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Nephrology
Dialysis
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European Best Practice Guidelines 5
Target haemoglobin

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Results

Key points from the EBPG

- Target haemoglobin (Hb): ⩾85% of chronic renal failure (CRF) patients should achieve an Hb >11 g/dl; to attain this target, the population median will be 12.0–12.5 g/dl.
- The target Hb may need to be varied for CRF patients with specific co-morbidities.

Key findings from ESAM

- The vast majority of patients had target haemoglobin levels set at or exceeding the recommended level.
- The relative consistency of target haemoglobin levels across countries suggests a broad consensus on appropriate levels.
- High target haemoglobin levels (>13 g/dl) and low target haemoglobin levels (<9.0 g/dl) were each associated with certain aetiologies and concomitant pathologies.
- Haemoglobin reached target levels in only 53.6% of patients.

Target haemoglobin levels

Target haemoglobin refers to the desired patient haemoglobin concentration to be achieved during treatment of renal anaemia. The EBPG acknowledge that clear evidence on optimal haemoglobin concentration is not currently available, but EBPG 5 proposes a target of >11 g/dl for 85% or more of the patient population. The mean target haemoglobin level for the entire sample was 11.4 g/dl (SD = 0.8; range = 6.5–15.0 g/dl), and 82.2% of patients had target levels set equal to or exceeding the recommended level.The highest mean target haemoglobin value was observed in Sweden, while the lowest was observed in France (see Figure 9). The relative consistency of target haemoglobin levels across the participating countries suggests a broad consensus on appropriate target levels.

In the haemodialysis group, 43.7% of patients had target haemoglobin levels between 11.0 and 11.9 g/dl, and 32.5% had target levels between 12.0 and 12.9 g/dl (Figure 10). Thus, 76.2% of haemodialysis patients reported target haemoglobin levels in the range of 11.0–12.9 g/dl. Note that 18.6% of haemodialysis patients had target levels below the EBPG recommended level of 11 g/dl. Similarly, target haemoglobin levels for peritoneal dialysis patients ranged from 6.7 to 14.0 g/dl, with a mean level of 11.5 (SD = 0.8). Here too, more than three-quarters of the cohort (81.3%) were within the 11.0–12.9 range (38.5% between 11.0 and 11.9, and 42.4% between 12.0 and 12.9 g/dl); 11.0% had target levels below the EBPG recommended level. At the end of the survey, 47.0% of haemodialysis and 39.5% of peritoneal dialysis patients failed to achieve haemoglobin concentrations of at least 11.0 g/dl.

Figure 11 presents measures of target haemoglobin for a combined sample of haemodialysis and peritoneal dialysis patients in relation to various concomitant pathologies. Although there are variations in observed minimum and maximum levels across these categories, mean values and standard deviations are consistently similar to, and on average above, the EBPG recommended level of 11 g/dl.

We also examined the sub-cohort of patients with target haemoglobin levels ⩾13.0 g/dl ($n = 750$) and compared them with patients with target levels between 9.1 and 12.9 g/dl ($n = 12\,829$) in terms of age, primary cause of chronic renal failure, concomitant pathology, epoetin dose at each month and country of origin. Both sub-cohorts did not differ significantly in terms of age (both had means of 61.0; $SD_{\geqslant 13} = 15.5$, $SD_{<13} = 15.3$). The group with Hb ⩾13 g/dl included proportionately more patients with chronic glomerulonephritis (34.5% *vs* 25.2%), renovascular disease (16.3% *vs* 13.8%) and multiple myeloma (1.3% *vs* 0.7%). This group had fewer patients with undefined cause of chronic renal failure (15.0% *vs* 17.4%), diabetic nephropathy (12.8% *vs* 17.9%), tubulo-interstitial disease (10.5% *vs* 13.8%), polycystic kidney disease (5.8% *vs* 6.8%) and failed renal transplants (1.6% *vs* 2.3%). The overall test of differences across aetiology by target haemoglobin group was significant ($\chi^2 = 48.586$, $df = 8$, $P < 0.001$). In terms of concomitant pathology, the group with Hb ⩾13 g/dl included more patients

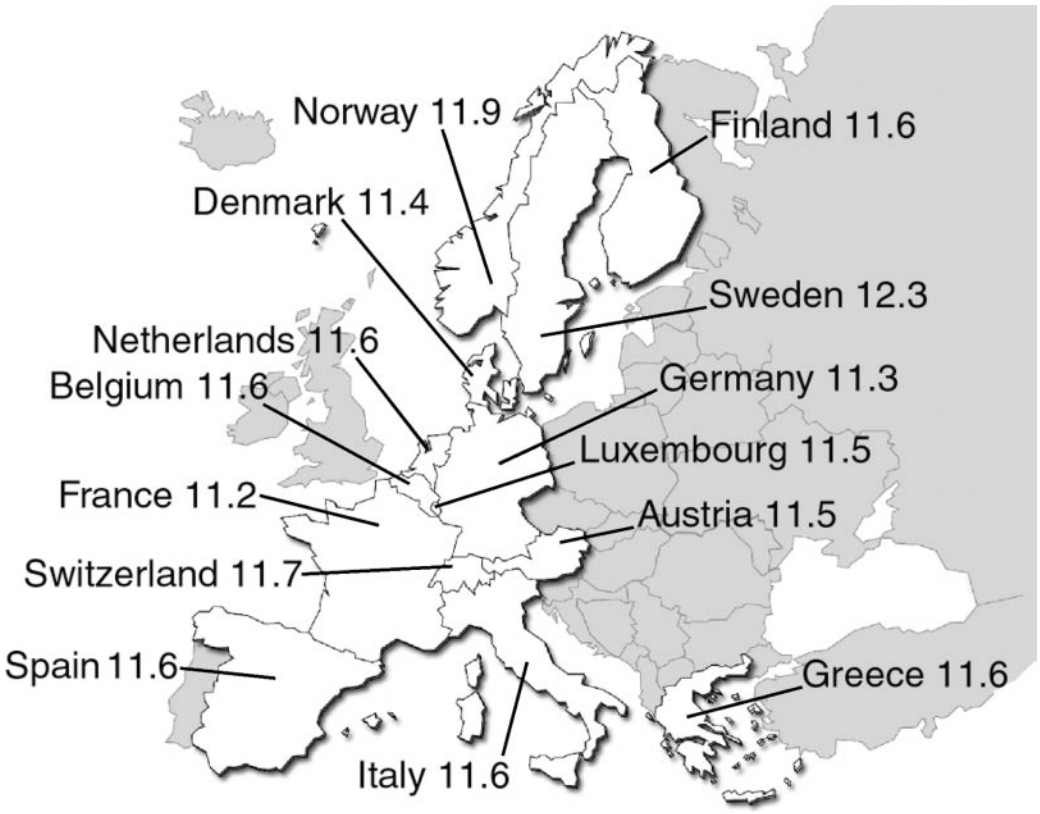

Fig. 9. Mean target Hb by country.

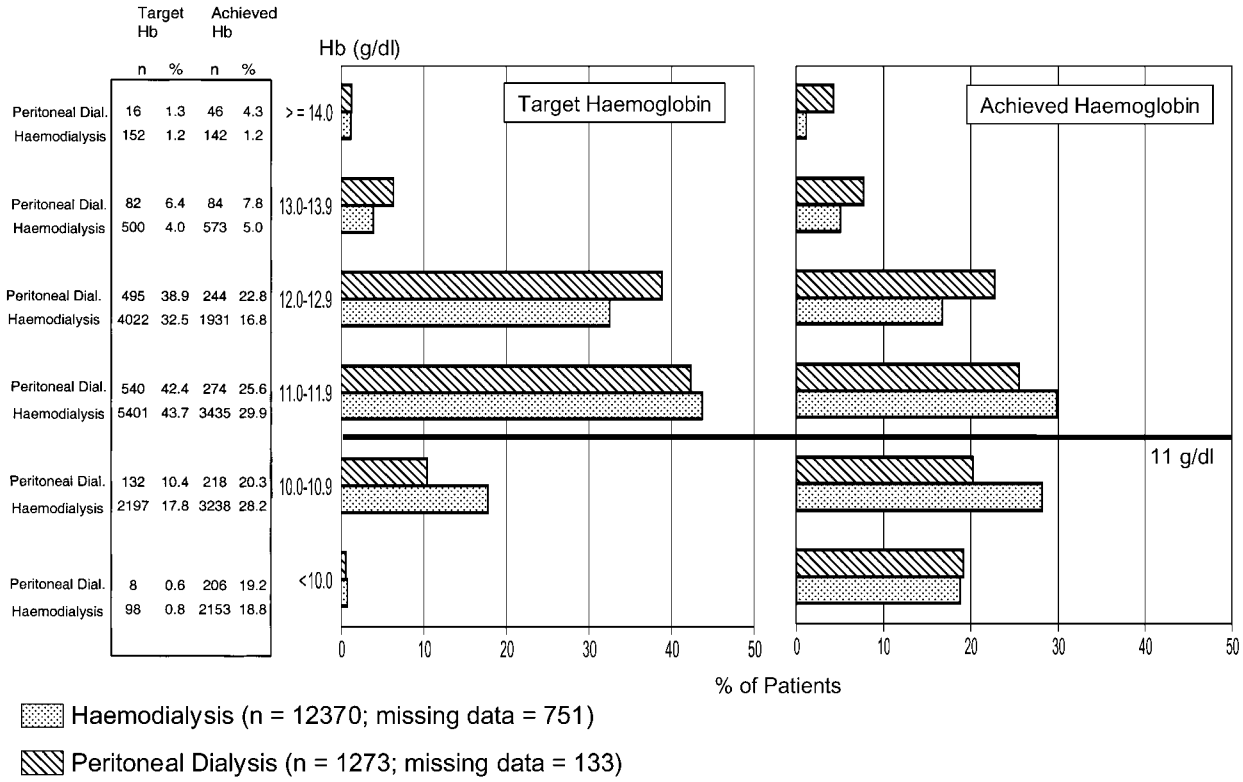

Fig. 10. Distributions of stated target and achieved Hb level by type of dialysis.

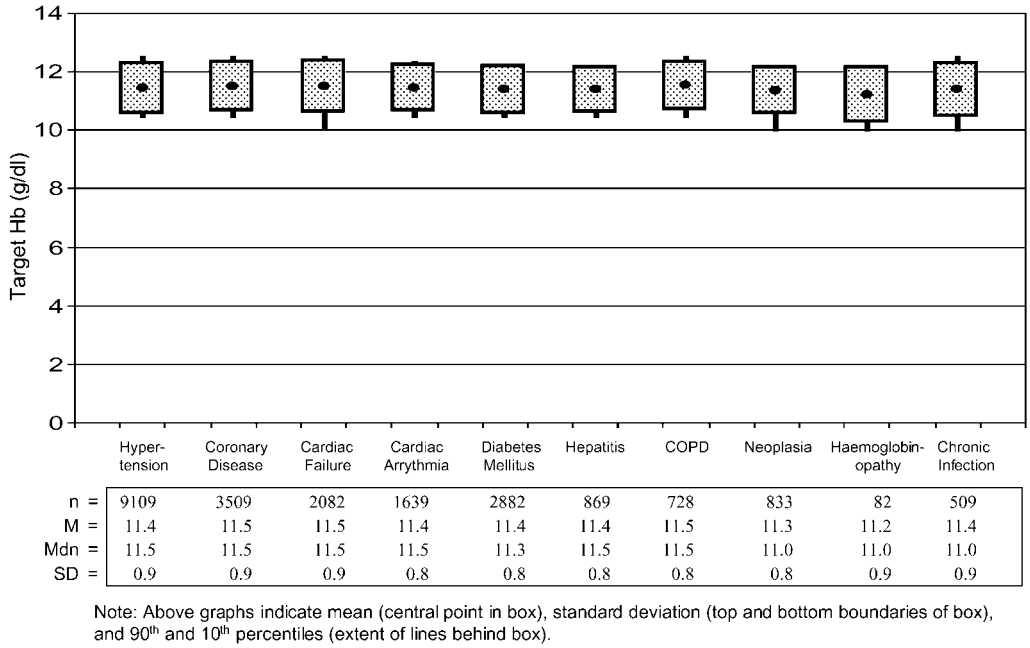

Fig. 11. Stated target Hb by concomitant pathology.

with hypertension (68.9% *vs* 66.6%), coronary artery disease (30.5% *vs* 25.4%), cardiac failure (18.1% *vs* 15.1%), cardiac arrhythmias (12.5% *vs* 12.0%) and chronic obstructive pulmonary disease (6.5% *vs* 5.3%), but fewer patients with diabetes mellitus types I and II (17.9% *vs* 21.5%), neoplasia (5.5% *vs* 6.1%), hepatitis (5.1% *vs* 6.5%), chronic infection (4.5% *vs* 3.7%) or haemoglobinopathy (0.3% *vs* 0.6%). Since the concomitant pathologies are not mutually exclusive, an overall test of significance by target haemoglobin group cannot be conducted. For coronary artery disease, cardiac failure and diabetes mellitus type I, significant differences were observed by target haemoglobin groups (respectively, $\chi^2 = 9.674$, df = 1, $P < 0.01$; $\chi^2 = 5.045$, df = 1, $P < 0.05$; $\chi^2 = 5.361$, df = 1, $P < 0.05$).

We also examined the lower end of the target haemoglobin range more closely; specifically, the 64 patients with a target haemoglobin of 9.0 g/dl or less. The very small number of patients in this sample precludes statistical comparison, even at the descriptive level. Notwithstanding, the following data for this sample may merit clinical consideration. Cardiovascular co-morbidities were especially prevalent in this cohort: hypertension (84.4%), coronary artery disease (28.1%), cardiac failure (14.1%) and cardiac arrhythmias (9.4%). Diabetes mellitus (type I) as a co-morbidity was 21.9%. Smaller numbers of patients had co-existing neoplasia (7.8%), hepatitis (4.7%) and chronic obstructive pulmonary disease (1.6%). Dosages of epoetin across the 6-month period ranged from 113.5 IU/kg/week (SD = 70.6) at month 1 to 128.5 IU/kg/week (SD = 94.4) at month 4. The mean age was 57.7 years (SD = 14.8).

Achieved haemoglobin levels

Although the results on achieved haemoglobin levels are reported elsewhere in this supplement (see section on EBPG 9–13), an initial examination of target and achieved Hb levels may be helpful in interpreting the relevance of target levels, and in introducing the results on achieved levels. Figure 12 shows the association between target Hb levels and actual Hb levels achieved at month 6 of the survey. If anaemia management practice was 'perfect', and in line with EBPG, one would expect: (i) target Hb levels to be at least 11 g/dl; (ii) target and achieved Hb levels to be either identical, or the achieved levels higher than the target levels; (ii) the variability within the scatter plot to be limited and, if anything, to be skewed to the left; (iv) the majority of co-ordinate points to fall on a regression line between 11.0 and 13.0 g/dl with a slope coefficient of 1 (indicating 1 unit increase in achieved Hb for each unit increased in target Hb level); and (v) most co-ordinates with any residual to be distributed abnormally in the upper right sector of the graph. Figure 12 illustrates that none of these criteria were convincingly met. In a significant number of patients (17.8%), target haemoglobin levels were below 11.0 g/dl. Only 53.6% of patients achieved haemoglobin levels equal to or exceeding the recommended target of 11.0 g/dl. Co-ordinates are widely distributed around the ideal regression line. This distribution is patterned in all directions with a slight skew to the right, indicating that the achieved level at month 6 tended to be lower than the target level. Although the trend is towards convergence of target and achieved levels ($r = 0.304$,

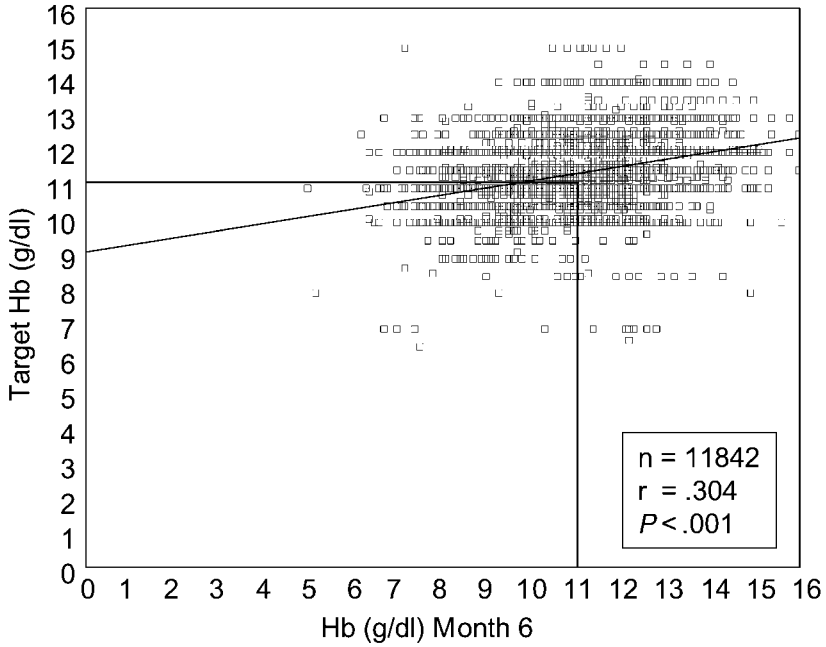

Fig. 12. Distribution of stated target Hb by achieved Hb at month 6.

$P<0.001$), only 9.2% of the variance in achieved haemoglobin at month 6 is accounted for by the target haemoglobin level ($R^2=0.092$).

Comments

The goal of administering epoetin to patients with CRF prior to or during renal replacement therapy is to improve the symptoms or morbidity associated with renal anaemia. The considerable benefits of correcting anaemia in renal patients in terms of improvement of quality of life and reduction in patient morbidity and mortality have been firmly established in recent years [1–5]. The optimal correction of anaemia in terms of target haemoglobin remains a matter of debate, fuelled by many recent publications [6–10]. The NKF-DOQI guidelines recommended a target haematocrit of 33–36% [11] and the EBPG advocate that 85% of the patient population should have an Hb concentration >11 g/dl (haematocrit $\geqslant 33\%$). To achieve this goal, the mean or median Hb level for the total population should be 12–12.5 g/dl [12].

The results of the target Hb distribution in ESAM show that for three-quarters of the haemodialysis and the peritoneal dialysis populations enrolled in the survey the target Hb ranged between 11 and 12.9 g/dl, the lowest concentration being recorded in France (11.2 ± 0.7 g/dl) and the highest in Sweden (12.3 ± 0.7 g/dl).

A target haemoglobin below the recommended level (11 g/dl) was selected for 18.6 and 11.4% of the haemodialysis and peritoneal dialysis patients, respectively. A very low target haemoglobin level, 9.0 g/dl or less, was recorded for 64 patients (0.5%), mainly from France and Germany, where cardiovascular co-morbidities were very common.

A target haemoglobin higher than 13 g/dl was reported for 750 (5.5%) patients who were treated mainly in Germany, Greece and Belgium. The issue of normalizing the haemoglobin level in terms of cost–benefit and benefit–risk ratios remains controversial [13]. Various benefits of raising the haemoglobin to normal or near-normal concentration have been reported, including improved cognitive function [1,14,15], exercise performance [16] and quality of life [2,4]. Somewhat alarming results were obtained by normalizing the haematocrit in a population of renal patients in the USA who had co-existent congestive heart failure or severe ischaemic heart disease [17]. An increase in the incidence of myocardial infarctions and/or strokes was observed in this study, and similar results were seen in a non-selected population in Japan [18].

In contrast, several other studies did not reveal such negative results, at least in patients without severe cardiovascular or cerebrovascular co-morbidities [2,4]. Normalizing haematocrit in haemodialysis patients with cardiac disease did not cause an increase in ambulatory blood pressure [19]. A study in peritoneal dialysis patients with diabetes mellitus showed that even a moderate increase of haematocrit level (25.8% up to $31\pm7.7\%$) may be associated with a significant augmentation of peripheral vascular complications [20]. However, the potential deleterious effects of not correcting the anaemia in such patients cannot be ignored.

The results reported in many studies, along with individually acquired clinical experience, are achieving a widespread consensus (also confirmed in this study)

for a target haemoglobin above 11 g/dl. The optimal target haemoglobin level in dialysis patients, however, remains undefined. The target haemoglobin should thus be individualized for each patient [2–21].

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