Chapter 18: Survival in dialysis patients: associations with haemoglobin achieved and blood pressure control.

Haemoglobin achieved

Subjects

The study sample consisted of patients on dialysis on 1/1/1998 at 8 centres on the Renal Registry database who had been receiving renal replacement therapy for at least one year, from whom quarterly data for 1997 had been received. Patients from three other centres were not included because of concerns about completeness and accuracy of data. Patients were included in the analysis regardless of their previous treatment and transplant history. For inclusion at least 2 or more haemoglobin values for 1997 had to be received.. The final sample size was 1,916 patients.

Methods

A Cox Proportional Hazards Model was used to analyse the relationship between haemoglobin and risk of death over the one year period from January 1st to December 31st 1998. Patients were censored, and analysed as being alive, at the time of transfer to a non Renal Registry treatment centre, and at transplantation.

The mean haemoglobin was computed for 1997 in each patient. Two analyses were performed. Firstly, outcomes in patients with haemoglobin ≥ 10g/dl were compared with outcomes in patients with < 10g/dl. This was chosen to test the current Renal Association Standards recommendation, which states that 'a target haemoglobin concentration of not less than 10 g/dl (approximately equal to a haematocrit >31%) should be achieved in >85% of patients after 3 months on renal replacement therapy. Analysis using quintiles of mean haemoglobin was also performed :the quintiles were ≤ 8.9g/dl, 9.0 – 9.9g/dl, 10.0 – 10.9g/dl, 11.0 – 11.9g/dl and ≥ 12.0g/dl. This approach was chosen to mirror recent large-scale analyses, mostly from the United States, which demonstrated that relationships between haemoglobin and mortality, while monotonic, are semi-linear.

Three models are presented:-

Model I: haemoglobin and mortality rates are analysed without adjustment for putative confounders or modifiers.

Model II: adjustment is made for age, log-transformed length of time on ESRF treatment, a primary diagnosis of diabetes, and treatment centre on January 1st 1998.

Model III is similar to Model II, with mean albumin levels as an additional adjustment factor. For this analyses were performed using the mean harmonised serum albumin from 1997, obtained from patients with 2 or more albumin readings in 1997. Patients from one centre were excluded from this last analysis, as the BCP method was used to measure albumin. This analysis was performed to try to eliminate the effects of other intercurrent illnesses which frequently reduce both haemoglobin

and serum albumin in a non-specific way. Any association between low haemoglobin and increased mortality in this model is more likely to be causal.

Results

The results are shown in table 18.1

Mean Haemoglobin	**MODEL I** Unadjusted Analysis (n = 1,828) Hazard Ratio [95% CI][a]	**MODEL II** Adjusted[b] Analysis (n = 1,763) Hazard Ratio [95% CI][a]	**MODEL III** Adjusted[b] Analysis + Mean Albumin (n = 1,516) Hazard Ratio [95% CI][a]
< 10 g/dl	1.25 [0.98-1.59]	1.33 [1.03-1.71]	1.41 [1.07-1.86]
≥ 10 g/dl	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
P-value	p = 0.08	p = 0.03	p = 0.02
< 8.9 g/dl	1.62 [1.11-2.35]	1.81 [1.22-2.67]	2.15 [1.41-3.29]
9.0 – 9.9 g/dl	1.08 [0.77-1.50]	1.22 [0.87-1.71]	1.23 [0.84-1.79]
10.0 – 10.9 g/dl	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
11.0 – 11.9 g/dl	1.00 [0.77-1.50]	1.07 [0.76-1.51]	1.10 [0.76-1.61]
≥ 12 g/dl	0.99 [0.67-1.46]	1.12 [0.76-1.66]	1.11 [0.72-1.72]
Overall p-value	p = 0.13	p = 0.07	p = 0.02
P-value for linear trend	p = 0.05	p = 0.06	p = 0.03
Pooled hazards ratio assuming linearity assumption valid[c]	0.91 [0.82-1.00]	0.90 [0.81-1.00]	0.88 [0.78-0.98]

Table 18.1. Relationship between haemoglobin and one year hazard of death

a. CI denotes 'confidence interval'. Confidence intervals that do not include 1 imply a statistically significant ($p < 0.05$) difference in mortality rates from the reference category. A hazard ratio above 1 implies a greater death risk, while a hazards ratio under 1 implies a lower death risk.

b. Adjusted for age, log-transformed duration of ESRF, presence or absence of diabetes as primary renal diagnosis and treatment centre.

c. Estimate of the average change in hazards ratio associated with going up 1 haemoglobin category.

Discussion

Mortality of Patients with Haemoglobin < 10g/dl and Haemoglobin ≥ 10g/dl.

Achievement of the recommendation of the Standards document of a haemoglobin of at least 10 g/dl was associated with lower mortality in adjusted analyses, with and without inclusion of mean serum albumin levels. The associated increments in mortality with haemoglobin levels below 10 g/dl were estimated at 33% and 41% respectively. In the unadjusted analysis, the association between haemoglobin values below 10 g/dl and mortality failed to reach statistical significance, with a p value of 0.08.

Mortality With Mean Haemoglobin Categorised by 1g/dl

Haemoglobin levels below 9 g/dl were associated with higher mortality in all 3 Models. Compared to haemoglobin levels of 10 to 10.9 g/dl, the associated mortality increments were 62% in Model I, 81% in Model II, and 115% in Model III. Tests for a linear relationship between haemoglobin band and mortality did not quite reach statistical significance in Model I (p for trend 0.05) and Model II (p for trend 0.06). The corresponding p-value was statistically significant at 0.03 in Model III. In this model, moving up 1 haemoglobin band was associated with an average mortality reduction of 12% (95% CI 2% to 22%), a figure quantitatively similar to those observed in Model I and Model II.

Conclusion

This analysis supports the evidence that low haemoglobin over a period of time in associated with increased mortality in dialysis patients. Whilst the relationship between haemoglobin and mortality is not entirely linear, there may be some additional gain from increasing the haemoglobin above 10 g/dl.

The Association Between Blood Pressure and Risk of Death

This section examines the association between observed blood pressure and short term prognosis over one year of patients established on dialysis.

Sample

The sample consisted of patients who were established on dialysis on 1/1/1998, who were receiving treatment at one of the 11 centres on the Renal Registry database with quarterly data for 1997. The sample only included patients who started ESRF treatment before 1/10/1997. The sample totalled 2,699 patients.

The last blood pressure from the last quarter of 1997 was used in the analysis.

In four Centres, less than 75% of patients had blood pressure readings available. Patients from these centres were excluded from the analysis. This resulted in a sample of 1,638 patients, of which 1,451 patients had appropriate blood pressure data available.

Methods

The analysis was carried out with the systolic blood pressure and diastolic blood pressure separately. Blood pressure was divided into quintiles.
For systolic blood pressure the quintiles were: ≤ 117, 118 – 131, 132 – 146, 147 – 161 and ≥ 162.
For diastolic blood pressure the quintiles were: ≤ 65, 66 – 74, 75 – 80, 81 – 90 and ≥ 91.
The analysis was carried out for the mean arterial blood pressure and pulse pressure. For mean arterial pressure the quintiles were ≤ 83, 84 - 93, 94 - 103, 104 - 112 and ≥ 113.

The pulse pressure was defined as the difference between the systolic blood pressure and the diastolic blood pressure. The analysis was carried out dividing the pulse blood pressure into quintiles, which were defined as: ≤ 45, 46 - 55, 56 - 66, 67 - 80 and ≥ 81.

The outcome was death during 1998. A Cox Proportional Hazards Model was used to analyse the relationship between blood pressure and risk of death over the one year period in 1998, adjusting for age, length of time on RRT, whether the patient had a primary diagnosis of diabetes and treatment centre on 1.1.1998. Age and length of time on RRT were entered into the model as continuous variables. The length of time on RRT was measured in days on the 1/1/1998 and its log transform was used in the model. Patients without a primary diagnosis were excluded from the adjusted analysis, as were patients who had been on RRT for an unknown duration.

The adjusted and unadjusted survival analysis was stratified by centre. Stratifying by centre enables a separate underlying hazard to be estimated at each centre but assumes that the effect of blood pressure and confounding variables on the hazard to be the same at each centre.

Patients were censored if they transferred out from a Renal Registry Site to a non Renal Registry Site or if they had a transplant. Note that if a patient died on the day of transplant, then the death has not been counted.

Systolic Blood Pressure

The results (table 18.2) show a weak but significant association between systolic blood pressure and survival in the adjusted analysis, such that higher pressures are associated with lower hazard

Systolic Blood Pressure	Unadjusted Analysis (n = 1451) Hazard Ratio [95% CI]	Adjusted Analysis (n = 1391) Hazard Ratio [95% CI]
≤ 117	0.92 [0.62 – 1.35]	0.78 [0.52 – 1.17]
118 – 131	REF	REF
132 – 146	0.65 [0.42 – 1.00]	0.55 [0.35 – 0.85]
147 – 161	0.79 [0.53 – 1.18]	0.64 [0.42 – 0.97]
≥ 162	0.67 [0.44 – 1.02]	0.55 [0.36 – 0.85]
X^2	6.2	10.6
p-value	0.1828	0.0320

Table 18.2. Systolic pressure and hazard of death

Diastolic Blood Pressure

The results (table 18.3) show a highly significant association between diastolic blood pressure and survival in the unadjusted and adjusted analyses, such that higher pressures are associated with lower hazard

Diastolic Blood Pressure	**Unadjusted Analysis (n = 1451)** *Hazard Ratio [95% CI]*	**Adjusted Analysis (n = 1391) Hazard Ratio [95% CI]**
≤ 65	1.59 [1.09 – 2.32]	1.37 [0.93 – 2.02]
66 – 74	1.31 [0.88 – 1.94]	1.14 [0.76 – 1.71]
75 – 80	0.69 [0.44 – 1.08]	0.61 [0.38 – 0.98]
81 – 90	REF	REF
≥ 91	0.51 [0.30 – 0.87]	0.58 [0.34 – 1.00]
X^2	31.7	20.6
p-value	< 0.0001	0.0004

Table 18.3. Diastolic pressure and hazard of death

The unadjusted association could not be completely explained by a linear trend, since although there was a statistically significant linear trend ($X^2 = 23.7$, d.f = 1, $p < 0.0001$), there was also a statistically significant departure from trend ($X^2 = 8.0$, d.f = 3, $p = 0.0461$).

This was also the case with the adjusted analysis, since there was a statistically significant linear trend ($X^2 = 11.9$, d.f = 1, $p = 0.0005$) and a statistically significant departure from trend ($X^2 = 8.7$, d.f = 3, $p = 0.0341$).

Mean Arterial Blood Pressure

The results (table 18.4) show a weakly significant association between mean arterial pressure and survival in the unadjusted analysis which is not present in the adjusted analysis.

Mean Arterial Blood Pressure	**Unadjusted Analysis (n = 1451) Hazard Ratio [95% CI]**	**Adjusted Analysis (n = 1391) Hazard Ratio [95% CI]**
≤ 83	1.57 [1.07 – 2.30]	1.58 [1.06 – 2.36]
84 - 93	1.29 [0.86 – 1.93]	1.44 [0.95 – 2.17]
94 - 103	REF	REF
104 - 112	1.00 [0.64 – 1.58]	1.06 [0.66 – 1.70]
≥ 113	0.83 [0.53 – 1.29]	0.96 [0.61 – 1.51]
X^2	11.1	8.8
p-value	0.0253	0.0662

Table 18.4. Mean arterial pressure and hazard of death

The weak statistically significant association found in the unadjusted analysis conformed to a linear association ($X^2 = 10.4$, d.f = 1, $p = 0.0012$), such that moving up one mean arterial

blood pressure quintile was associated with a decrease in hazard of 0.85 [95% CI: 0.77 – 0.94]. This association was abolished by adjustment.

Pulse Pressure

Results are shown in table 18.5. No association was found between pulse pressure and hazard of death.

Pulse Blood Pressure	Unadjusted Analysis (n = 1451) Hazard Ratio [95% CI]	Adjusted Analysis (n = 1391) Hazard Ratio [95% CI]
≤ 45	REF	REF
46 – 55	0.93 [0.61 – 1.42]	0.79 [0.51 – 1.23]
56 – 66	0.98 [0.63 – 1.51]	0.78 [0.50 – 1.22]
67 – 80	0.98 [0.66 – 1.47]	0.73 [0.48 – 1.12]
≥ 81	1.23 [0.81 – 1.88]	0.84 [0.54 – 1.30]
X^2	2.1	2.3
p-value	0.7243	0.6784

Table 18.5. The association between pulse pressure and hazard of death

Comment

This study is short term and uses a relatively small sample. The pitfalls of such analysis are considerable and are discussed in chapter 10. The lack of the expected relationship between hypertension and poor outcome in several studies in renal replacement therapy has already been considered in chapter 10. Similar results are found from this Registry data, with hypertension appearing to be a marker for good prognosis. No relationship was found between pulse pressure and short term prognosis. As discussed, the measured blood pressure reflects many things including myocardial function, arterial rigidity and resistance, salt and water balance, and hypotensive treatment given. It is probable, given current dialysis practice, that those with good myocardial function develop hypertension, and that lower blood pressure is may often be a marker of poor myocardial function and thus poor prognosis.

It **must not** be deduced from these analyses that better blood pressure control, whether by means of better dialysis, salt, water control, or use of drugs, would not improve long term survival of dialysis patients.