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*Original Article*

# Anaemia in haemodialysis patients of five European countries: association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS)

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## Abstract

**Background.** The Dialysis Outcomes and Practice Patterns Study (DOPPS) is a prospective, observational study based on data collected from nationally representative samples of haemodialysis facilities. The burden of anaemia in haemodialysis patients is substantial, leading to considerable morbidity, mortality and reduced quality of life. This study examines anaemia management and outcomes based on data from five European countries participating in the DOPPS: France, Germany, Italy, Spain and the UK.

**Methods.** Baseline data on demographics, co-morbidities and anaemia management in 4591 haemodialysis patients from 101 nephrology facilities were collected in 1998–2000. Using multivariate Cox survival analyses to adjust for patient characteristics, relationships between haemoglobin concentration at study entry and rates of mortality and hospitalization were evaluated.

**Results.** For a year 2000 sample of prevalent patients on haemodialysis >180 days, mean haemoglobin concentration was 11.0 g/dl; 53% had a haemoglobin concentration ≥11 g/dl [1998–1999 = 44% ($P < 0.05$)]. In 2000, 84% of prevalent patients were prescribed recombinant human erythropoietin (rHuEpo). Higher haemoglobin concentrations were associated with decreased relative risk (RR) for mortality (RR = 0.95 for every 1 g/dl higher haemoglobin, $P = 0.03$) and hospitalization (RR = 0.96, $P = 0.02$). Patients with haemoglobin <10 g/dl were 29% more likely to be hospitalized than patients with haemoglobin 11–12 g/dl ($P < 0.001$).

**Conclusion.** Even after adjustment, lower haemoglobin concentrations were associated with higher morbidity and mortality in European haemodialysis patients. A trend to increased haemoglobin concentrations was observed following publication of the European Best Practice Guidelines (EBPG) on anaemia management for chronic kidney disease patients, but efforts must continue to achieve EBPG goals.

**Keywords:** anaemia; chronic kidney disease; morbidity; mortality; haemodialysis; rHuEpo

## Introduction

The Dialysis Outcomes and Practice Patterns Study (DOPPS) has been developed to provide data on current practice in haemodialysis management and to relate this to patient outcomes. The DOPPS is designed as a prospective, observational study of nationally representative samples of randomly selected haemodialysis facilities and patients [1]. The first phase of data collection in the DOPPS began in 1996 in the US, followed by the participation of France, Germany, Italy, Spain and the UK in 1998, and Japan in 1999. The DOPPS has used the same data collection instrument translated into the native language of each country to allow for direct comparison of haemodialysis practices across countries.

In recent decades, several important advances have been made in the treatment of end-stage renal disease

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(ESRD) [2], not least the management of anaemia associated with chronic kidney disease (CKD). The burden of anaemia in these patients is substantial, causing considerable morbidity and dramatically reducing their quality of life [3–6]. Until 15 years ago, the mainstay of treatment was blood transfusion, with all its associated risks. However, the management of renal anaemia has been transformed over the past decade by the introduction of recombinant human erythropoietin (rHuEpo). Over this period, rHuEpo has become accepted as an effective and well-tolerated treatment, and its clinical benefits in patients with CKD are well documented [7–16]. As a result of the introduction of rHuEpo into routine nephrology practice, guidelines have been developed for the treatment of anaemia for CKD patients. Contributions have included the European Renal Association's Best Practice Guidelines (EBPG) [17] and the Dialysis Outcomes Quality Initiative of the US National Kidney Foundation (NKF-DOQI) [18].

The present study investigated the level of anaemia in a representative cross-section of maintenance haemodialysis patients and correlations of anaemia with morbidity and mortality in five European countries. In addition, anaemia management treatment practices also are reported.

## Subjects and methods

### *Euro-DOPPS: facility participation*

Nationally representative samples of haemodialysis facilities were recruited for participation in the DOPPS from five European countries, with 21 facilities participating from Germany and 20 facilities each from France, Italy, Spain and the UK (total = 101 dialysis units, called Euro-DOPPS for purposes of this paper). Although the Euro-DOPPS countries do not represent all European haemodialysis practices, they account for ~84% of all haemodialysis patients in the European Union, according to the report of the European Renal Registry and National Registries for 1995 [19].

The facility selection protocol included the following key aspects. Facilities participating in the Euro-DOPPS were randomly selected from a list of all dialysis units within each country. Only facilities having more than 24 haemodialysis patients were eligible for study participation. These facilities typically serve ≥95% of all facility-based haemodialysis patients in each country. Selection was stratified such that facility samples provide proportional representation of the types of haemodialysis units and geographic regions within each country. Among randomly selected facilities, >90% agreed to participate. Data were collected from Euro-DOPPS dialysis units from May 1998 through to November 2000, with 98% of all participating dialysis units entering the DOPPS between May 1998 and February 1999. Additional details of the DOPPS data collection protocol and study design have been described previously [1].

### *Data source: patient samples used for analysis*

Limited data were collected from all haemodialysis patients ($n = 11\ 422$, census patients) >17 years of age, receiving chronic maintenance haemodialysis, haemodiafiltration or haemofiltration at each participating Euro-DOPPS dialysis unit during study participation from 1998 to 2000. From the list of census patients, a sample of patients was selected randomly at each DOPPS facility at the beginning of the study to achieve an average of 30 randomly selected patients per facility (range 20–40 patients, dependent on facility size; average facility size = 60 haemodialysis patients). For these random sample patients ($n = 4591$), detailed longitudinal data were collected, including patient demographics, over 65 indications of baseline co-morbidity, measures of socio-economic status, baseline and longitudinal laboratory data, vascular access use and procedures, hospitalization and outpatient events, characteristics of haemodialysis treatment, prescribed and delivered haemodialysis dose, medications, measures of anaemia and mineral metabolism management, residual renal function, patient quality of life assessments, primary causes of ESRD, modality history during ESRD and pre-ESRD care.

Informed patient consent was obtained, and consent rates approached or exceeded 90% in each country. To maintain an approximately constant random sample patient cohort over time, additional patients entering the unit since the time of the previous random selection were routinely randomly selected to replace sample patients who left the study for any reason (e.g. death, transfer to different facility, change in modality, transplant). The total number of random sample patients for whom data were collected in each country were France ($n = 981$), Germany ($n = 908$), Italy ($n = 869$), Spain ($n = 936$) and the UK ($n = 897$).

Analyses presented in this paper were based on either all patients in the random sample patient group or three sub-samples of the random sample patient group. (i) A point-prevalent (cross-sectional at one point in time) patient sample pertaining to random sample patients dialysing in Euro-DOPPS units on June 1, 2000 ($n = 2590$); this sample served to provide a recent estimate of anaemia management practices after publication of the EBPG on Anaemia Management in September 1999 [17]. (ii) A point-prevalent sample ($n = 2595$) of haemodialysis patients entering the Euro-DOPPS at the time of facility entry into the study (i.e. between May 1998 and April 1999). This 1998–1999 sample was used to indicate baseline characteristics of the patient population at the time of study entry and also to indicate anaemia management practices prior to publication of the EBPG for anaemia. (iii) An incident patient subgroup ($n = 1023$), consisting of random sample patients who received their first dialysis treatment as chronic ESRD patients within 10 days before study entry. The purpose of the incident patient subgroup was to study anaemia levels and rHuEpo therapy at the time patients first started dialysis and whether rHuEpo treatment was provided during the pre-ESRD period.

### *Measures of anaemia management*

The measures of anaemia management studied were based upon longitudinal collection of patient haemoglobin concentrations, type and amount of i.v. iron preparation administered, type, dose and route of rHuEpo administration, and whether rHuEpo was prescribed prior to starting dialysis. In addition, medical directors at 97 of the 101 Euro-DOPPS facilities provided information on dialysis unit policies

regarding whether a patient's haematocrit or haemoglobin level was required to fall below a predetermined threshold before rHuEpo therapy could be initiated at the unit.

### *Statistical analysis*

All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC, USA). Many of the statistical models that used patient haemoglobin concentrations were restricted to patients on haemodialysis for >180 days to allow a sufficient time for patient haemoglobin values to reflect haemodialysis treatment practices. For a similar reason, models examining rHuEpo use were restricted to patients on haemodialysis for >90 days. The time period of 180 days for haemoglobin analyses and 90 days for rHuEpo-use analyses were based on the time-trend results found for incident haemodialysis patients shown in Figure 4. In the case of mortality and hospitalization analyses, the main models used the patient haemoglobin value at study entry (i.e. baseline) without a restriction for the amount of time on dialysis. However, sensitivity analyses, limited to patients on haemodialysis for >180 days, also were performed for mortality and hospitalization, as indicated.

### *Unadjusted analyses*

Unadjusted mean, median or percentile values were calculated for the many different measures shown in the tables and figures. Mean or median values provided for All Euro-DOPPS are not weighted by the haemodialysis population of each country. Comparisons were made relative to specific haemoglobin concentrations in some cases to permit evaluation of how well anaemia management practices in year 2000 met certain goals recommended by the EBPG for anaemia management [17].

### *Adjusted analyses*

Logistic regression, mixed linear regression and Cox survival models were developed to examine the relationship between anaemia management and outcomes for haemodialysis patients, as well as factors associated with the level of achieved haemoglobin. All of these models were adjusted for age and gender, 14 classes of co-morbidity, country and facility clustering effects. Additional adjustments, if any, are indicated in the tables and figures. The 14 classes of co-morbidity included: coronary artery/cardiac disease, congestive heart failure, other cardiac disease, peripheral vascular disease, hypertension, cerebrovascular disease, diabetes mellitus, lung disease, dyspnoea, history of ever having cancer (active or inactive, excluding skin cancer), gastrointestinal bleeding in the 12 months prior to study entry, neurologic disease, psychiatric disease and recurrent skin disease (including gangrene).

### *Predictors of i.v. iron use, rHuEpo use and level of anaemia*

Logistic regression was used to examine the following outcomes: (i) odds of whether i.v. iron was prescribed (yes *vs* no) for prevalent haemodialysis patients; (ii) odds of rHuEpo being prescribed (yes *vs* no) for prevalent haemodialysis patients and during the pre-ESRD period for patients new to haemodialysis; and (iii) the likelihood of a patient having a low haemoglobin (≤10 g/dl) *vs* higher haemoglobin (≥11 g/dl) concentration in a prevalent haemodialysis patient sample; and (iv) the likelihood of a patient having a haemoglobin >11 g/dl (yes *vs* no) as a function of a dialysis unit initiating rHuEpo therapy at a higher (>10 g/dl) *vs* lower (<10 g/dl) haemoglobin threshold value.

Logistic regression analyses employed the GENMOD procedure (generalized linear model) of SAS with a binomial error distribution and logit link function. Facility clustering effects were modelled using an exchangeable correlation matrix.

### *Effect of patient characteristics and rHuEpo treatment practices on study population mean haemoglobin value*

Mixed linear regression models were used to analyse the effect of patient demographic characteristics, facility characteristics (e.g. i.v. iron use), route of rHuEpo administration and 14 classes of co-morbidity upon the observed mean haemoglobin value for the study population. Mixed linear regression models used the mixed linear regression procedure of SAS, with facility treated as a random effect to account for facility clustering.

### *Mortality and hospitalization analyses*

Cox regression analysis was used to model time to death (for mortality analyses) or time to first overnight hospital admission (for hospitalization analyses). Mortality and hospitalization models used either baseline haemoglobin as a continuous variable or categories of baseline haemoglobin (<10 g/dl, 10.0–10.99 g/dl, 11.0–11.99 g/dl, ≥12 g/dl). Models were adjusted for patient characteristics and other covariates, as indicated, and included all study patients participating in the Euro-DOPPS from 1998 to 2000. Observation time was censored either when a patient departed from the facility or at the last date of known follow-up, whichever was earliest.

Cox regression analyses employed the PHREG procedure (proportion hazards regression) of SAS, providing adjustments for standard error estimates based on the sandwich estimator [20] to account for facility clustering effects.

## Results

### *Baseline characteristics of prevalent and incident samples*

The baseline characteristics of prevalent and incident patient samples, by country, are shown in Tables 1 and 2. Substantial differences were seen among prevalent haemodialysis patients across the Euro-DOPPS countries regarding these selected patient characteristics. Mean age of prevalent patients ranged from 57.2 years in the UK to 61.5 years in Italy. Diabetes mellitus as a co-morbidity or cause of ESRD varied from 15% in Italy to 31% in Germany; coronary artery disease was more common among haemodialysis patients in Germany (44%) compared with the other four

**Table 1.** Prevalent haemodialysis patients: demographic characteristics and selected baseline co-morbidities, by Euro-DOPPS country

| | France ($n=545$) | Germany ($n=505$) | Italy ($n=561$) | Spain ($n=491$) | UK ($n=493$) | All Euro-DOPPS ($n=2595$) |
|---|---|---|---|---|---|---|
| Age, years[a] | 60.5 (16.0) | 60.4 (14.2) | 61.5[b] (13.3) | 61.2 (15.0) | 57.2[b] (17.3) | 60.2 (15.2) |
| Male gender, % | 56.5 | 58.2 | 56.7 | 56.6 | 60.4 | 57.6 |
| Body weight, kg[a] | 64.3[b] (14.9) | 70.6[b] (13.8) | 63.3[b] (13.6) | 62.9[b] (13.1) | 68.2[b] (15.7) | 65.8 (14.5) |
| Body mass index, kg/m$^{2a}$ | 23.5[b] (4.9) | 24.7[b] (4.4) | 23.5[b] (4.2) | 23.8 (4.3) | 24.5[b] (5.1) | 24.0 (4.6) |
| Diabetes mellitus, % (as primary cause of ESRD) | 10.9[b] | 25.3[b] | 10.9[b] | 18.7[b] | 12.8[b] | 15.6 |
| Diabetes mellitus, % | 17.8 | 30.7[b] | 15.0[b] | 21.4 | 16.4[b] | 20.1 |
| Peripheral vascular disease, % | 25.3 | 25.5 | 18.5[b] | 24.4 | 18.7[b] | 22.5 |
| History congestive heart failure, % | 27.9 | 22.8 | 12.3[b] | 30.5[b] | 32.9[b] | 25.0 |
| History coronary artery disease, % | 27.7 | 44.2[b] | 21.7[b] | 24.0[b] | 30.4 | 29.4 |
| Time on dialysis, years[a] | 6.3[b] (6.9) | 4.1[b] (4.6) | 5.8[b] (6.0) | 4.8 (5.2) | 4.2[b] (4.5) | 5.1 (5.6) |

Prevalent sample of random sample patients at time of facility entry into the DOPPS.
[a]Mean (±SD); [b]$P < 0.05$ when compared with the All Euro-DOPPS mean. Body weight pertains to prescribed patient dry weight.

**Table 2.** Incident haemodialysis patients: demographic characteristics and selected baseline co-morbidities, by Euro-DOPPS country

| | France ($n=235$) | Germany ($n=184$) | Italy ($n=190$) | Spain ($n=259$) | UK ($n=155$) | All Euro-DOPPS ($n=1023$) |
|---|---|---|---|---|---|---|
| Age, years[a] | 60.4[b] (16.4) | 60.6 (13.5) | 67.6[b] (12.4) | 62.0 (13.4) | 60.1[b] (16.3) | 62.1 (14.7) |
| Male gender, % | 63.4 | 65.8 | 60.5 | 59.1 | 62.6 | 62.1 |
| Body weight, kg[a] | 67.8 (15.2) | 77.1[b] (15.9) | 64.4[b] (13.2) | 68.1 (12.3) | 73.6 (17.4) | 69.6 (15.1) |
| Body mass index, kg/m$^{2a}$ | 24.9[b] (5.1) | 26.6[b] (4.9) | 23.9[b] (4.3) | 25.1 (4.3) | 26.8[b] (6.6) | 25.3 (5.0) |
| Diabetes mellitus, % (as primary cause of ESRD) | 17.0[b] | 29.3[b] | 23.3 | 21.2 | 23.2 | 22.4 |
| Diabetes mellitus, % | 24.3 | 39.1[b] | 27.9 | 23.9[b] | 29.7 | 28.3 |
| Peripheral vascular disease, % | 22.6 | 26.1[b] | 16.8 | 13.9[b] | 22.6 | 19.9 |
| History congestive heart failure, % | 28.1 | 17.9[b] | 22.6 | 21.2 | 34.2[b] | 24.4 |
| History coronary artery disease, % | 25.1 | 41.8[b] | 17.4[b] | 19.3[b] | 32.2 | 26.3 |

Incident patients defined as study patients entering the DOPPS within 10 days of first ever chronic dialysis treatment.
[a]Mean (± SD). [b]$P < 0.05$ when compared with the All Euro-DOPPS mean. Body weight pertains to prescribed patient dry weight.

Euro-DOPPS countries (22–30%). The mean time on dialysis ranged from 4.1 years in Germany to 6.3 years in France. Similarly, there were also a number of differences across countries for incident haemodialysis patients, who were defined as patients entering the DOPPS within 10 days of their first chronic dialysis treatment. The percentage of some co-morbidities differed substantially between incident and prevalent haemodialysis patients. As expected, the percentage of diabetes in all five Euro-DOPPS countries was higher among incident haemodialysis patients compared with prevalent patients, likely because of the higher death rate known for diabetic compared with non-diabetic haemodialysis patients. Although the percentage of incident patients with congestive heart failure was similar in Italy, Spain and Germany, the percentage of Italian haemodialysis patients with congestive heart failure was considerably lower for the prevalent haemodialysis patient sample. Furthermore, in Spain, the percentage of patients with peripheral vascular disease or congestive heart failure was substantially higher in prevalent patients compared with incident haemodialysis patients. To account for these country differences in patient mix, analyses were adjusted for these and other factors, as indicated. These adjustments also help to overcome difficulties associated with the possibility that, in some cases, anaemia may be a marker for co-morbidity, such that treatment of anaemia with rHuEpo in these cases may not necessarily yield the expected increase in haemoglobin or haematocrit.

### *Anaemia*

The median haemoglobin value for prevalent haemodialysis patients in year 2000 was found to vary widely across the five Euro-DOPPS countries, ranging from 10.8 in Italy to 11.6 in Spain (Figure 1). For all five Euro-DOPPS countries combined, the median haemoglobin increased from 10.8 g/dl for patients treated in year 1998–1999 to 11.1 g/dl in year 2000 (data not shown). Correspondingly, over this time period, the percentage of patients with a haemoglobin $<10$ g/dl decreased from 30 to 23%, while the percentage of patients with a haemoglobin $\geq 11$ g/dl increased from 46 to 53%. The mean haemoglobin concentration in year 2000 (11.0 g/dl) was significantly higher than that in year 1998–1999 (10.9 g/dl, $P < 0.01$).

### *Iron management*

Because of blood loss in the extracorporeal system during haemodialysis, effective iron management is

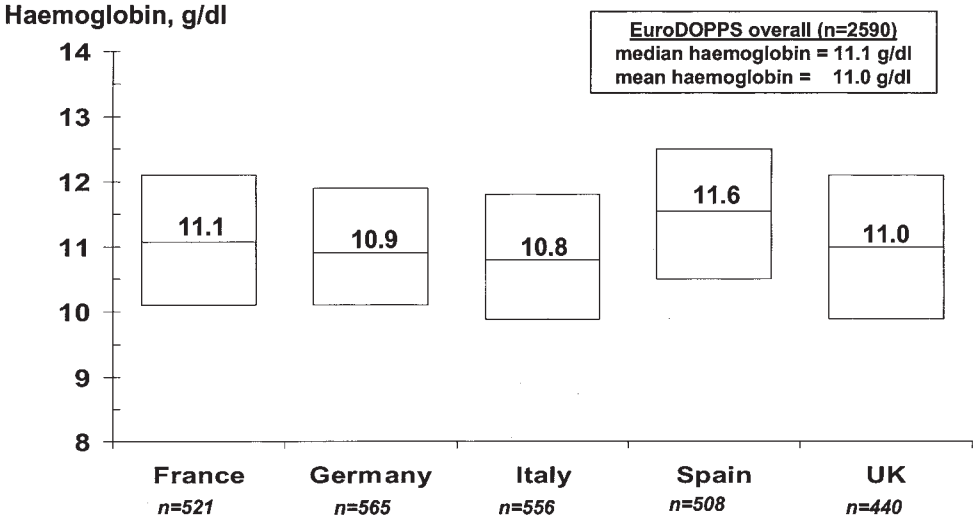


**Fig. 1.** Median haemoglobin concentration among prevalent haemodialysis patients, by country. Values shown are the median haemoglobin concentration in each Euro-DOPPS country for a point-prevalent sample of year 2000 haemodialysis patients on dialysis >180 days. Lower and upper horizontal bars correspond to the 25th and 75th percentiles of the haemoglobin concentration distribution in each country. Mean haemoglobin concentrations in Italy and Spain were significantly different ($P < 0.01$) from the Euro-DOPPS average haemoglobin concentration when adjusted for patient demographics and 14 classes of co-morbidity (data not shown).

**Table 3.** Iron management, by Euro-DOPPS country: percentage of patients prescribed i.v. iron and percentage of patients for whom serum ferritin, serum iron, or TIBC was measured

| Country | I.v. iron use | | Per cent of patients for whom iron-related measurements were performed | | |
|---|---|---|---|---|---|
| | I.v. iron use (% of patients) | Major types of i.v. iron preparation used | Serum ferritin (% of patients) | Serum iron (% of patients) | TIBC* (% of patients) |
| France | 59 ($n=590$) | 100% ferric hydroxide polymaltose | 95[a] ($n=717$) | 78[a] ($n=717$) | 64[a] ($n=717$) |
| Germany | 71[a] ($n=606$) | 97% iron gluconate | 63[a] ($n=725$) | 73 ($n=725$) | 19[a] ($n=725$) |
| Italy | 43[a] ($n=600$) | 81% iron gluconate; 18% iron sucrose | 90[a] ($n=697$) | 88[a] ($n=697$) | 60[a] ($n=697$) |
| Spain | 66[a] ($n=561$) | 100% iron gluconate | 96[a] ($n=679$) | 93[a] ($n=679$) | 69[a] ($n=679$) |
| UK | 62 ($n=564$) | 93% iron sucrose; 7% iron gluconate | 93[a] ($n=599$) | 32[a] ($n=599$) | 22[a] ($n=599$) |
| Euro-DOPPS overall | 60 ($n=2821$) | - | 87 ($n=3417$) | 74 ($n=3417$) | 47 ($n=3417$) |

For i.v. iron use, sample = prevalent patients on dialysis >90 days in year 2000; for analysis pertaining to whether iron-related measurements were performed, the analysis was based on the first 8 months of DOPPS participation for all random sample patients with ≥8 months of study participation. TIBC, total iron-binding capacity.
[a] $P < 0.05$ when compared to the All Euro-DOPPS mean in a given column.

essential for the management of anaemia. In the Euro-DOPPS, the fraction of haemodialysis patients who were prescribed i.v. iron within a 4-month data collection interval in year 2000 ranged from 43% of patients in Italy to 71% in Germany (Table 3). A large variation in i.v. iron use was seen among dialysis units in the Euro-DOPPS. Although median facility i.v. iron use was 60%, i.v. iron was administrated to ≤40% of patients in 22% of dialysis units (data not shown). Mean patient haemoglobin, however, did not statistically differ for patients treated in facilities with high i.v. iron use (>70% of patients given i.v. iron) compared with facilities having low i.v. iron use (<40% of patients given i.v. iron, $P = 0.84$).

The type of i.v. iron preparation provided to patients differed substantially by country (Table 3): ferric hydroxide polymaltose (Maltofer®) served as the only i.v. iron preparation used in France, while ferric or ferrous gluconate comprised >80% of i.v. iron used in Germany, Italy and Spain, and iron sucrose (Venofer®) accounted for >93% of i.v. iron use in the UK. The adjusted probability of i.v. iron being prescribed was similar if patients had a haemoglobin concentration in the range from 9 to 13 g/dl but was significantly lower when a patient's haemoglobin concentration was >13 g/dl (data not shown, adjusted for age, gender, 14 classes of co-morbidity, years since onset of ESRD, whether new to dialysis, country, and facility clustering effects; haemoglobin value was reported in the 4-month interval just prior to determining whether i.v. iron was prescribed; $n = 2588$). The decline in i.v. iron use at high haemoglobin concentrations (>13 g/dl) is expected, as therapy is often curtailed once patients surpass target haemoglobin concentrations of rHuEpo. In this analysis, the likelihood of i.v. iron being administered also declined with number of years since onset of ESRD

[adjusted odds ratio (AOR) = 0.96 for every 1 year longer with ESRD, $P < 0.01$]. However, i.v. iron use was not found to be significantly related to the dose of rHuEpo given to patients (AOR = 0.99 for every 100 U increase in rHuEpo dose/kg body weight/week, $P = 0.92$). Intravenous iron use in France, Germany, Spain and the UK (AOR range = 1.9–3.0, $P < 0.001$) was significantly higher than in Italy in these analyses.

Guideline 7 of the EBPG on anaemia management recommends that the percentage of hypochromic red cells (or TSAT) and serum ferritin should be determined at least once every 3–6 months for patients attaining the target haemoglobin concentration of >11 g/dl. To evaluate the frequency of monitoring iron stores in haemodialysis patients, the DOPPS determined the percentage of haemodialysis patients participating in the study for at least 8 months for whom serum iron, serum ferritin or total iron binding capacity (TIBC) were measured (Table 3). Ferritin was the most commonly performed measure of iron status, as reported for ≥90% of haemodialysis patients in France, Italy, Spain and the UK but for only 63% of patients in Germany. Patients with either a ferritin or a TIBC measurement during the first 8 months of study participation accounted for 67% of German haemodialysis patients. Serum iron was not routinely measured in the UK (32% of patients), and TIBC was not routinely measured in Germany or the UK (reported for 19–22% of patients).

### *rHuEpo therapy*

The distribution of rHuEpo dose in prevalent haemodialysis patients who had been on dialysis >90 days is shown in Figure 2. The mean dose of rHuEpo was 109 IU/kg/week, with nearly 75% of patients having an rHuEpo dose in the range from 18 to 144 IU/kg/week. The mean rHuEpo dose varied substantially across countries from 86 IU/kg/week in Germany to 132 IU/kg/week in Italy (Table 4). After adjusting for country, haemoglobin concentration, 14 classes of co-morbidity and years of ESRD treatment, the mean weekly rHuEpo dose was found to be significantly higher if rHuEpo was administered intravenously [22.5 U higher compared with subcutaneous (s.c.) administration ($P < 0.001$)], or if patients were female (17.6 U higher compared with males, $P < 0.001$), or older than 74 years (11.9 U higher compared with age 45–64 years, $P = 0.03$).

The drug, rHuEpo, was prescribed for 84% of prevalent patients, ranging from 75% in France to 92% in the UK (Table 4). Figure 3 shows the likelihood of prevalent haemodialysis patients being prescribed rHuEpo as a function of patient haemoglobin concentration. The results reveal odds that are several fold higher of a patient being prescribed rHuEpo when the haemoglobin concentration is within the range of 9–10 g/dl compared with 12–13 g/dl. Over the haemoglobin range from 9–14 g/dl, every 1 g/dl increase in patient haemoglobin concentration was associated with a 59% lower adjusted odds ($P < 0.001$) of a patient being prescribed rHuEpo. The decline in rHuEpo use at higher haemoglobin concentrations is expected, as therapy often is reduced as patients exceed target haemoglobin levels. Even though there appears to be a lower level of rHuEpo prescription for patients with a haemoglobin <9 g/dl compared with patients having a haemoglobin of 9–10 g/dl, the difference was not statistically significant ($P > 0.05$), and a large overlap was seen in the confidence intervals for these two haemoglobin categories.

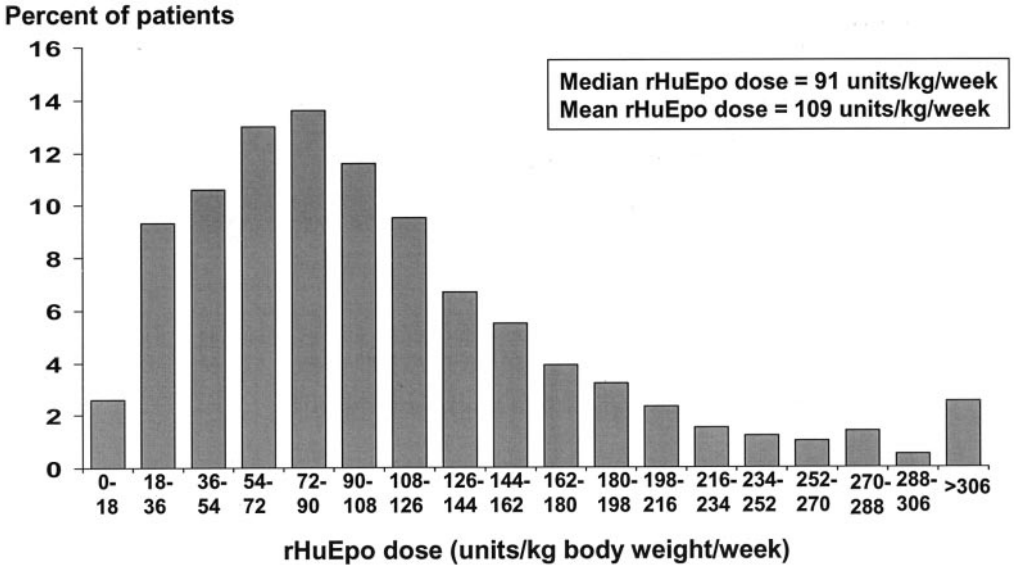


**Fig. 2.** Distribution of rHuEpo doses prescribed for prevalent haemodialysis patients in Euro-DOPPS. The distribution of rHuEpo doses and the mean and median rHuEpo dose are shown for a point-prevalent sample of haemodialysis patients in the Euro-DOPPS who were receiving rHuEpo therapy in year 2000; $n = 2494$. Patients on dialysis <90 days were excluded. For comparison, the median rHuEpo dose for a year 1998–1999 point-prevalent sample was 88 U/kg body weight/week.

**Table 4.** rHuEpo therapy, by Euro-DOPPS country

| Country | rHuEpo therapy | | |
|---|---|---|---|
| | rHuEpo use (% of patients) | rHuEpo given subcutaneously (% of rHuEpo-treated patients) | Mean prescribed rHuEpo dose[a] (units/kg body weight/week) |
| France ($n=581$) | 75 ± 1.8 | 79 ± 1.94 | 102 ± 4.81 |
| Germany ($n=586$) | 77 ± 1.73 | 19 ± 1.83 | 86 ± 2.92 |
| Italy ($n=595$) | 86 ± 1.44 | 83 ± 1.67 | 132 ± 4.04 |
| Spain ($n=551$) | 91 ± 1.25 | 78 ± 1.82 | 114 ± 3.7 |
| UK ($n=454$) | 92 ± 1.3 | 99 ± 0.41 | 107 ± 3.6 |
| Euro-DOPPS overall ($n=2767$) | 84 ± 0.71 | 71 ± 0.93 | 109 ± 1.76 (median = 91) |

Mean value ± standard error of the mean; prevalent patients on dialysis >90 days in year 2000. [a]Among rHuEpo-treated patients.

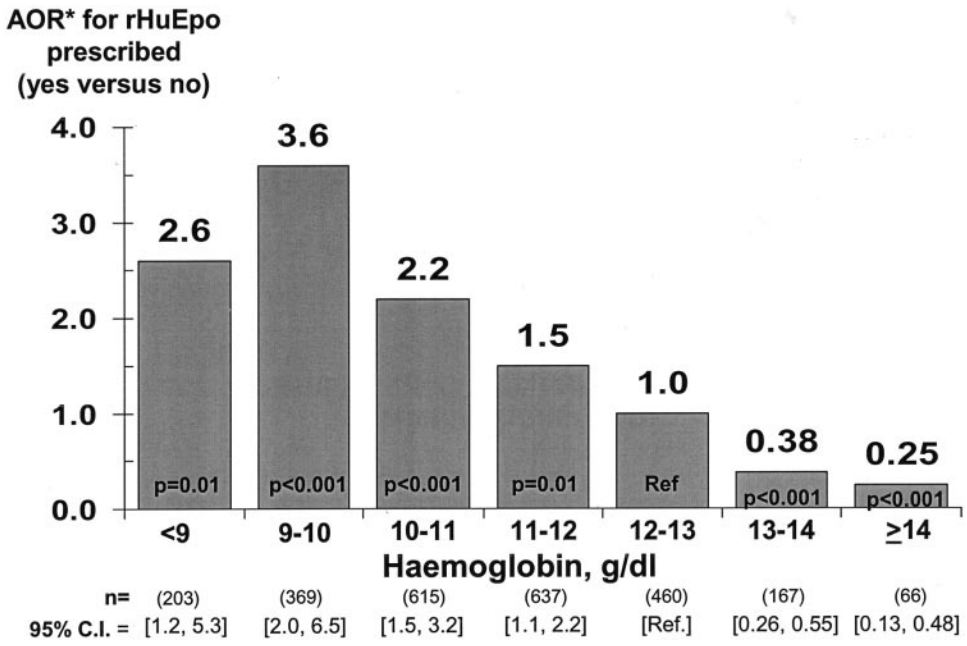


**Fig. 3.** *Adjusted odds ratios of rHuEpo being prescribed, by patient haemoglobin group. Logistic regression was used to model the odds of rHuEpo being prescribed (yes *vs* no) for a point-prevalent sample of year 2000 haemodialysis patients. The model was adjusted for age, gender, 14 classes of co-morbidity, years on dialysis, whether new to haemodialysis, country and facility clustering effects. Patients on dialysis <180 days were excluded; 95% confidence interval (CI) is shown at the bottom of each bar; $n=2520$.

There were notable differences in the route of rHuEpo administration across Euro-DOPPS countries (Table 4). The drugs were administered subcutaneously for the large majority of rHuEpo patients in France (79%), Italy (83%), Spain (78%) and the UK (99%). In contrast, in Germany a minority of rHuEpo patients (19%) received the drug via this route. Only 14% of patients received rHuEpo once per week, while the drug was most often prescribed three times per week (55%) or twice per week (30%) (Table 5). However, 70% of patients received rHuEpo three times per week if administered intravenously, whereas only 48% of patients received rHuEpo three times per week with SC administration. The most frequently used dose of rHuEpo per administration was 2000 IU.

Italy displayed the highest percentage of patients receiving rHuEpo during the pre-ESRD period (49%) compared with 21–28% in the other four Euro-DOPPS countries. Recent results by Rayner *et al.* [21] from the DOPPS have shown that 81% of Euro-DOPPS patients saw a nephrologist at least 1 month prior to starting dialysis (country range 72–87%), and 76% saw a nephrologist ≥4 months prior to starting dialysis.

Several factors were associated with higher odds of whether a haemodialysis patient was prescribed rHuEpo during the pre-ESRD period. These included referral to a nephrologist at least 1 month prior to ESRD (AOR = 10.7, $P=0.001$), female gender (AOR = 1.5, $P<0.001$) and absence of coronary artery disease (AOR = 1.5, $P=0.09$).

A time-trend analysis was performed to determine how rHuEpo administration and mean haemoglobin concentrations changed during the first year of haemodialysis therapy. The results shown in Figure 4 indicate that 42% of new ESRD patients in the Euro-DOPPS were prescribed rHuEpo when first starting

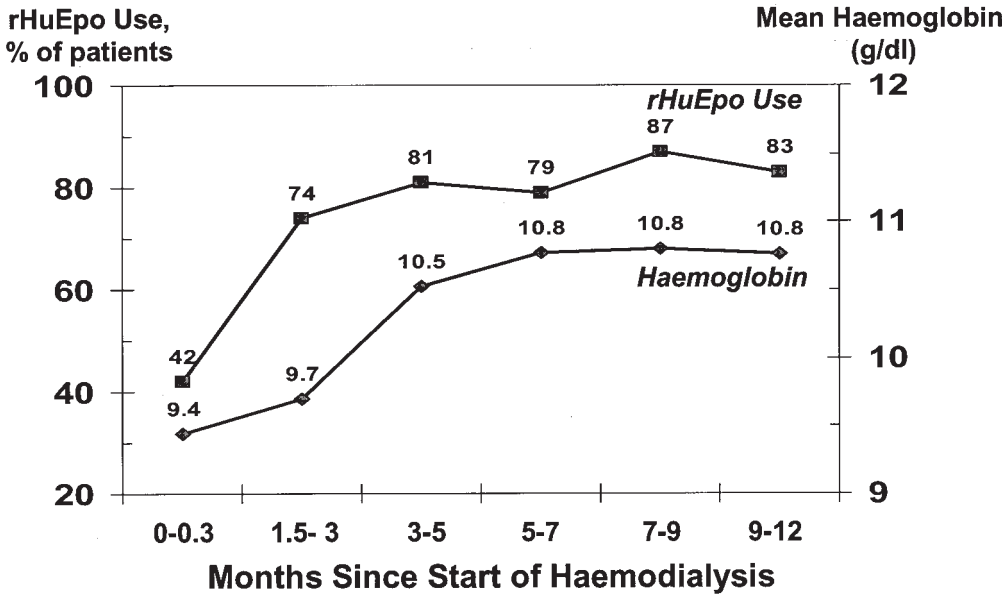


**Fig. 4.** Time trend in rHuEpo use and mean haemoglobin concentration for new ESRD patients after initiating haemodialysis. The percentage of patients receiving rHuEpo and the mean haemoglobin concentration was determined at six time points during the first year of haemodialysis therapy for a cohort of new ESRD patients entering the DOPPS within 10 days of their first-ever dialysis treatment. The six time points for this analysis were 0–0.3 months, 1.5–3 months, 3–5 months, 5–7 months, 7–9 months and 9–12 months; $n = 1133$. rHuEpo use (filled squares); mean haemoglobin concentration (filled diamonds).

**Table 5.** Number of rHuEpo doses prescribed per week: patient distribution by Euro-DOPPS country and by route of administration

| Country | Doses per week (% of patients) | | |
|---|---|---|---|
| | Three doses | Two doses | One dose |
| France ($n = 442$) | 47 | 38 | 14 |
| Germany ($n = 467$) | 71 | 17 | 11 |
| Italy ($n = 527$) | 50 | 30 | 18 |
| Spain ($n = 510$) | 49 | 36 | 15 |
| UK ($n = 422$) | 60 | 31 | 8 |
| Euro-DOPPS overall ($n = 2368$) | 55 | 30 | 14 |
| S.c. route ($n = 1675$) | 48 | 35 | 15 |
| I.v. route ($n = 670$) | 71 | 18 | 20 |

*Prevalent rHuEpo-treated patients on dialysis >90 days in year 2000. For Euro-DOPPS overall, the percentage distribution for the number of rHuEpo units per dose was as follows: ~1000 U/dose (14%), ~2000 U/dose (39%), ~3000 U/dose (18%), ~4000 U/dose (19%) and >4500 U/dose (9%).

haemodialysis. For this incident patient cohort, rHuEpo treatment increased markedly during the first 3 months of haemodialysis and attained a steady state of >80% rHuEpo administration within 3–5 months after initiating haemodialysis. Mean haemoglobin concentrations also dramatically increased during the first year of haemodialysis, from an initial mean concentration of 9.4 g/dl to a steady-state value of 10.8 g/dl. The increase in mean haemoglobin concentration occurred ~1.5–3 months after the increase in rHuEpo use. This is consistent with the established relationship that increased rHuEpo administration results in a subsequent increase in patient haemoglobin concentration.

### *Patient characteristics associated with lower haemoglobin concentrations*

Several characteristics were associated with lower mean concentrations in prevalent haemodialysis patients in the Euro-DOPPS (data not shown) who were prescribed rHuEpo. These characteristics included female gender (−0.16 g/dl, $P = 0.01$), peripheral vascular disease (−0.22 g/dl, $P = 0.02$), gastrointestinal bleeding in the 12 months prior to study entry (−0.30 g/dl, $P = 0.03$), history of cancer (−0.34, $P = 0.001$) and if the patient had not received i.v. iron during the 4 months prior to the haemoglobin reporting date (−0.20 g/dl, $P = 0.02$). This analysis was adjusted for patient age, gender, 14 classes of co-morbidity, country of residence and facility clustering effects. The lower mean haemoglobin values for females, patients having had gastrointestinal bleeding within the prior 12 months, or patients with a history of cancer are not surprising, based on similar observations in non-ESRD patients.

An analysis adjusted for patient demographics and 14 classes of co-morbidity also was performed to determine which patient characteristics were associated with a lower haemoglobin level of ≤10 g/dl compared with a higher haemoglobin level (≥11 g/dl). Prevalent patients with low haemoglobin were more likely to have had cancer, gastrointestinal bleeding within the 12 months prior to study entry, or diabetes ($P < 0.05$). However, the following characteristics were not significantly related ($P > 0.05$) to whether a patient

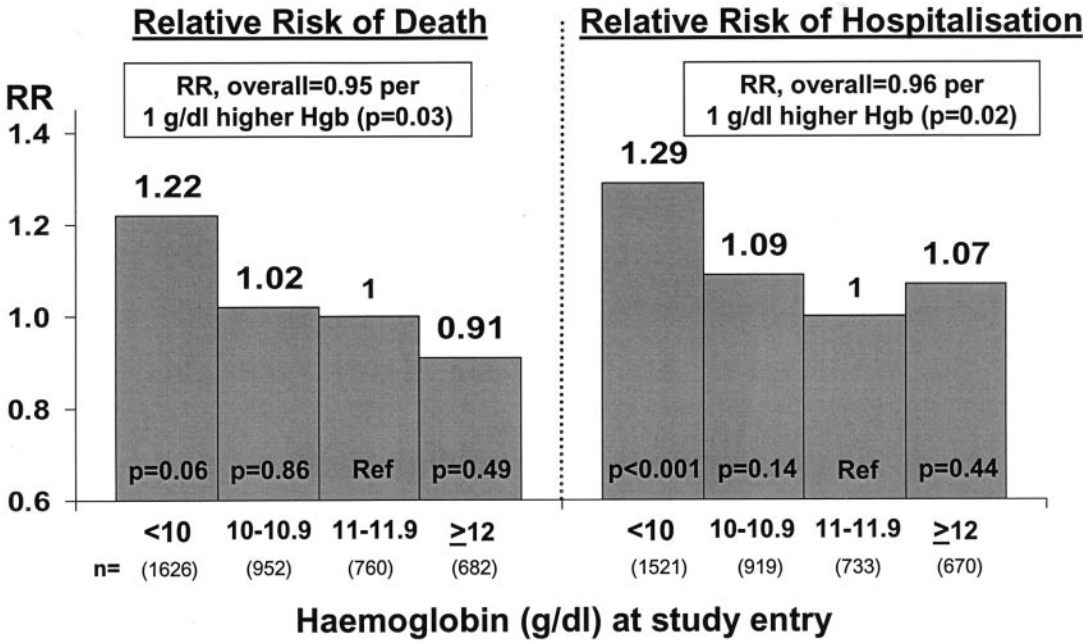


**Fig. 5.** Relationship between patient haemoglobin concentration and adjusted relative risks of death and hospitalization. Cox regression analysis was used to determine the relative risk of death or time to first hospitalization as a function of a patient's haemoglobin concentration at the time of study entry. Analyses were adjusted for age, gender, 14 co-morbidity classes, ability to walk without assistance, malnourishment, ability to eat independently, years with ESRD, first 180 days of ESRD, country of residence and facility clustering effects. RR, relative risk. For the mortality analysis, there were a total of 759 deaths with a mean follow-up time of 1.25 years. For the hospitalization analysis, there were a total of 2240 hospitalizations and mean follow-up time to first hospitalization was 0.73 years.

had a low *vs* high haemoglobin: age, coronary artery disease, congestive heart failure, other cardiac disease, hypertension, cerebrovascular disease, peripheral vascular disease, dyspnoea, neurologic disease, psychiatric disease or recurrent cellulitis/gangrene.

### *Facility practices associated with lower haemoglobin concentrations*

Two different facility practices were examined for their effect on the odds of a patient having a haemoglobin $\geq$11 *vs* $<$11 g/dl. The first practice, level of facility rHuEpo, indicated a 1.6-fold higher AOR ($P = 0.06$) of a patient having a haemoglobin $\geq$11 g/dl if the patient dialysed in a unit within the highest quartile of rHuEpo use ($\geq$92% of patients prescribed rHuEpo) compared with those treated in a facility within the lowest quartile of rHuEpo use ($>$37–76% of patients prescribed rHuEpo).

The second facility practice examined was the policy in some units to require a patient's haemoglobin concentration to fall below a predetermined level before rHuEpo was prescribed. A survey completed by 97 Euro-DOPPS medical directors indicated that 55% of these haemodialysis units have such a policy. The AOR of having a haemoglobin concentration $\geq$11 g/dl was 53% higher ($P = 0.05$) for patients treated in facilities initiating rHuEpo treatment at a haemoglobin concentration of $\geq$10.0 g/dl compared with dialysis facilities initiating treatment at a haemoglobin threshold concentration of $<$10 g/dl (data not shown).

### *Morbidity and mortality associated with anaemia*

The relationship between mortality or hospitalization with patient haemoglobin concentration was examined in models adjusted for patient demographic and co-morbid characteristics (Figure 5). Higher haemoglobin concentrations were associated with a 5% lower RR of mortality (RR = 0.95) for every 1 g/dl increase in haemoglobin (95% CI = 0.90–0.99, $P = 0.03$, Figure 5). A similar RR of mortality was seen if the analysis was restricted to patients on dialysis $>$180 days (RR = 0.94) for every 1 g/dl higher haemoglobin (95% CI = 0.89–0.99, $P = -0.01$, $n = 2609$). Furthermore, a significant relationship between mortality and haemoglobin was found (RR = 0.92 per 1 g/dl higher haemoglobin, 95% CI = 0.86–0.99, $P = 0.02$) if the adjusted mortality analyses excluded patients having a history of cancer or peripheral vascular disease or gastrointestinal bleeding in the past 12 months. These were the only co-morbidities (indicated in the previous section) to be significantly associated with a lower mean haemoglobin concentration.

The relationship between different categories of haemoglobin concentration and mortality risk differed for haemodialysis patients $\leq$65 years old compared with those $>$65 years (Figure 6). Patients 18–65 years old with a haemoglobin concentration $<$10 g/dl displayed a 51% higher risk of death (95% CI = 1.05–2.16, $P = 0.024$) compared with 18–65-year-old patients having a haemoglobin concentration of 11–11.99 g/dl. The patterns indicated for these two age groups also were seen when the analysis was restricted to patients

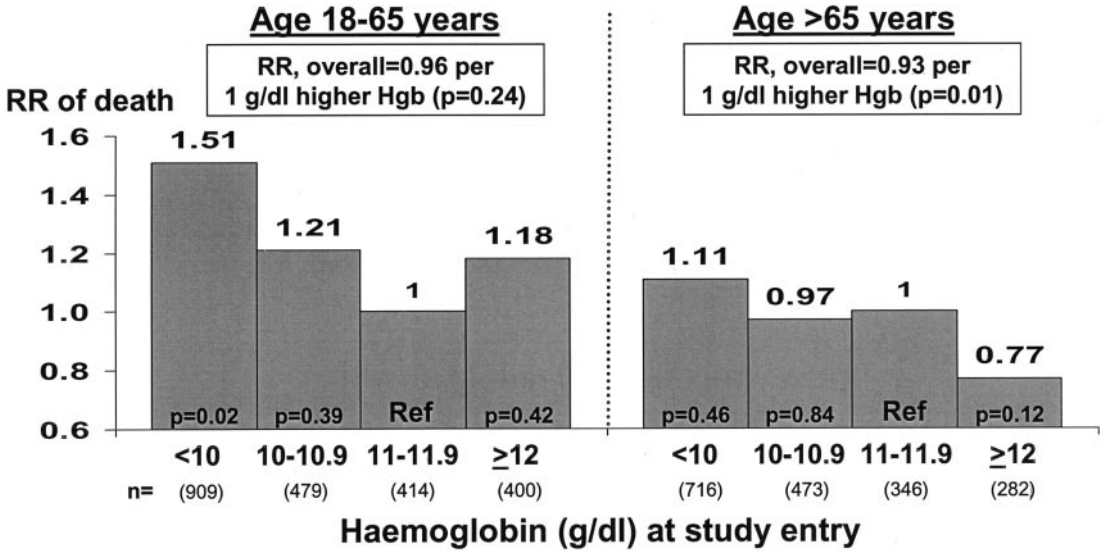


**Fig. 6.** Relationship between patient haemoglobin concentration and adjusted relative risk of death for patients 18–65 years *vs* >65 years of age. Cox regression analysis was used to determine the relative risk of death as a function of a patient's haemoglobin concentration at the time of study entry for patients 18–65 years *vs* >65 years of age. Analyses were adjusted for age, gender, 14 co-morbidity classes, ability to walk without assistance, malnourishment, ability to eat independently, years with ESRD, first 180 days of ESRD, country of residence and facility clustering effects. RR, relative risk.

on dialysis for >180 days, although in this latter analysis a tendency for improved survival was seen for both age groups when haemoglobin concentrations were ≥12 g/dl.

Higher haemoglobin concentrations were associated with a 4% lower RR of hospitalization (RR = 0.96) for every 1 g/dl higher haemoglobin (95% CI = 0.93–0.99, $P = 0.02$, Figure 5). A similar pattern was seen when the analysis was restricted to patients on dialysis >180 days. Patients with a haemoglobin concentration <10 g/dl had a 29% higher risk of hospitalization than patients with a haemoglobin of 11–12 g/dl.

The sample size in Euro-DOPPS was not large enough to show, by individual country, the relationship between patient haemoglobin concentrations and risk of mortality or hospitalization with the numerous adjustments used in these models. Consequently, these analyses were performed only for the five Euro-DOPPS countries combined into one model. However, these analyses were stratified by country, so the results reflect the mean relationship across all five countries.

## Discussion

Effective anaemia management is an essential component for the treatment of patients with CKD. The burden of anaemia in these individuals is substantial, and this study further documents a clear association with morbidity and mortality. Prior to the availability of rHuEpo, patients were subjected to repeated blood transfusions and generally remained profoundly anaemic. The advent of rHuEpo has revolutionized anaemia management in CKD patients. Best practice guidelines for the treatment of anaemia were published in the USA in 1997 [22] and in Europe in 1999 [17]. The impact of these guidelines for Europe may be better shown in future years; however, the current study provides an early insight into how anaemia treatment practices have changed in Europe. In this analysis, DOPPS data were used to examine anaemia management in Europe and have demonstrated that, despite the recommendations of the EBPG in 1999 [17], there is still wide variation in facility anaemia management practices. The European guidelines recommend that at least 85% of haemodialysis patients should attain a haemoglobin concentration of ≥11 g/dl. In the present investigation, 55% of haemodialysis patients in 1998–1999 and 49% in year 2000 had a haemoglobin concentration below the EBPG recommendation. The data are in agreement with previous reports of the Lombardy Registry [23] and the USRDS [13]. However, an encouraging trend is seen toward an increase in target haemoglobin concentration from 1998 to 2000.

Large variations were observed in the median haemoglobin value across the Euro-DOPPS countries. With the current study sample size, the mean haemoglobin concentration in Italy was significantly lower than that of all five Euro-DOPPS countries combined. This was observed both with and without adjustment for patient mix and differences in i.v. iron use.

The country with the highest median haemoglobin value, Spain (median = 11.6 g/dl *vs* <11.1 g/dl for the four other Euro-DOPPS countries, Figure 1) had relatively high values in the three major categories of anaemia management practice: rHuEpo use (91%), mean rHuEpo dose (114 IU/kg body weight/week) and prevalence of i.v. iron use (66%) (Table 3). The facility practice patterns analyses indicated that initiating

rHuEpo therapy at higher haemoglobin threshold values was associated with attaining a higher mean haemoglobin concentration. The survey responses from Euro-DOPPS unit medical directors indicated that the majority of Spanish dialysis units had a policy of initiating rHuEpo therapy at relatively high haemoglobin threshold values. The high mean haemoglobin concentration observed for Spanish haemodialysis patients would appear to be largely a consequence of a country-wide practice of initiating rHuEpo use at a relatively high haemoglobin threshold value in conjunction with high use of rHuEpo, at a moderately high dose and maintaining sufficiently high iron levels for haemodialysis patients. Spanish dialysis units also displayed the highest prevalence of comprehensive monitoring of patient iron status through widespread use of serum iron, serum ferritin and TIBC measurements.

Large differences were seen between some of the Euro-DOPPS countries regarding the type of i.v. iron preparation prescribed for patients. However, this difference may be a reflection of what preparations are available for use in a given country, rather than preferences of the nephrologist for a particular type of i.v. iron.

The present cross-sectional study includes patients at various stages of ESRD therapy. This allowed evaluation of patterns at different time points of dialysis. The low mean haemoglobin concentration of 9.4 g/dl displayed by new ESRD patients when initiating haemodialysis underscores the failure of pre-ESRD health care programmes to adequately address the anaemia management needs of this patient population. As a consequence of their high level of anaemia, new ESRD patients require 3–5 months of rHuEpo therapy after initiating haemodialysis in order to achieve a mean haemoglobin concentration comparable with that of patients on haemodialysis therapy for longer times (Figure 4). Clearly, much greater efforts are needed to ensure a seamless correction of anaemia from the earliest stages of progressive CKD into renal replacement therapy. Most analyses in the present study adjust for years with ESRD and adjust additionally for being in the first 180 days of ESRD, due to the lack of steady state for haemoglobin in this early phase of ESRD.

It is apparent from the findings of the present study that a patient's haemoglobin concentration affects morbidity and mortality. The risk of hospitalization was 4% lower for every 1 g/dl higher haemoglobin concentration. Higher cardiac-related morbidity has been associated with lower haemoglobin values [3–6,10]. The question arises to what extent cardiac-related hospitalization could be reduced if higher haemoglobin concentrations or levels $>11$ g/dl were obtained for haemodialysis patients. Moreover, the risk of mortality in these patients was 5% lower for each 1 g/dl higher haemoglobin concentration (Figure 5). These statistically significant results are in agreement with previous reports of the Lombardy Registry [23] and USRDS [2,7,24].

The data clearly indicate a strong association of higher haemoglobin concentration with improved health outcomes. Although observational studies cannot prove causality, this study suggests that, if the EBPG guidelines are followed, a trend for improved outcomes in anaemic CKD patients may be expected. The EBPG on anaemia, based on expert review of evidence, thus receives additional supportive evidence from the present study. Despite the dissemination of the EPBG, many European haemodialysis patients still have haemoglobin concentrations below the minimum recommended level of 11 g/dl. This suggests a major opportunity for improved anaemia management for haemodialysis patients.

This study and two companion papers reviewing treatment and mortality in the Euro-DOPPS countries seek to present a comprehensive overview of the haemodialysis and anaemia practices and outcomes for the European study population [25,26]. The findings of this study indicate that anaemia control according to the EBPG is significantly associated with lower morbidity and mortality in haemodialysis patients. Although a trend toward increasing haemoglobin concentrations is evident over recent years, further efforts are required if the EBPG target of a haemoglobin concentration $\geq 11$ g/dl in 85% of patients is to be achieved. Moreover, anaemia management should be particularly improved in pre-dialysis patients.

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