between changes in haemoglobin and subsequent survival, probably due to a lack of power with regards to follow-up after the second haemoglobin assessment at 12 months. Florea et al.31 have shown that decreasing haemoglobin levels are associated with a poor outcome.

Patients with CHF are usually on several different types of medication and it is important that the potential effects of these on plasma haemoglobin levels are adequately assessed. Studies have shown that treatment with angiotensin-converting enzyme (ACE) inhibitors can lower haemoglobin levels significantly via the inhibition of erythropoietin synthesis.32,33 We found that the changes in haemoglobin were not significantly different between patients taking the ACE-inhibitor captopril or the angiotensin receptor antagonist losartan.

Theoretically, chronic diuretic therapy may be expected to lead to an elevated haematocrit (and haemoglobin) level due to volume contraction. Although in the present study the reverse was found to be the case (patients taking loop diuretics had lower haemoglobin level than those not on these drugs: Hb 13.9 vs 14.1 g/dL, P < 0.001), it is unlikely that this small difference is clinically relevant. In addition, we noted that there was no significant difference in plasma haemoglobin levels between patients taking thiazide diuretics and those not on these drugs (14.1 vs 14.0 g/dL, P = 0.10). Patients on anti-platelet agents and/or anti-coagulants may be expected to have a lower haemoglobin level than patients not on these drugs through an increased tendency for bleeding in the former group. We found that the relationship of aspirin to plasma haemoglobin was weak (patients on aspirin had a slightly lower haemoglobin; 13.9 vs 14.1 g/dL, P = 0.01). There was no difference in haemoglobin level between patients on either aspirin, warfarin or heparin as compared to those patients not on any of these drugs (Hb 14.0 g/dL for both groups).
Analysis in our study and other emerging data indicate that the U-shaped relationship between haemoglobin and survival is limited to patients not taking β-blockers.

Study limitations

The major limitation of this study is that it was retrospective in design. However, the ELITE II trial itself was a large prospective study and we were able to obtain the haemoglobin results and survival data on 97% of the patients that were recruited. The primary diagnosis for all patients recruited in the ELITE II trial was CHF, for patients with polycythaemia there is an increased risk of co-morbidity (such as COPD) which is likely to predispose to an elevated haemoglobin concentration. Whilst COPD was not a specific exclusion criterion of the ELITE II trial, we note that this diagnosis was present as a co-morbidity in only 260 (i.e., 8.5%) patients in this study. The relationship between haemoglobin and survival did not change significantly when patients with co-existing COPD were excluded from the analysis. Indeed, the optimal haemoglobin level (i.e., 14.5 g/dL) was exactly the same for the study population whether the COPD patients were included or excluded from the analysis.

The results of our analyses are based on the population of the ELITE II trial. Our results need further validation in an unscreened CHF population. As patients with clinically important anaemia were excluded from this trial, the prevalence of low (and probably for similar reasons of high) haemoglobin levels may also be underestimated by this report.

No special technique was used to adjust the P-values of individual comparisons. Since the risk of type I error was 0.05 for each, the cumulative risk of there being at least one type I error in the study may be large.

Acknowledgements

S.D.A. is supported by a Vanderwell Fellowship and a donation from Dr. Hubert Bailey. The Division of Applied Cachexia is supported by a grant from Charité Medical School. R.S. was supported by the Robert Luff Foundation. A.J.S.C. was supported by the Viscount Royston Trust Fund.

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