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Nephrology
Dialysis
Transplantation

European Best Practice Guidelines 1–4
Evaluating anaemia and initiating treatment

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Results

Key points from the EBPG

- Evaluate anaemia in chronic renal failure (CRF) patients when haemoglobin (Hb) is <12 g/dl (adult males), <11 g/dl (pre-menopausal females).
- Consider epoetin treatment in all CRF patients if Hb is consistently <11 g/dl.

Key findings from ESAM

- Epoetin treatment is initiated most often after dialysis has begun. Some variability is observed between countries.
- Haemoglobin levels at initiation of epoetin therapy (mean 8.7 g/dl) are much lower than the EBPG recommendation. Once again, variability between countries is seen.
- For haemodialysis patients with diabetic nephropathy, renovascular disease and polycystic kidney disease, the average haemoglobin levels are higher when epoetin is started than for other aetiologies. No comparable pattern is found for peritoneal dialysis patients.

As EBPG 1–3 are narrative guidelines for which no empirical support is available, the data reported here pertain mainly to EBPG 4 [1]. They are complemented with additional results that support the main issues in this cluster of guidelines.

The relationship between the start of dialysis and initiation of epoetin treatment was examined. As shown in Figure 2, the patterns are different for haemodialysis and peritoneal dialysis patients. Most often, for haemodialysis (52.8%) and peritoneal dialysis patients (42.4%), epoetin therapy was initiated after dialysis had begun. Few haemodialysis patients (11.2%) received epoetin before starting dialysis, whereas for peritoneal dialysis patients this proportion was greater (31.2%). Epoetin therapy and dialysis were initiated within 30 days of each other in 36.0% of haemodialysis and 26.4% of peritoneal dialysis patients. Table 11 summarizes the results by country, and some between-country variation is observed. Figure 3 presents aggregate findings for both cohorts of patients. In 35.1% of patients, the start of dialysis and initiation of epoetin therapy were simultaneous. Only 7.9% of patients were started on epoetin in the 6 months preceding dialysis, while 27.8% were started on epoetin in the 6-month period after the initiation of dialysis. The remaining 29.2% were in the '>6 months before' and '>6 months after' time periods.

EBPG 4 B recommends that epoetin therapy be initiated at a haemoglobin level <11 g/dl (haematocrit $<33\%$). The starting haemoglobin levels in ESAM differed for haemodialysis and peritoneal dialysis patients (Mann–Whitney U $=7210526.00$, $Z=-3.007$, $P<0.01$) and ranged from 5.0 to 13.0 g/dl for haemodialysis patients (mean $=8.7$ g/dl, SD $=1.2$) and also from 5.0 to 13.0 g/dl for peritoneal dialysis patients (mean $=8.8$ g/dl, SD $=1.2$). Of the haemodialysis patients, 96.4% had starting haemoglobin levels of 11.0 g/dl or less, as did 95.3% of peritoneal dialysis patients (Figure 4); 57.5% of haemodialysis and 56.6% of peritoneal dialysis patients had starting haemoglobin levels of 9.0 g/dl or less. The mean haemoglobin level at the initiation of epoetin therapy was 8.7 g/dl for the entire sample of patients. It is important to note that $>25\%$ of haemodialysis patients and $>30\%$ of peritoneal dialysis patients started epoetin therapy with haemoglobin levels between 8 and 8.9 g/dl, and $>25\%$ of dialysis patients started treatment below 8 g/dl. These starting haemoglobin levels were consistent regardless of the relationship between start of dialysis and initiation of epoetin therapy for both haemodialysis and peritoneal dialysis patients (Figure 5). Some variability between Western European countries was observed (Figure 6), with markedly low levels in certain countries. Treatment was started at mean haemoglobin levels >9 g/dl in only three countries (Sweden, The Netherlands and Finland).

Since epoetin was introduced in Europe in 1988–1989, we examined whether starting haemoglobin levels increased as time went on. Figure 7 shows the mean haemoglobin levels at initiation of epoetin

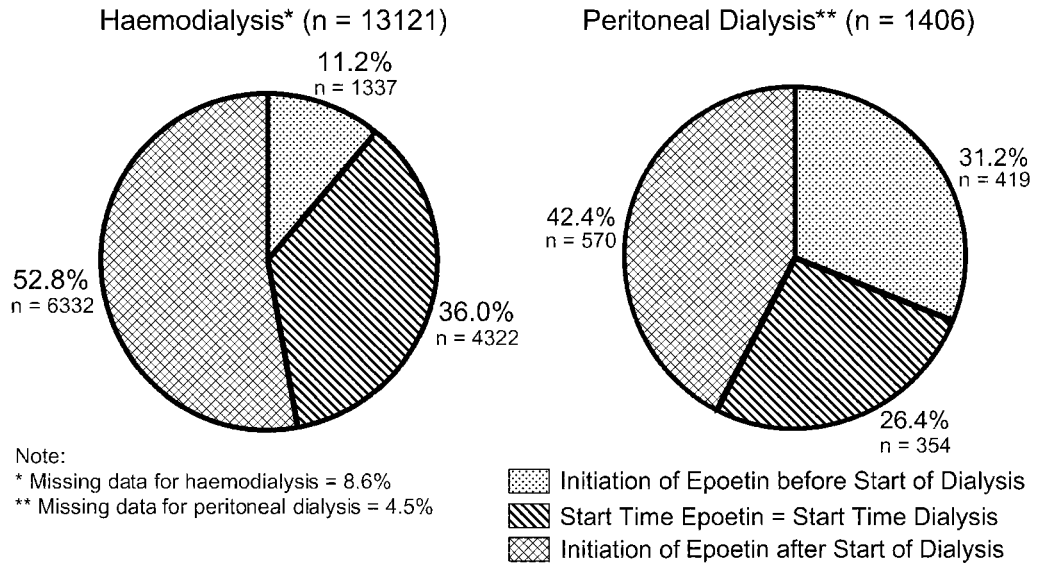

Fig. 2. Distribution of patients by epoetin initiation in relation to dialysis.

Table 11. Epoetin initiation in relation to type of dialysis, by country

Country (*n*)	Haemodialysis				Peritoneal dialysis			
	n	Start epoetin before (%)	Start epoetin at dialysis (%)	Start epoetin after (%)	*n*	Start epoetin before (%)	Start epoetin at dialysis (%)	Start epoetin after (%)
Total (13 334)[a]	11 991	11.2	36.0	52.8	1343	31.2	26.4	42.4
Austria (591)	531	16.4	53.9	29.8	60	21.7	41.7	36.7
Belgium and Luxembourg (1004)	956	19.0	45.4	35.6	48	41.7	22.9	35.4
Denmark (209)	146	20.5	25.3	54.1	63	39.7	20.6	39.7
Finland (317)	239	25.5	22.2	52.3	78	57.7	11.5	30.8
France (3552)	3188	7.8	22.0	70.1	364	24.7	29.9	45.3
Germany (4040)	4022	7.1	42.7	50.2	18	16.7	11.1	72.2
Greece (1259)	1207	4.6	42.0	53.4	52	0	1.9	98.1
Italy (353)[b]	5	20.0	80.0	0	348	24.4	29.6	46.0
Netherlands (356)	248	15.3	38.7	3.2	108	34.3	30.6	35.2
Norway (157)	135	23.0	43.0	34.1	22	63.6	22.7	13.6
Spain (655)	620	11.9	27.7	60.3	35	8.6	28.6	62.9
Sweden (538)	429	45.9	28.0	26.1	109	69.7	17.4	12.8
Switzerland (303)	265	17.4	51.7	30.9	38	21.14	36.8	42.1

[a]Missing data for haemodialysis = 8.6%; missing data for peritoneal dialysis = 4.5%.
[b]Italy supplied few haemodialysis patients to the study due to a national haemodialysis survey that was completed just prior to the current study.

therapy by cohort across three time periods. For haemodialysis patients, the mean levels increased significantly over time ($F = 106.91$, df = 2,11 008, $P < 0.001$). Both the 1991–1993 to 1994–1996 and the 1994–1996 to 1997–1999 increases were significant and contributed to the overall statistical significance. For peritoneal dialysis patients, an overall significance was also observed ($F = 5.109$, df = 2, 1284, $P < 0.01$), but this was due mainly to a significant difference in mean levels between the 1991–1993 period and the 1997–1999 period. However, in spite of this increase, the mean haemoglobin levels at initiation of epoetin therapy remain in the range of 8–9 g/dl.

We also investigated the relationship between starting haemoglobin levels and selected variables. As shown in Figure 8, there were small but significant differences between age groups (<50, 50–64, 65–80 and >80 years of age) for haemodialysis patients (Kruskal–Wallis $\chi^2 = 161.72$, df = 3, $P < 0.001$), with mean values ranging from 8.4 g/dl (SD = 1.3) to 8.8 g/dl (SD = 1.0). Patients less than 50 years of age started epoetin therapy at haemoglobin levels lower than older patients. For peritoneal dialysis patients, haemoglobin levels across age groups were consistent, and no significant differences were noted ($F = 1.37$, df = 3,1430, P = NS). Mean haemoglobin values for

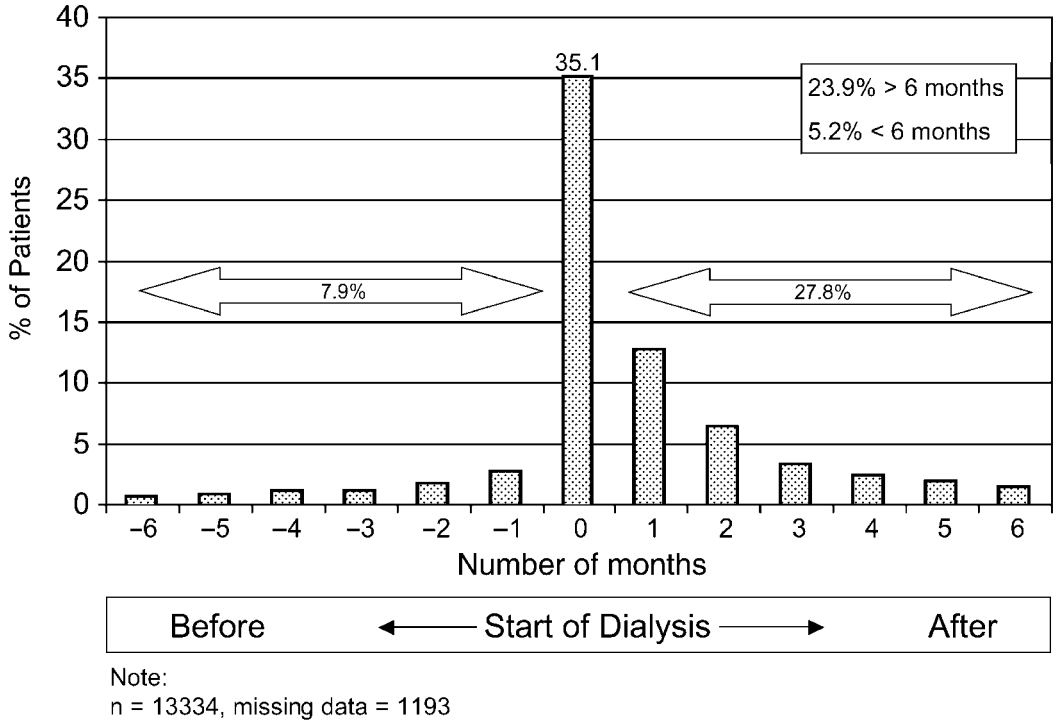

Fig. 3. Initiation of epoetin therapy in relation to start of dialysis.

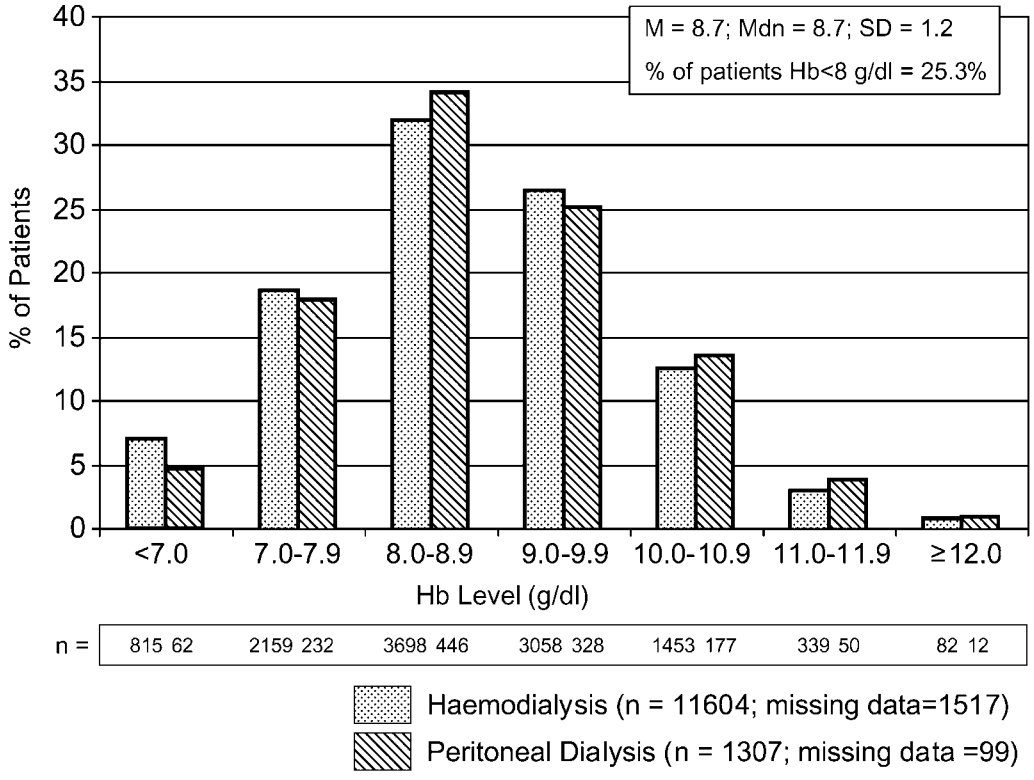

Fig. 4. Hb level at initiation of epoetin therapy.

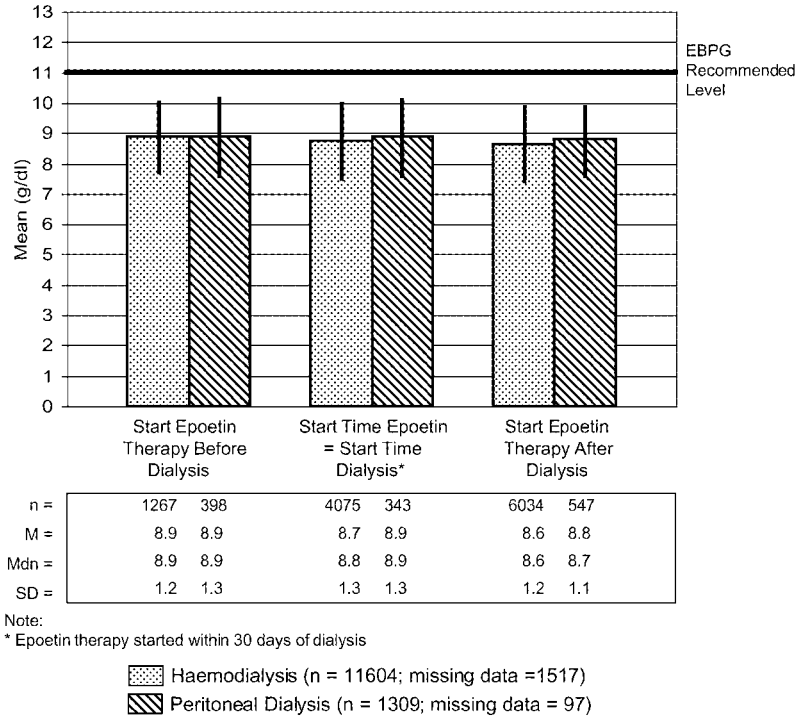

Fig. 5. Hb level by start time of dialysis/initiation of epoetin therapy.

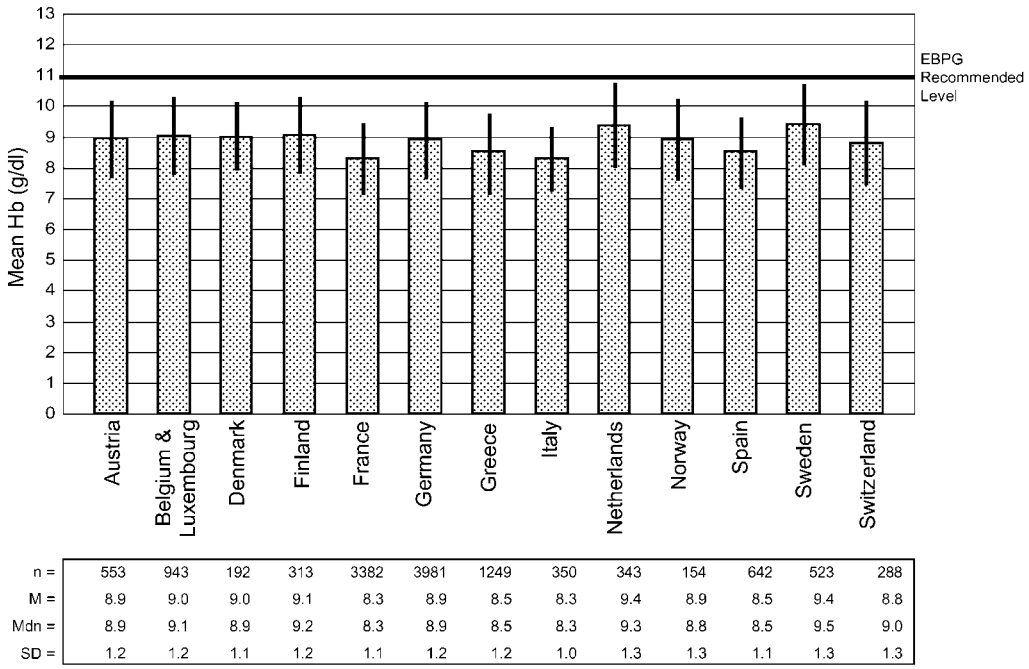

Fig. 6. Hb level at initiation of epoetin therapy by country.

this cohort ranged from 8.7 g/dl (SD = 1.1) to 8.9 g/dl (SD = 1.2).

Table 12 summarizes selected measures of starting haemoglobin across different causes of renal failure. Significant differences were observed across aetiologies for haemodialysis (Kruskal–Wallis $\chi^2 = 178.096$, df = 8, $P < 0.001$), with higher mean haemoglobin levels in patients with diabetic nephropathy, renovascular disease and polycystic kidney disease. Starting haemoglobin levels were within the range of similarity across aetiology for peritoneal dialysis patients (Kruskal–Wallis $\chi^2 = 12.033$, df = 8, P = NS).

Diabetic nephropathy and polycystic kidney disease were compared in relation to the time between

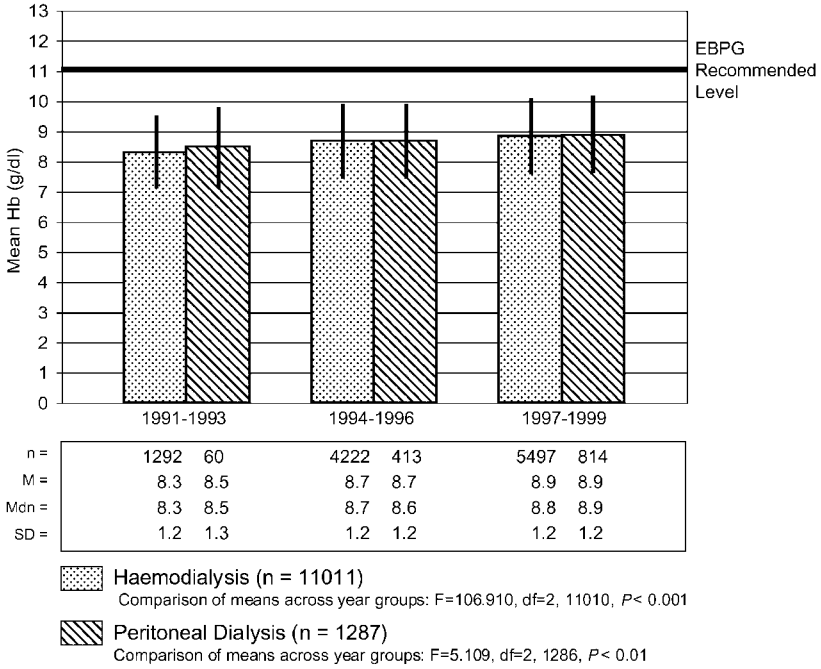

Fig. 7. Hb level at initiation of epoetin by year of initiation of epoetin therapy.

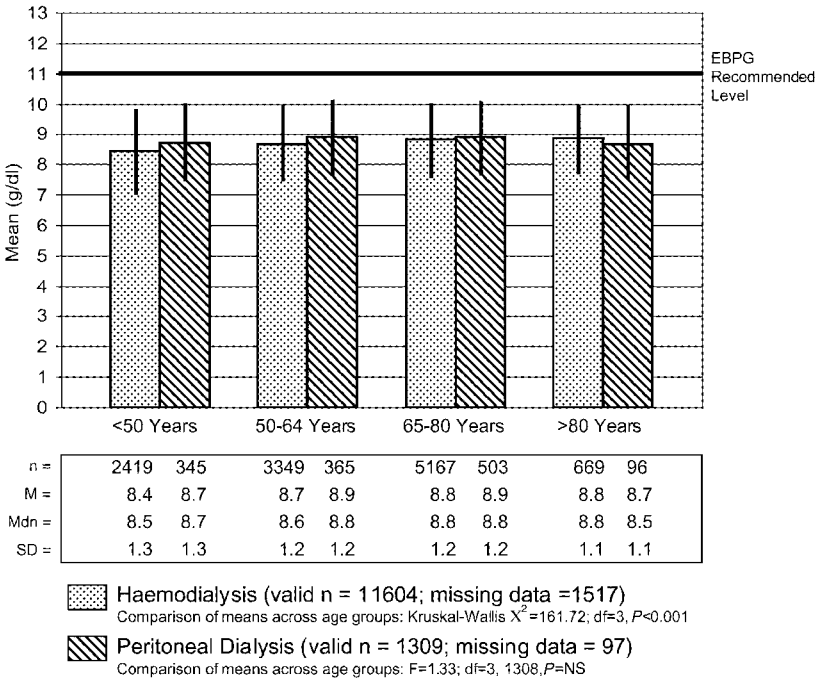

Fig. 8. Hb level at initiation of epoetin treatment by age.

initiation of dialysis and epoetin therapy (Table 13). For the entire sample, the relationship between the two aetiologies and the dialysis/epoetin time differential was statistically significant ($\chi^2 = 82.30$, df = 4, $P < 0.001$). Proportionately more polycystic kidney disease patients (52.9%) than diabetic nephropathy patients (43.7%) started epoetin therapy after dialysis. In contrast, the latter cohort had proportionately more patients (41.7%) starting dialysis and epoetin therapy simultaneously than the polycystic kidney patients (30.9%). Both cohorts had similar proportions of patients receiving epoetin before starting dialysis (diabetic nephropathy 14.6% *vs* polycystic kidney disease 16.2%).

Table 12. Hb level at initiation of epoetin therapy by aetiology of chronic renal failure

Aetiology	*n*	Mean (g/dl)	Median (g/dl)	SD (g/dl)
Chronic glomerulonephritis	3177	8.6	8.6	1.3
Diabetic nephropathy	2255	8.9	8.9	1.2
Renovascular disease	1764	8.8	8.8	1.2
Tubulo-interstitial nephropathy	1658	8.6	8.5	1.2
Polycystic kidney disease	855	8.9	8.9	1.2
Hereditary renal disease	275	8.5	8.5	1.2
Failed renal transplant[a]	258	8.6	8.5	1.3
Multiple myeloma	101	8.3	8.3	1.4
Undefined	2126	8.6	8.6	1.2

Missing data = 2058; tests for differences in Hb across aetiologies were performed for haemodialysis (Kruskal–Wallis $\chi^2 = 178.096$, df = 8, $P < 0.001$) and for peritoneal dialysis (Kruskal–Wallis $\chi^2 = 12.033$, df = 8, P = NS).
[a]After allograft rejection.

Table 13. Initiation of epoetin therapy by diabetic nephropathy and polycystic kidney disease for all patients

	Diabetic nephropathy		Polycystic kidney disease		All other patients	
	%	*n*	%	*n*	%	*n*
Initiation of epoetin therapy before start of dialysis ($n = 1695$)	14.6	340	16.2	143	12.5	1212
Start time epoetin = start time dialysis[a] ($n = 4540$)	41.7	968	30.9	272	34.1	3300
Initiation of epoetin therapy after start of dialysis ($n = 6641$)	43.7	1016	52.9	466	53.3	5159
Total patients		2324		881		9671

$\chi^2 = 82.30$, df = 4, $P < 0.001$.
[a]Dialysis and epoetin treatment were initiated within 30 days of each other.

Comments

EBPG 1–3 recommend when to start the work-up for the diagnosis of anaemia, how to evaluate anaemia in uraemic patients and how to diagnose anaemia associated with chronic renal failure. These diagnostic aspects were not studied in ESAM, and all the questions in this section of the questionnaire refer to EBPG 4: indications for starting treatment with epoetin. The recommendation of the guideline is to consider epoetin treatment when the haemoglobin concentration is consistently <11 g/dl for pre-dialysis and dialysis patients [1].

It is interesting to note the strikingly low percentage of patients starting epoetin therapy in the pre-dialysis phase. Only 11% of haemodialysis and 31% of peritoneal dialysis patients received epoetin before dialysis. Of the 14 European countries participating in ESAM, only two (Sweden and Finland) initiated epoetin therapy before haemodialysis in >25% of the patients (45.9 and 25.5%, respectively). Obrador *et al.* [2] recently reported that only 23% of a sample of 155 051 dialysis patients in the USA received epoetin before initiation of dialysis, but this is clearly higher than that observed in ESAM.

The haemoglobin levels when epoetin therapy was initiated were very low in relation to the EBPG recommendations. The number of patients starting epoetin therapy with haemoglobin levels of between 10 and 10.9 g/dl is <15% of the total sample, and >20% of the patients started treatment with severe anaemia (haemoglobin levels below 8 g/dl). It is interesting to note that the haemoglobin level for initiating epoetin therapy was similar when the treatment began before the initiation of dialysis, simultaneously and after starting dialysis.

In recent years, there has been a tendency to start epoetin therapy with higher haemoglobin levels, but still with severe anaemia (haemoglobin levels below 9 g/dl), and this falls short of the EBPG recommendations. It is hard to understand why patients under 50 years of age started treatment with lower haemoglobin levels than did older patients.

This late start in anaemia treatment gives additional time for deleterious effects. The decrease in exercise capacity and oxygen uptake by muscle tissue will reduce exercise capacity [3]. Appetite and nutrition, sleep–awake patterns, depression, sexual dysfunction and quality of life deterioration will develop as a consequence of the anaemia [3–6], but the most severe deleterious effects are on the heart. Left ventricular hypertrophy is more frequent as renal function declines and anaemia progresses. No fewer than 75% of the patients who start dialysis have left ventricular hypertrophy [7], which can improve (but rarely normalizes) with treatment of the anaemia [8,9].

Anaemia often starts to be symptomatic when haemoglobin levels are below 11 g/dl. However, it is more difficult to know when the cardiovascular effects of anaemia, and specifically left ventricular hypertrophy, start to develop. Recently, a Canadian study found that a decline in haemoglobin (independent of the anaemia) and an increase in systolic blood pressure were associated with the development of left ventricular hypertrophy [7].

Various studies have correlated morbidity and mortality to the degree of anaemia [10–12], which means that early correction of anaemia may well prevent left ventricular hypertrophy, as well as reduce morbidity and mortality. Early anaemia treatment will not accelerate the decline in renal function, and there is evidence from small uncontrolled studies that correction of anaemia can even slow down the progression of renal impairment in non-diabetic patients [13].

The principal conclusion of this section of ESAM is that very few patients started treatment of anaemia in the pre-dialysis phase. Moreover, epoetin therapy often was initiated when the patients had very low haemoglobin levels, irrespective of the age of the patient and the cause of renal failure.

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