A prospective multicentre study of the role of anaemia as a risk factor in haemodialysis patients: the MAR Study

José Portolés1, Juan Manuel López-Gómez2 and Pedro Aljama3, on behalf of the MAR Study Group

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Abstract
Background. Retrospective studies have shown hospitalization and mortality rates during haemodialysis (HD) to be associated with anaemia.

Methods. The prospective, multicentre Morbidity-and-mortality Anaemia Renal (MAR) study was designed to establish the burden of anaemia by controlling for other risk factors. Charlson index was used for comorbid adjustment. Finally, 1428 patients from 119 centres (60% men, aged 64.4 years, time on HD 15.3 months, Charlson comorbidity index 6.5 ± 2.3) completed follow-up. They had hypertension (75.8%), diabetes mellitus (25.9%), heart failure (13.9%) and coronary disease (16.7%). Of the total patients, 94.8% were receiving erythropoietin (111.6 ± 70.6 U/kg/week) and 76.7% i.v. iron, and haemoglobin (Hb) at inclusion was 11.7 ± 1.5 g/dl.

Results. Hospitalization rate was 1.1 admissions/patient/year. Yearly mortality was 12% [35% cardiovascular (CV)]. The relative risk and confidence interval (CI) for hospitalization and death were 0.86 (0.81–0.91) and 0.82 (0.73–0.91), respectively, per 1 g/dl increase in initial Hb after adjustment for comorbidity, vintage, aetiology, access type, albumin and Kt/V.

The probability of remaining free from hospitalization (CI) was 0.34 (0.27–0.41) for initial Hb <10 g/dl, 0.47 (0.41–0.53) for Hb 10–11 g/dl, 0.54 (0.49–0.59) for Hb 11–12 g/dl, and 0.63 (0.59–0.67) for Hb >12 g/dl. Same analysis for patient survival was 0.77 (0.71–0.83) for Hb <10 g/dl vs 0.82 (0.77–0.87) for Hb 10–11 vs 0.89 (0.86–0.92) for Hb 11–12 vs 0.92 (0.90–0.94) for Hb >12 g/dl, P < 0.001. The Cox regression model for hospitalization-free survival included the risk factors initial Hb (relative risk 0.86 per 1 g/dl increase, P < 0.001) Charlson, albumin and prior CV event.

Conclusion. Hb level predicted 1-year-survival and hospitalization. This effect persisted after adjustment for comorbidity and other prognostic factors.

Keywords: anaemia; chronic renal failure; erythropoietin; haemodialysis; hospitalization-free survival; survival analysis

Introduction
High mortality among patients on haemodialysis (HD) is the result of multiple factors that make it difficult to establish the specific contribution of each. Most patients begin HD at an advanced age and have a history of hypertension, left ventricular hypertrophy (LVH), diabetes, dyslipidaemia or cardiovascular (CV) events [1,2]. Interventions for these risk factors have failed to diminish CV mortality in patients on HD to the same extent as in the general population [2]. Other emerging risk factors such as chronic inflammatory status, oxidative stress or hyperparathyroidism are especially linked to chronic kidney disease (CKD). This disorder worsens the prognosis for CV events [3,4]. It is therefore unsurprising that almost half of the deaths during HD are of CV origin [5,6,7].

Anaemia can be considered a new CV risk factor that acts via ventricular overloading and LVH. In fact, it has been shown that the appearance and progression of LVH are associated with severity of anaemia, with an increased risk of death, and that ventricular damage can regress with appropriate control of blood pressure and anaemia. Moreover, data from kidney disease registries and retrospective studies have shown that in patients who died, anaemia was not as well-controlled as in patients who survived and found also an association between hospitalization and degree of control of anaemia [8–10]. The DOPPS project recorded patterns of HD management and clinical course and led to similar conclusions [11].

A number of expert committees have called for well-designed prospective studies aimed at identifying the

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independent role of anaemia in morbidity and mortality [12–14]. In response to these proposals, we designed the Morbidity-and-mortality Anaemia Renal (MAR) study in 2000.

Subjects and methods

Study design

This prospective, observational, multicentre cohort study aimed to establish the role of anaemia as a risk factor for overall and CV morbidity and mortality [15]. Our ultimate aims were to assess the specific burden of anaemia separately and to provide new evidence for the role of anaemia as a CV risk marker per se.

The study is based on a representative sample of patients with CKD of any cause who were on HD. The reference population consisted of prevalent patients on HD who were at least 18 years old at the time of the study, who had started treatment between January 1999 and March 2001, and who had not undergone kidney transplantation. The recruitment period lasted 4 months from March 2001 to July 2001, and results are presented here for the first year of follow-up. Although study was partially supported by Johnson & Johnson, patients may be under erythropoietin (Epo) treatment or not. Participating physicians were urged to follow the recommendations of the European Best Practice Guidelines (EBPG) for the management of anaemia in patients with CKD [16].

Information was recorded by nephrologists in specially designed case report form notebooks. Researchers entered information on demographic characteristics, sex, age at inclusion, transplant candidate status, employment status, initial cause of CKD and date of diagnosis, concomitant conditions, treatment parameters and results with dialysis, and time-averaged concentration (TAC) of urea [18]. The clinical data recorded were dialysis parameters (Kt/V Daugirdas), normalized protein catabolic rate (nPCR), and time-averaged concentration (TAC) of urea [18]. The biological parameters were anaemia treatment protocol, use of antihypertensive medication, presence of hyperlipidaemia, CV and non-CV events, hospitalizations, kidney transplantation and death when it occurred.

Fulfilment of the clinical and treatment goals was evaluated on the basis of the following guidelines: EBPG for the management of anaemia [16], NKF K/DOQI clinical practice guidelines for managing dyslipidaemias in CKD [19], NKF K/DOQI clinical practice guidelines for HD adequacy [18], EDTA guidelines for the control of hyperparathyroidism [20], and the hypertension target based on recommendations in the EDTA guidelines for pre-dialysis values (140/90 mmHg) [13].

Sample characteristics

Reference population was prevalent Spanish patients on HD at the end of 2000. We estimated the population size from data of 1998 renal registry plus an increment based on mean of annual increase of previous years. Estimation of number of events was obtained from mortality rates of 1998 renal registry [21]. Sampling process was a two-stage cluster sampling with stratification of first-stage sampling units (centres). Stratification criteria were centre size measured as number of prevalent patients. We used proportional allocation by strata. In each stratum, we selected centres with probabilities proportional to size and patients in each centre with equal probabilities. Allocation by centre was constant in each stratum (range 10–20). Finally, we used a simple random sampling in each centre to select patients among those who start HD between January 1999 and March 2001 (see inclusion criteria). So, we have a self-weighted sample in the sense of all patients had the same probability to be included.

A total of 119 centres participated (65 hospital units and 54 dialysis centres), all of them within the public health financial system.

The initial sample was 1710 cases which represent a sampling fraction more than 8% of the prevalent patients on HD at the end of 2000, and has been described in detail elsewhere [15]. Finally, 1428 completed follow-up (753 treated at hospital HD units and 675 treated at dialysis centres). Mean age was 64.4 ± 13.5 years, and men predominated (60.1%, Table 1). Mean time on HD was 15.3 ± 7 months at the start of the study.

The main causes of CKD were diabetes mellitus (22.1%), glomerular disease (15.8%), ischaemic nephropathy (13%), interstitial nephropathy (10.3%) and polycystic kidney disease (8.8%), with no cause determined in 21.9% of the patients.

The most relevant concomitant conditions at the start of the study were: hypertension (75.8% of the patients), coronary artery disease (16.7%), heart failure (13.9%), arrhythmia (11.6%), stroke (1.7%), peripheral artery disease (5.5%), dyslipidaemia (34.1%), 69.5% of them receiving treatment, type II diabetes mellitus (21.5%), type I diabetes mellitus (4.4%) and chronic obstructive lung disease (10%). Mean Charlson comorbidity index was 6.53 ± 2.3. Slightly more than one-third of the patients (36.7%) were on the waiting list for transplantation (indirect comorbidity index).

At the time of inclusion, 9.9% of the patients were receiving dialysis by catheter. 80.7% with native arteriovenous fistula (AVF) and 9.4% with a synthetic graft (PTFE-Gore®). The patients received three weekly sessions of conventional HD for a mean time of 11.1 h per week, 39.8% with high-permeability biocompatible filters (UF coefficient >20 ml/min/mmHg). At inclusion, 84.6% of the patients had a Kt/V of >1.3 and 76.5% had a nPCR >1 g/kg/day.

Management of anaemia

At the time of inclusion mean Hb value was 11.6 ± 1.5 g/dl (68.8% with Hb >11 g/dl), mean ferritin level was 377.6 ± 305.5 ng/ml (66.5% with ferritin >100 ng/ml) and mean transferrin saturation index (TSI) was 29.4 ± 12.5%.
Characteristics of the sample and comparison by subgroup according to outcome (died vs survived and hospitalized vs not hospitalized)

<table>
<thead>
<tr>
<th></th>
<th>Died (n = 172)</th>
<th>Survived (n = 1256)</th>
<th>RR (95% CI)</th>
<th>Hospitalized (n = 643)</th>
<th>Not hospitalized (n = 785)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70.9 (9.7)</td>
<td>63.7 (13.7)</td>
<td>*</td>
<td>66.1 (12.6)</td>
<td>63.3 (14.1)</td>
<td>*</td>
</tr>
<tr>
<td>Women (%)</td>
<td>45.9</td>
<td>49</td>
<td>1.3 (0.9–1.8)</td>
<td>43.4</td>
<td>36.9</td>
<td>1.3 (1.0–1.6)</td>
</tr>
<tr>
<td>Months on dialysis</td>
<td>15.7 (7.1)</td>
<td>15.3 (7.0)</td>
<td>NS</td>
<td>15.8 (7.0)</td>
<td>15.6 (7.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Out transplant list (%)</td>
<td>89.0</td>
<td>50.5</td>
<td>5.2 (3.2–8.7)</td>
<td>70.1</td>
<td>58.9</td>
<td>1.6 (1.3–2.0)</td>
</tr>
<tr>
<td>Charlson index (%)</td>
<td>8.0 (2.2)</td>
<td>6.4 (2.2)</td>
<td>7.1 (2.1)</td>
<td>6.2 (2.1)</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Diabetes CKD (%)</td>
<td>27.9</td>
<td>21.3</td>
<td>1.5 (1–2.0)</td>
<td>25.5</td>
<td>19.2</td>
<td>1.4 (1.1–1.8)</td>
</tr>
<tr>
<td>With catheter (%)</td>
<td>16.5</td>
<td>7.6</td>
<td>2.4 (1.5–3.8)</td>
<td>12</td>
<td>5.9</td>
<td>2.2 (1.5–3.2)</td>
</tr>
<tr>
<td>With initial albumin &lt;35 g/l (%)</td>
<td>41.2</td>
<td>16.5</td>
<td>3.5 (2.5–5.0)</td>
<td>25.5</td>
<td>14.5</td>
<td>2.0 (1.5–2.6)</td>
</tr>
<tr>
<td>Kt/V &lt; 1.3 1st month (%)</td>
<td>17.5</td>
<td>15.6</td>
<td>1.0 (0.7–1.8)</td>
<td>18.7</td>
<td>13.4</td>
<td>1.5 (1.1–2.0)</td>
</tr>
<tr>
<td>Met all HD targets (%)</td>
<td>67.7</td>
<td>66.1</td>
<td>4.9 (3.5–6.9)</td>
<td>32.4</td>
<td>12.5</td>
<td>3.1 (2.3–4.0)</td>
</tr>
<tr>
<td>With final albumin &lt;35 g/l (%)</td>
<td>50.3</td>
<td>17.1</td>
<td>2.3 (1.6–3.3)</td>
<td>25.8</td>
<td>13.1</td>
<td>2.3 (1.7–3.0)</td>
</tr>
<tr>
<td>With CV event (%)</td>
<td>32</td>
<td>17</td>
<td>1.4 (0.8–2.3)</td>
<td>15.4</td>
<td>4.6</td>
<td>3.8 (2.5–5.6)</td>
</tr>
<tr>
<td>With access-related event (%)</td>
<td>9.3</td>
<td>4.9</td>
<td>1.9 (1.1–3.5)</td>
<td>8.7</td>
<td>2.8</td>
<td>3.3 (2.0–5.5)</td>
</tr>
</tbody>
</table>

Statistical analysis according to variables: The student's t-test and Mann-Whitney U-test were used according to the nature of variables (mean and SD in parentheses). The relative risk (RR) and 95% confidence interval (CI) were used for categorical variables (column% referred to every subgroup).

*Student’s t-test P < 0.001; **Mann-Whitney U-test, P < 0.001.

(TSI >20% in 66.5%). Few patients (8.0%) had needed transfusions during the four preceding months. At the start of the study 94.8% of the patients were receiving treatment with Epo at a mean dose of 111.6 U/kg per week. The route of administration was subcutaneous in 76.8%, with a mean of 2.2 injections per week, and the most frequent dosage protocol was 3 doses/week (48.2%). Slightly more than one-fourth of the patients (28.7%) had started Epo treatment before HD (8.5 ± 9.6 weeks), 42.7% started Epo and HD at the same time, and 28.6% started Epo after they had started HD. Most patients (80.8%) were receiving iron supplements (79.2% intravenous). Table 1 shows other relevant information regarding how anaemia was managed in our patients at the beginning and at the end of the study period.

Statistical analysis

Comparison between groups (for example death vs alive patients at the end of the study) was performed using based chi-squared test for categorical values and based Student’s t-test for continuous variables. For the analysis of mortality (time to death from the start of the study) and morbidity (time to hospitalization) we used the Kaplan–Meier model to estimate conditional survival probabilities. Cox regression analysis was used to identify variables that predicted mortality and morbidity. The models were fitted introducing haemoglobin (Hb) level as a continuous or a categorical variable (<10, 10.0–10.99, 11.0–11.99 and ≥12 g/dl). The initial Hb was used as the main variable and in some models was corrected by time-dependent-Hb [Hb(t)]. The Hb(t) was the Hb value in the 3-month period previous to the event, and the last Hb value for those without any event. Except for Hb level, all models were fitted by including as possible predictive variables of comorbidity and mortality the following: age, sex, time on HD, cause of CKD, previous CV morbidity, previous vascular access events, non-CV comorbidity (acute bleeding, blood transfusion, acute infection, surgery, other), type of access, albumin level and compliance with the HD targets (Kt/V, nPCR, TAC urea).

All statistical analyses were done with SPSS software (version 11.5).

Results

Mortality

Cumulative mortality was 12% for the year-long study period. The main causes of death were CV (35.2%), stroke (11.7%), sudden death (9.4%), infectious processes (14.8%), gastrointestinal disease (4.5%), liver disease (2.3%), interruption of treatment (3.9%) and other causes (18.2%). For the purposes of subsequent analyses the cause of death was classified as CV (56.3%) or non-CV (43.7%). Global 1-year probability of survival according to the Kaplan–Meier analysis was 0.87 [95% CI (0.85–0.89)].

A comparison of patients who died vs those who survived showed that anaemia was more severe in the former group, and that these patients were older, had greater comorbidity and lower albumin levels (Tables 1 and 2).

Figure 1 shows the results of the Kaplan–Meier analysis with stratification by Hb level at the start of the study. The probabilities of 1-year survival were 0.77 (CI 0.71–0.83) for initial Hb <10 g/dl, vs 0.82 (0.77–0.87) for Hb 10–11 vs 0.89 (0.86–0.92) for Hb 11–12 vs 0.92 (0.90–0.94) for Hb >12 g/dl. Survival analyses yielded a relative risk (OR) of death of 0.76 per 1 g/dl increase in Hb, with a CI of (0.69–0.84) (P < 0.001). In the stratified analysis the OR with respect to the reference category (Hb 11–12 g/dl) was 2.27 (CI 1.5–3.52) for Hb <10 g/dl, 1.72 (1.12–2.65) for Hb 10–11 g/dl, and 0.72 (0.47–1.10) for Hb >12. The OR adjusted for sex, age, transplantation waiting list, time on HD, cause of CKD, type of access,
comorbidity, albumin level, Kt/V value and fulfilment of HD targets are shown in Figure 2.

The multivariate regression model of survival with the Cox formula included the following variables (OR): per 1 g/dl increase in initial Hb, OR 0.82 (CI 0.73–0.91) ($P < 0.001$); presence of diabetes mellitus, OR 1.24 ($P < 0.04$); previous CV event, OR 1.91 ($P < 0.001$); initial albumin < 35 g/l, OR 2.45 ($P < 0.001$); per year increase in age, OR 1.03 ($P < 0.01$). The model based on Charlson index as the only comorbidity parameter included age and diabetes mellitus, and the OR for initial Hb was 0.80 per 1 g/dl increase ($P < 0.001$), a value close to that obtained with the previous model.

Initial Hb was significant in the model that included changes in Hb($t$) with reference to Hb during the 3 months prior to the event. In this case OR for initial Hb was 0.86 (0.76–0.96) ($P < 0.02$) and the OR for Hb($t$) was 0.85 (0.75–0.95) ($P < 0.005$).

Because of the low number of events, the survival analysis for death from CV causes lacked statistical power.

Morbidity

Almost half of the patients (45.0%) were hospitalized at least once. The final rate of hospitalization in the sample was 1.1 per patient per year, and mean length of stay was 12.6 days per patient per year at risk. Of the patients who were hospitalized, 23.2% had two stays, 10.1% had three stays, and 10.7% had more than three stays. About one-third of all hospitalizations (32.1%) were for CV causes and 15.7% were for problems with vascular access. The most relevant causes of hospitalization among CV causes were angina (19.7%), acute myocardial infarction (5.2%), heart failure (10%), peripheral artery disease (14.7%), stroke

### Table 2. Relevant parameters in the management of anaemia at the start and the end of the study period

<table>
<thead>
<tr>
<th></th>
<th>Died ($n = 172$)</th>
<th>Survived ($n = 1256$)</th>
<th>Hospitalized ($n = 643$)</th>
<th>Not hospitalized ($n = 785$)</th>
<th>Hospitalized for CV event ($n = 219$)</th>
<th>Not hospitalized for CV event ($n = 1209$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial mean Hb</td>
<td>11.1 (1.5)*</td>
<td>11.7 (1.4)*</td>
<td>11.4 (1.5)*</td>
<td>11.9 (1.3)</td>
<td>11.3 (1.5)*</td>
<td>11.7 (1.4)*</td>
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<tr>
<td>Hb intervals</td>
<td></td>
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<tr>
<td>&lt;10 g/dl</td>
<td>26.2</td>
<td>12.4</td>
<td>20.2</td>
<td>8.9</td>
<td>22.8</td>
<td>12.4</td>
</tr>
<tr>
<td>10.1–11 g/dl</td>
<td>25</td>
<td>16.9</td>
<td>20.2</td>
<td>15.9</td>
<td>17.8</td>
<td>17.9</td>
</tr>
<tr>
<td>11.1–12 g/dl</td>
<td>24.4</td>
<td>29.2</td>
<td>28.2</td>
<td>29</td>
<td>31.5</td>
<td>28.1</td>
</tr>
<tr>
<td>&gt;12 g/dl</td>
<td>24.4</td>
<td>93.9</td>
<td>94.2</td>
<td>46.1</td>
<td>27.9</td>
<td>41.6</td>
</tr>
<tr>
<td>Receiving Epo (%)</td>
<td>97.7***</td>
<td>90.0</td>
<td>94.5</td>
<td>95.4</td>
<td>94.2</td>
<td></td>
</tr>
<tr>
<td>Dose U/kg/week</td>
<td>139.7 (81.2)**</td>
<td>110.0 (69.9)</td>
<td>126.4 (74.0)*</td>
<td>103.4 (68.7)</td>
<td>136.6 (78.4)*</td>
<td>109.5 (70.0)</td>
</tr>
<tr>
<td>Final mean Hb</td>
<td>11.0 (1.6)*</td>
<td>11.8 (1.4)*</td>
<td>11.5 (1.5)*</td>
<td>11.9 (1.2)*</td>
<td>11.2 (1.5)*</td>
<td>11.8 (1.4)*</td>
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<tr>
<td>Hb intervals:</td>
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<tr>
<td>&lt;10 g/dl</td>
<td>26.2</td>
<td>10.6</td>
<td>17.4</td>
<td>7</td>
<td>22.8</td>
<td>10.6</td>
</tr>
<tr>
<td>10.1–11 g/dl</td>
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<td>21.8</td>
<td>15.3</td>
<td>24.7</td>
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</tr>
<tr>
<td>11.1–12 g/dl</td>
<td>21.5</td>
<td>29.1</td>
<td>25.8</td>
<td>32.1</td>
<td>24.2</td>
<td>28.8</td>
</tr>
<tr>
<td>&gt;12 g/dl</td>
<td>27.9</td>
<td>43.2</td>
<td>35</td>
<td>45.6</td>
<td>28.3</td>
<td>43.3</td>
</tr>
</tbody>
</table>

Comparison between patients who died and who survived, in patients who were and were not hospitalized, and patients who were and were not hospitalized for a cardiovascular event. Statistical significance according to methods: Student’s $t$-test for quantitative variables (mean followed by standard deviation in parentheses) and the chi-squared test for categorical variables.

* $P < 0.001$; ** $P < 0.05$. 

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**Fig. 1.** Time to first hospitalization (A) and survival of patient (Kaplan-Maier) (B) stratified by Hb subgroup. The probability of hospitalization-free survival after 1 year in each subgroup by increasing Hb concentration was 0.33, 0.47, 0.54 and 0.63. The probability of survival after 1 year in each subgroup by increasing Hb concentration was 0.76, 0.82, 0.89 and 0.92.
(13.8%), arrhythmia (12.2%), peripheral vascular disease (20%) and hypertension crisis (2.5%). The likelihood of remaining free from hospitalization estimated with the Kaplan–Meier formula was 0.53 CI (0.50–0.56).

In general, comparison of the patients who were hospitalized vs those who were not showed that anaemia was worse in the former group, the proportion of men was larger, more patients had diabetes, and nutritional and dialysis parameters were less favourable (Table 1). The results of the Kaplan–Meier analysis stratified by initial Hb level are shown in Figure 1. The probability of remaining free from hospitalization after 1 year was 0.34 (CI 0.27–0.41) for initial Hb <10 g/dl, 0.47 (0.41–0.53) for Hb 10–11 g/dl, 0.54 (0.49–0.59) for Hb 11–12 g/dl, and 0.63 (0.59–0.67) for Hb >12 g/dl. Survival analysis for time to first hospitalization yielded a risk of hospitalization of 0.81 per 1 g/dl increase in Hb (CI 0.77–0.86). In the stratified analysis the OR of hospitalization with respect to the reference category (Hb 11–12 g/dl) was 1.75 (1.39–2.19) for Hb <10 g/dl, 1.23 (0.99–1.54) for Hb 10–11 g/dl, and 0.77 (0.63–0.94) for Hb >12. Figure 2 shows the results obtained when the OR were adjusted for sex, age, inclusion in the waiting list for transplantation, time on HD, cause of CKD, type of access, comorbidity, albumin level, Kt/V and dialysis targets.

The model for survival (time to first hospitalization) obtained with Cox regression analysis included the variables (and OR with 95% CI): increase in initial Hb [OR 0.86 (CI 0.81–0.91), P < 0.001], diabetes mellitus (OR 1.24, P < 0.04), previous CV event (OR 1.65, P < 0.001), previous non-CV event (OR 1.92, P < 0.003), initial albumin level <35 g/l (OR 1.47, P < 0.001), and failure to meet Kt/V targets (OR 1.27, P = 0.03). When the Charlson index was used as the only comorbidity parameter, the OR for initial Hb was 0.86 per 1 g/dl increase (P < 0.001). The model also included albumin level <35 g/l (OR 1.28, P < 0.04), point increase in the Charlson index (OR 1.08, P < 0.002), and previous CV event (OR 1.63, P < 0.001).

Initial Hb remained significant in the model that included changes in Hb(t) with reference to Hb during the 3 months prior to the event. In this model the OR for anaemia was between that found for initial Hb [0.89, 95% CI 0.83–0.95, P < 0.001] and Hb(t) [0.9 (0.85–0.95), P < 0.01].

When hospitalizations for CV causes were analysed separately, anaemia was found to be less well-controlled in patients who were hospitalized (Table 2). The reduction in risk per gram increase in Hb was 0.86 CI (0.81–0.91) after adjustment for the remaining factors. The regression model for hospitalization due to CV causes included the variables initial Hb 0.84 (CI 0.75–0.94) per g/dl increase in Hb (P < 0.01), Charlson index (1.17 per point increase, P < 0.001), failure to meet HD targets (1.76, P < 0.01), and previous CV event (3.81, P < 0.01).

Safety considerations

According to the study protocol, the investigators were required to report adverse reactions to Epo. No such reactions were reported during the study period. At the end of the study, the case report forms were collected and analysed retrospectively to identify possible adverse events. The adverse events identified did not modify the risk–benefit relationship established under the current conditions of authorized use of Epo.

Discussion

To our knowledge, this is the first prospective study designed for the main purpose of analysing the relationship between anaemia and morbidity or mortality. In overall terms, the data we report here document the role of anaemia as a risk marker for the events we studied (hospitalization or death), which was maintained after adjustment for other risk factors.
In 1999, the Medicare Registry reported that the risk of death decreased steadily as control of anaemia improved, but they did not present data on comorbidity or other risk factors [7]. Other retrospective studies in Europe and the USA have also found an association between death or hospitalization and degree of control of anaemia [9,11,22].

However, no studies are available for the Spanish population, and the findings of studies from other settings cannot readily be extrapolated, because of differences between the study populations. In fact, CV risk, comorbidity factors, vascular access policies and HD practices differ, and these differences may account for the variability in mortality [7,21].

Our study analysed a representative sample of prevalent patients on HD for slightly more than 1 year. The design made it possible to reduce the recruitment period (which would normally be longer than 1 year for a sample of these characteristics) and made follow-up easier. This sample was intended to reflect habitual experiences in dialysis units in Spain, but we cannot extrapolate our results to an incident population on HD. The mortality rates we found were similar to those in the Spanish national registry and somewhat lower than in the incident Spanish sample included in the DOPPS study [11,21].

The observational design used here does not weaken the role of anaemia as a marker of CV risk, hospitalization and risk of death. Our sample represents a prevalent population of HD patients who are generally receiving appropriate treatment. However, the targets were not always achieved for various reasons, and this made it possible to classify patients according to the outcomes.

We found a linear reduction in risk of death for Hb values of <10, 10–11 and 11–12 g/dl. However, although this trend was maintained in the subgroup of patients with Hb >12 g/dl, the reduction in risk of death failed to reach statistical significance in comparison with the reference category (11–12 g/dl). As noted subsequently, the rate of hospitalization in this subgroup was significantly lower than in other Hb subgroups. This discrepancy may have resulted from the fact that normalization of Hb values (>12 vs 11–12 g/dl) had no effect on mortality, or the fact that the number of fatal events during the study period was too low to detect any effect (12% deaths vs 42% hospitalizations). The former hypothesis is supported by other highly powered retrospective studies that also failed to find improvements in the prognosis when Hb was >13 g/dl [9] or haematocrit was >36% [22].

The results recently published in the Euro-DOPPS study found a significant difference in risk only in patients with Hb <10 g/dl, and significance was not maintained in country-specific analyses [11]. Accordingly, ours is the first prospective study to show a reduction in the risk of death for increases in Hb level up to 12 g/dl. The multivariate models obtained here were stable after the introduction of the Hb(t) variable, a finding that further supports the importance of initial Hb as a prognostic factor. In our study, the effect was maintained after adjustment for all comorbidity variables (such as the Charlson index) and risk factors described. Diabetes mellitus and age stood out as the most relevant comorbidity factors both individually and jointly in the Charlson index, along with previous CV event. In fact, the OR for anaemia was similar in both models proposed above. Inadequate control of anaemia is associated with multiple factors such as poor dialysis, poor nutrition, comorbidity, bleeding and tumoural disease. We emphasize that the variable analysed here is the anaemia degree, not the use or type of treatment with erythropoiesis-stimulating factors. Interestingly, we have found that patients with the lowest Hb level and worst prognosis present higher requirements of Epo. This may be due not only to lower or unstable Hb levels, but also to some degree of resistance. Nevertheless, the effect of basal Hb in prognosis persisted after adjustment for a lot of variables (including Epo doses, comorbidity and albumin).

The univariate analysis identified other factors associated with mortality, such as malnutrition-inflammation, inadequate dialysis, age and comorbidity. Because many of these factors are associated in any given patient, the multivariate model identifies those that explain the greatest proportion of variability and disregards the rest. Our data support earlier experiences regarding the role of reversible risk factors such as low albumin level, inadequate dialysis and anaemia. The final multivariate model identified two areas where improvement could potentially reduce risk: more effective correction of anaemia in patients on HD. The rate of hospitalization in this study was somewhat lower than in the Spanish sample from the DOPPS study, and clearly lower than in the USRDS registry [7,21]. Differences in comorbidity and treatment protocols might account for this finding; unfortunately, no large-scale studies of hospitalization rates in the Spanish population are available for comparison. Of note was the finding that fewer than 16% of all hospitalizations were caused primarily by complications with vascular access; this represented a rate of 0.18 hospitalizations per year on HD, a lower rate than in the USDRS registry [7]. Differences in the distribution of the types of access, with more than 80% consisting of native AVF in the present study as compared with the predominance of grafts in the USRDS sample, might account for the discrepant results [7,23].

In our analysis of hospitalization, the multivariate analysis again suggested the importance of anaemia, and the reduction in risk was maintained at Hb values >12 g/dl. This novel finding has not previously been reported in any prospective study in Spain. In the European arm of the DOPPS study, the effect of anaemia on hospitalization rates was significant only for lower Hb values despite the adequate statistical power of this analysis [11]. In the present study albumin was found to play two roles—as an indicator of malnutrition and inflammation—although it was
not possible to distinguish between these two signals. Its inclusion in the final model ensures appropriate correction for these effects. Unfortunately, data for C-reactive protein concentrations were not available, as in 2000 this parameter had not yet been established as a prognostic indicator.

The role of anaemia as a CV risk factor has been previously documented. LVH is a consequence of hypertension and CKD, and is also an independent risk factor for mortality. In both advanced CKD and HD the appearance and progression of LVH has been related to hypertension and anaemia [24,25]. Preliminary evidence suggests that the control of anaemia and blood pressure favour the regression of LVH in patients with CKD stages 4–5, although no controlled study has confirmed it [24–27]. It was shown that patients in whom LVH regressed after blood pressure and anaemia were controlled had a better prognosis [28,29].

We found that the anaemia predicted the likelihood of non-fatal CV events during a 1-year study period, and therefore constituted a risk marker that is potentially modifiable in the short term. However, as expected, our analysis attributed the greatest influence to previous CV event.

In conclusion, anaemia is an independent factor that can predict survival and hospitalization after adjustment for comorbidity, time on HD, cause of CKD, type of HD access, albumin level and Kt/V. The degree of control of anaemia in a prevalent population can therefore condition 1-year overall and CV morbidity and mortality. Thus our findings add to the evidence of the role of anaemia as a marker of risk. This effect is supported by the pathophysiological relationship between anaemia and myocardial functioning and by evidence from the present prospective study, in which other risk factors were controlled for. However, a definitive analysis of causality resulting from anaemia must await the results of interventional studies with different target Hb values and intention-to-treat analysis. We do not know whether additional evidence will be forthcoming from future studies, but solid evidence meanwhile continues to accumulate for the burden anaemia represents as a risk factor, and specifically as a CV risk factor.

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