Nephrol Dial Transplant (2000) 15 [Suppl 4]: 43–50

Nephrology
Dialysis
Transplantation

European Best Practice Guidelines 14–16
Inadequate response to epoetin

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Results

Key points from the EBPG

- A need for >300 IU/kg/weekly epoetin defines an inadequate response ('resistance').
- Iron deficiency (absolute or functional) is the most common cause of an inadequate response to epoetin although patients must be screened for other causes, such as raised iPTH, malignancy, infection/inflammation, aluminium toxicity, etc.

Key findings from ESAM

- Of the 370 patients receiving an epoetin dose ⩾300 IU/kg/week, almost 70% had haemoglobin levels <11.0 g/dl. More than a third of the patients in this high-dose category received no iron during month 1 of the study.
- Angiotensin-converting enzyme (ACE) inhibitor therapy does not appear to affect the response to epoetin.

Table 25 compares data for haemodialysis patients with an epoetin dose ⩾300 IU/kg/week *vs* <300 IU/kg/week (in month 1). Since the cohort of patients with an epoetin dose ⩾300 IU/kg/week is very small ($n=370$), comparative analyses would be inappropriate. For the group of 'high-dose' patients, only 31.4% had haemoglobin levels of ⩾11.0 g/dl; 29.7% had levels between 10.0 and 10.9 g/dl, 21.1% between 9.0 and 9.9 g/dl, and the remaining 17.8% below 9.0 g/dl (Figure 39). The mean serum ferritin level was 481.2 μg/l (SD=472.9) and the mean transferrin saturation (TSAT) was 25.1% (SD=13.2). Of 313 patients for whom serum ferritin values were available, 36 (11.5%) had levels <100 μg/l; 87 of 223 patients (39.0%) had a TSAT of <20%. The mean C-reactive protein (CRP) for this 'high-dose' group was 21.8 mg/l with a median of 10.0 mg/l (SD=29.5).The mean iPTH level was 191.9 pg/ml with a median of 93.0 pg/ml (SD=283.8) and the mean serum aluminium level was 3.7 μmol/l (median=1.0 μmol/l, SD=4.9). There was a fairly marked skew in the distribution of these parameters. The mean age for this small cohort was 58 years (SD=16.1), Kt/V ranged from 0.6 to 2.2 with a mean of 1.3 (median=1.3, SD=0.3). These patients received on average 20.2 mg/day of ACE inhibitor medication (median=10.0, SD=28.6). Approximately 38.2% of the patients in this dose category received no iron at month 1, while 3.7% received oral and 58.1% received i.v. iron.

Epoetin dose and achieved haemoglobin may vary in relation to concomitant pathology with which

Table 25. Clinical and laboratory parameters for haemodialysis patients receiving a maintenance dose of epoetin, month 1, by level of epoetin dose

	<300 IU/kg/week		⩾300 IU/kg/week	
	n	Statistic	*n*	Statistic
Mean age (years)	10 534	62	370	58
Mean CRP (mg/l)	3927	14.9	189	21.8
Mean Kt/V	5285	1.3	223	1.3
Mean iPTH (pg/ml)	9143	208.3	313	191.9
Mean aluminium level (μmol/l)	3480	4.7	122	3.7
Mean haemoglobin (g/dl)	10 534	10.9	370	10.3
Mean transferrin saturation (%)	6017	27.4	223	25.1
Mean serum ferritin (μg/l)	8873	441.1	313	481.2
% of patients receiving oral iron supplementation	505	4.9	13	3.7
% of patients receiving i.v. iron supplementation	5669	55.4	205	58.1
% of patients receiving no iron supplementation	4063	39.7	135	38.2
Mean ACE inhibitor dose/day (mg)	2486	19.3	78	20.2

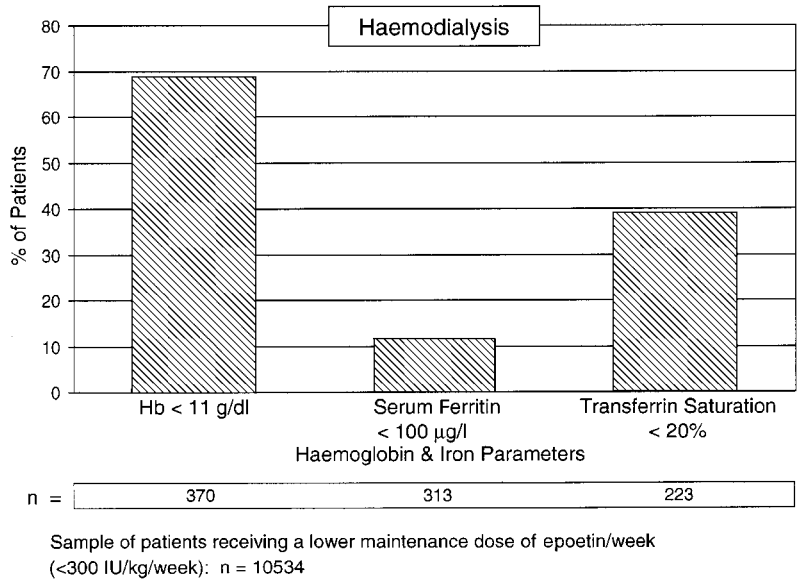

Fig. 39. Hb and iron parameters for patients receiving a higher maintenance dose of epoetin/week ($\geqslant$300 IU/kg/week) month 1 ($n=370$).

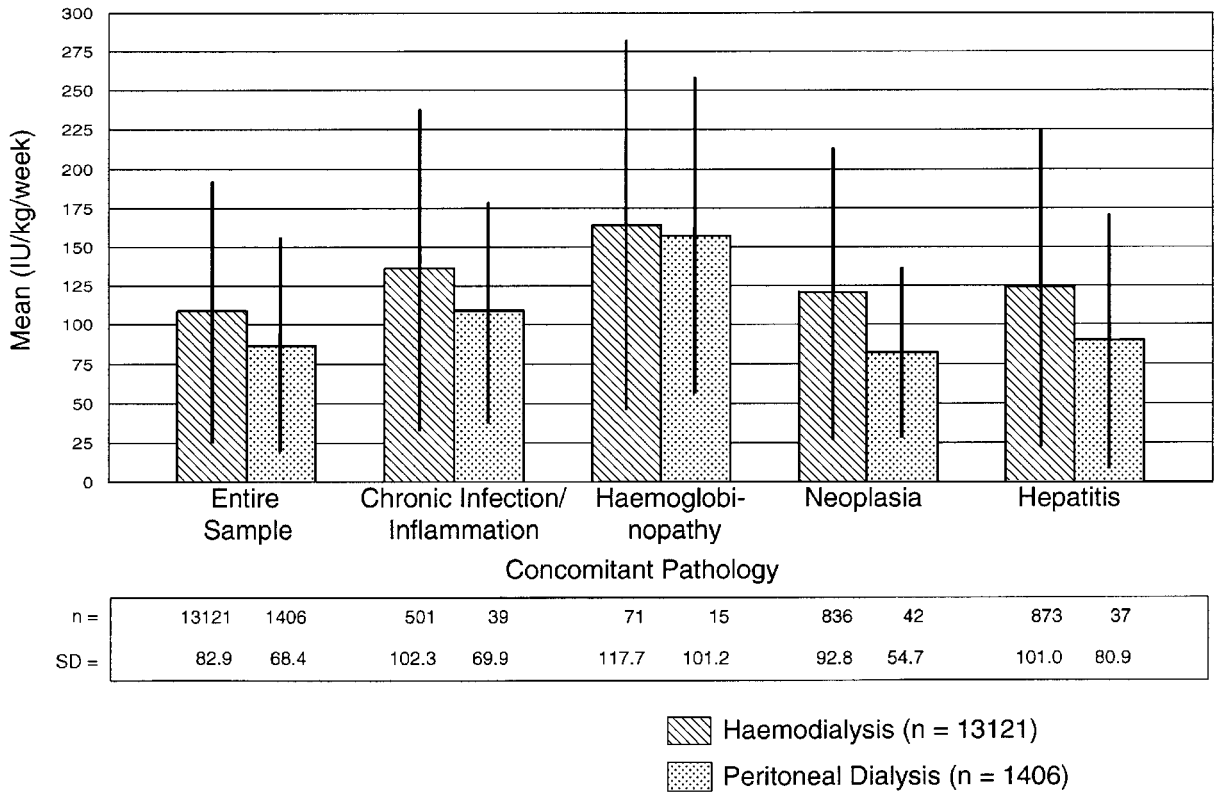

Fig. 40. Dose of epoetin by concomitant pathology (month 1).

the patient presents (Figure 40 and Table 26). Using month 1 data, the epoetin dose was consistently higher for haemodialysis patients than for peritoneal dialysis patients across all concomitant pathologies. The variability of epoetin dose for peritoneal dialysis patients was also consistently lower than for haemodialysis patients, as shown by the smaller standard deviations across all concomitant pathologies. A subsample of interest was a group of patients with a haemoglobinopathy, who were reviewed for differences in target haemoglobin relative to the remaining renal failure population. Patients with a haemoglobinopathy had significantly lower target haemoglobin levels than other patients with chronic renal failure who did not have a haemoglobinopathy ($t=-2.345$, df$=13\ 641$, $P<0.05$) (Figure 41, Table 27).

EBPG 14 recommends evaluation and, if reversible, treatment of infection/inflammation. Figure 42 summarizes data on epoetin dose and haemoglobin level, stratified by CRP levels: $\leqslant$10.0 mg/l ($n=3612$),

Table 26. Dose of epoetin, target Hb and achieved Hb by concomitant pathology

	Haemodialysis					Peritoneal dialysis				
	Target Hb (*n*)	Epoetin dose (*n*) at month 1	Achieved Hb			Target Hb (*n*)	Epoetin dose at month 1 (*n*)	Achieved Hb		
			Month 1 (*n*)	Month 3 (*n*)	Month 6 (*n*)			Month 1 (*n*)	Month 3 (*n*)	Month 6 (*n*)
Entire sample	11.4 (12 370)	108.9 (13 121)	10.8 (13 121)	11.0 (12 428)	11.0 (11 474)	11.6 (1273)	87.0 (1406)	11.2 (1406)	11.4 (1262)	11.3 (1073)
Chronic infection/ inflammation	11.4 (476)	135.7 (501)	10.5 (501)	10.8 (474)	10.9 (442)	11.3 (33)	108.4 (39)	11.0 (39)	11.2 (38)	11.4 (30)
Haemoglobinopathy	11.2 (68)	164.1 (71)	10.2 (71)	10.3 (67)	10.7 (64)	11.2 (14)	156.7 (15)	9.8 (15)	10.0 (13)	9.9 (14)
Neoplasia	11.3 (797)	120.1 (836)	10.7 (836)	10.9 (795)	10.8 (716)	11.4 (36)	81.9 (42)	11.3 (42)	11.2 (40)	11.3 (33)
Hepatitis	11.4 (835)	124.2 (873)	10.8 (873)	11.0 (847)	11.0 (795)	11.3 (34)	90.0 (37)	11.1 (37)	11.4 (34)	10.9 (26)

10.1–50.0 mg/l ($n=1594$), 50.1–100.0 mg/l ($n=248$) and >100.0 mg/l ($n=124$). Differences in month 1 mean epoetin dose by CRP category are statistically significant ($F=34.1$, df = 3, $P<0.001$). The dose increases from 104.3 IU/kg/week for the $\leqslant 10.0$ mg/l category to 146.0 IU/kg/week for the >100 mg/l category. Month 1 haemoglobin also varies significantly in relation to CRP category ($F=17.894$, df = 3, $P<0.001$), with haemoglobin decreasing across the first three CRP categories (from 11.1 g/dl for the $\leqslant 10$ mg/l category to 10.6 g/dl for the >100 mg/l category).

The database was then censored by eliminating patients with CRP levels of $\leqslant 10$ mg/l ($n=1966$). Again using month 1 data, there was a very weak but (due to the sample size) significant correlation between month 1 CRP levels and epoetin dose ($r=0.077$, $P<0.01$). Considering, therefore, that CRP level accounts for a minimal 0.6% of the variance in epoetin dose, the absence of an association between infection and dose within a single month may be inferred. This deduction seems warranted given also the very low correlation ($r=0.078$) between month 1 CRP level and month 2 epoetin dose (explained variance = 0.6%). However, when stratified on chronic infection/ inflammation, defined as a CRP level $\geqslant 50$ mg/l on any three or more months, there is consistently a statistically significant difference in epoetin dose. Figure 43 shows the difference in both epoetin dose and achieved haemoglobin between patients classified as having chronic infection/inflammation and those without chronic infection/inflammation.

Concomitant therapies

It has been suggested that concomitant therapies and vitamin supplementation may influence the response to epoetin therapy, although there are limited scientific data to support this. For example, the influence of ACE inhibitors on both absolute haemoglobin concentrations and response to epoetin therapy has been controversial in the literature [1–13]. Figure 44 illustrates the difference in mean epoetin dose (in the maintenance phase) by use of ACE inhibitors *vs* non-use both within dialysis groups and across dialysis groups. Prior to stratification by ACE inhibitor use, epoetin dose was significantly higher in haemodialysis patients. This holds true in both the use of ACE inhibitor group and the non-use group. Epoetin dose differences between ACE users and non-users were significant for peritoneal dialysis patients. Differences in maintenance epoetin dose and haemoglobin level between ACE inhibitor users and non-users are shown for all months in Table 28. Differences between the mean haemoglobin of ACE users and non-users range from 0 to 0.1 g/dl, and those for mean epoetin dose ranged from 0.4 to 1.8 IU/kg/week.

Another subsample of interest which was evaluated was those patients receiving enalapril, the ACE inhibitor used most frequently in the dialysis population. Table 29 provides the monthly breakdown of haemo-

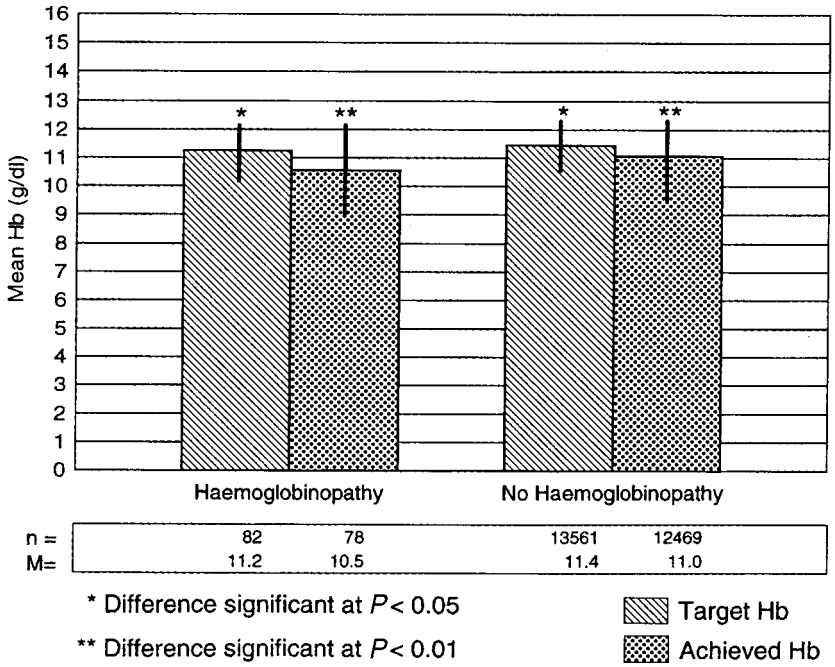

Fig. 41. Mean target Hb and achieved (month 6) Hb by haemoglobinopathy.

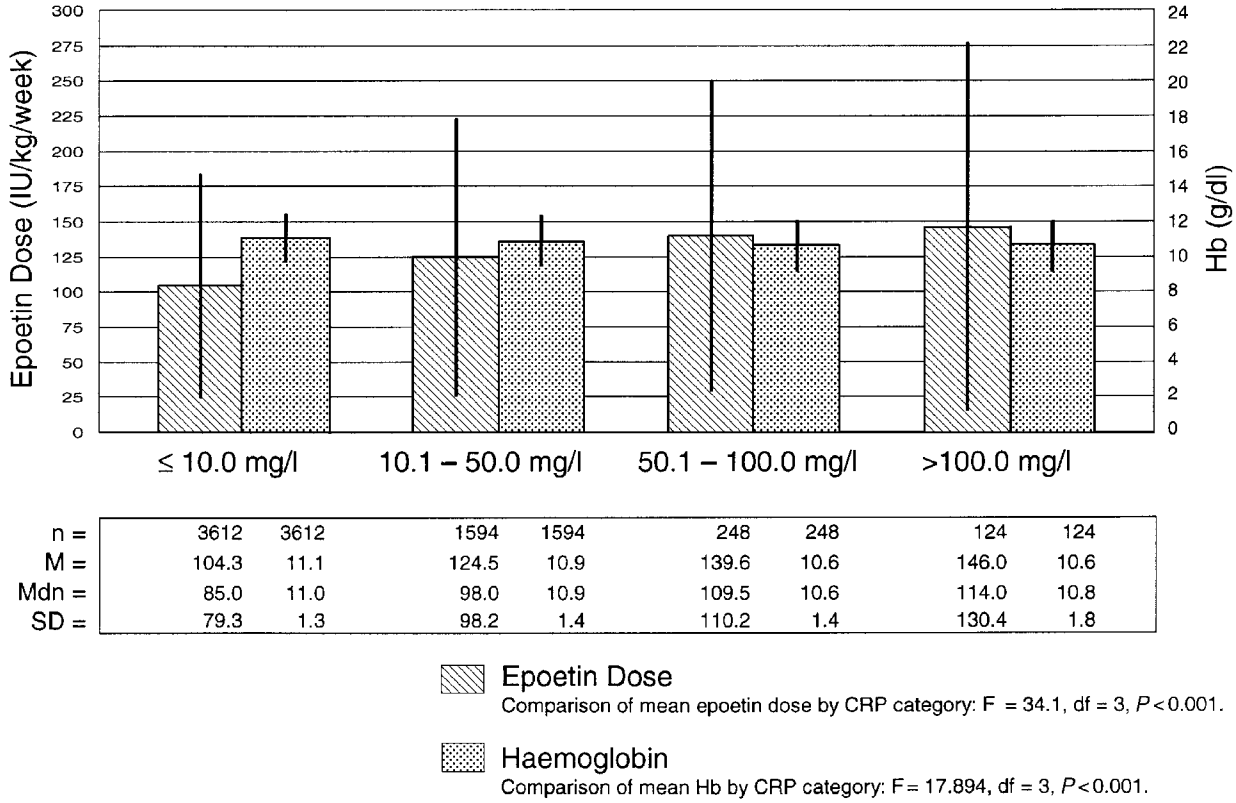

Fig. 42. Epoetin dose and Hb level by CRP (month 1).

globin and epoetin dosage by monthly enalapril dose (5 mg/day and 20 mg/day). The monthly achieved haemoglobin and epoetin dose variables correspond to the same month in which enalapril was evaluated. The target haemoglobin, however, was recorded only upon enrolment into ESAM but was evaluated repeatedly according to the monthly categorization of enalapril. Within all three variables (target haemoglobin, achieved haemoglobin and epoetin dose), and within all months, the values increased between those receiving 5 mg/day of enalapril and those receiving 20 mg/day. None of these differences is statistically

Table 27. Descriptive statistics for patients with/without haemoglobinopathy

	Patients with haemoglobinopathy	Patients without haemoglobinopathy
Mean target haemoglobin (g/dl)	11.2	11.4
Mean month 1 achieved haemoglobin (g/dl)	10.1	10.9
Mean month 1 epoetin dose (IU/kg/week)	162.8	106.4

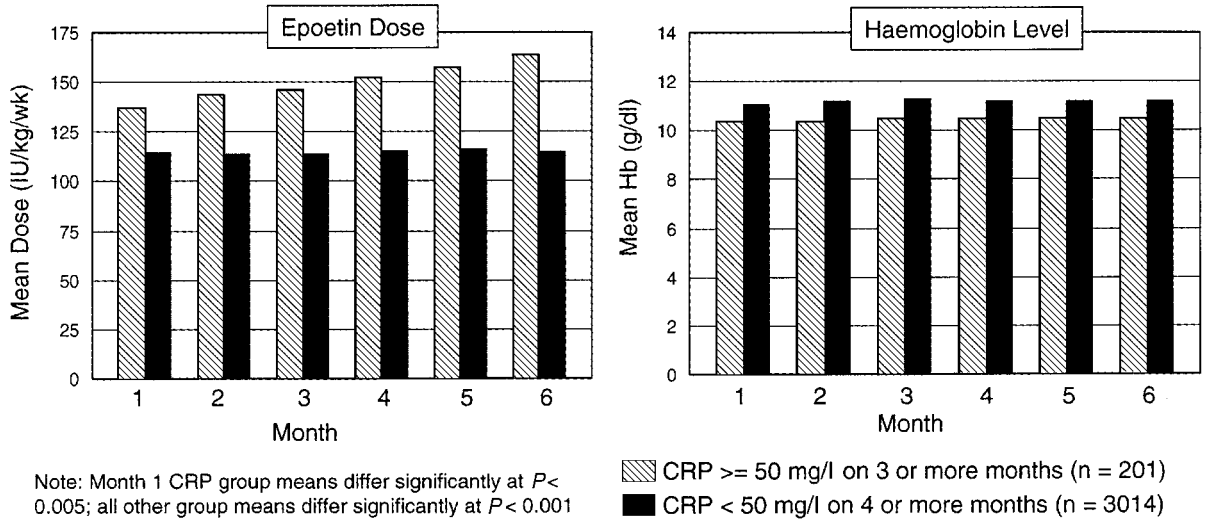

Fig. 43. Epoetin dose and Hb level assessment of patients with chronic infection/inflammation.

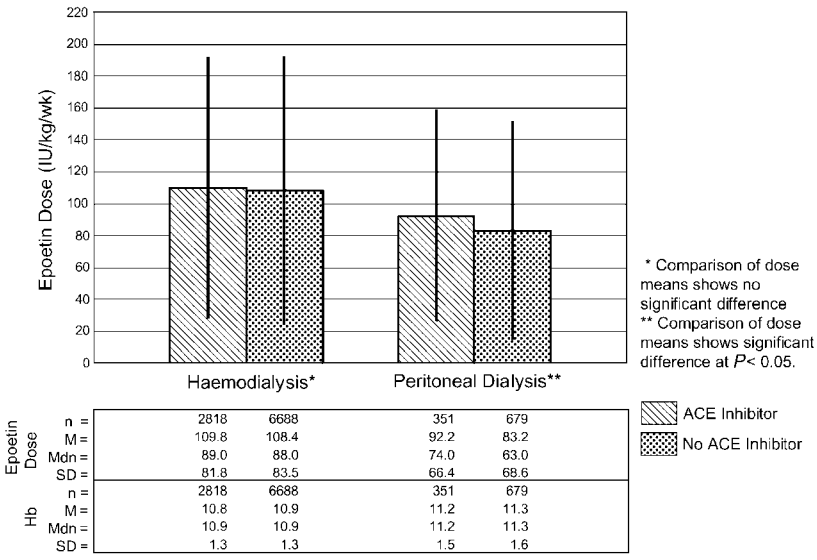

Fig. 44. Dose of epoetin (maintenance phase) by use of ACE inhibitor at month 1.

significant, however, with the exception of month 1 haemoglobin.

Use of vitamins, folate and L-carnitine supplementation was assessed for the entire ESAM sample (Table 30). There was considerable variability of supplementation across countries especially with regard to vitamin B_{12}, vitamin C and L-carnitine. Vitamin D and folic acid are the most frequently utilized supplementations. None of these supplementations had any influence on either haemoglobin or epoetin dose.

Comments

The most common cause of inadequate response to epoetin therapy is absolute or functional iron deficiency [14]. Of 313 patients receiving $\geqslant$300 IU/kg/week

Table 28. Dose of epoetin and Hb level by ACE inhibitor for patients on a maintenance dose of epoetin during the entire study period

		ACE inhibitor						No ACE inhibitor					
		n	Mean	Median	SD	Min	Max	*n*	Mean	Median	SD	Min	Max
Month 1	Epoetin dose (IU/kg/week)	3169	107.8	87.0	80.4	10.0	999.0	7367	106.0	86.0	82.6	7.0	999.0
	Hb level (g/dl)		10.9	10.9	1.3	5.3	15.9		11.0	11.0	1.3	5.6	15.9
Month 2	Epoetin dose (IU/kg/week)	3108	108.2	86.0	85.2	7.0	983.0	7555	107.0	86.0	85.3	7.0	999.0
	Hb level (g/dl)		11.0	11.0	1.3	5.1	16.0		11.1	11.0	1.4	5.3	15.8
Month 3	Epoetin dose (IU/kg/week)	3028	108.4	85.0	87.2	7.0	989.0	7601	107.8	85.0	88.9	7.0	999.0
	Hb level (g/dl)		11.0	11.0	1.3	5.2	15.6		11.1	11.1	1.3	5.6	16.0
Month 4	Epoetin dose (IU/kg/week)	2926	109.5	86.0	90.9	7.0	967.0	7579	108.2	85.0	90.1	7.0	970.0
	Hb level (g/dl)		11.0	11.0	1.3	5.8	15.7		11.1	11.1	1.3	5.7	16.0
Month 5	Epoetin dose (IU/kg/week)	2787	108.5	86.0	88.9	7.0	900.0	7398	107.8	85.0	87.5	7.0	999.0
	Hb level (g/dl)		11.0	11.0	1.3	5.7	15.9		11.1	11.1	1.3	5.9	16.0
Month 6	Epoetin dose (IU/kg/week)	2653	107.7	86.0	85.1	7.0	895.0	7163	108.1	86.0	87.1	7.0	945.0
	Hb level (g/dl)		11.0	11.0	1.3	5.0	15.3		11.0	11.0	1.3	5.0	16.0

of epoetin (Figure 39), 36 patients had absolute iron deficiency and 87 of 223 patients with transferrin saturation measurements had functional iron deficiency. The mean serum ferritin level (481.2 ± 472.9 µg/l) and mean transferrin saturation ($25.1 \pm 13.2\%$) reflect, however, 'adequate' iron status for the whole group of patients with an inadequate response to epoetin.

The mean CRP levels were greater in patients receiving the high maintenance dose of epoetin as compared with those receiving the lower dose (Table 25). At month 1, data on epoetin doses and haemoglobin levels increase and decrease, respectively, with each successively higher CRP category (Figure 42). CRP levels $\geqslant 50$ mg/l on three or more months result in significantly higher epoetin requirements and lower haemoglobin levels throughout the study period of 6 months as compared with haemodialysis patients with CRP levels <50 mg/l on four or more months (Figure 43). Bárány *et al.* [15] have also shown that elevated CRP values are associated with higher dose requirements of epoetin to keep the target haemoglobin values constant.

The achieved haemoglobin levels of patients with neoplasia or hepatitis were almost the same as for the entire sample, but epoetin doses were higher (Figure 40, Table 26). These findings are probably due to excessive cytokine production which reduces the epoetin response [16]. Other factors known to influence the response to epoetin were not different between the groups receiving <300 IU/kg/weekly or $\geqslant 300$ IU/kg/weekly (Table 25).

Differences in epoetin dose were not observed between ACE inhibitor users and non-users for haemodialysis patients but were observed (at $P<0.05$) for CAPD patients (Figure 44, see also Table 28). The effect of ACE inhibitors on both haemoglobin concentrations and response to epoetin therapy has been controversial [1–13]. Erturk *et al.* [17] switched ACE inhibitors to another antihypertensive medication in 23 out of 68 hypertensive haemodialysis patients receiving epoetin and an ACE inhibitor for >1 year. Withdrawal of ACE inhibitors resulted in an increase in haemoglobin level, and a decrease in epoetin dose. The inhibitory effect of ACE inhibitors on the action of epoetin is most apparent when high doses of ACE inhibitors are used, particularly if the patient is on a low dose of epoetin. However, neither 5 nor 20 mg of enalapril per day had a significant impact on epoetin response in the study presented here (Table 29). Macdougall [18] recommended that the indication for the ACE inhibitor therapy be reviewed if there is an inadequate response to epoetin. Switching to an alternative drug may be easier when used for treating hypertension than when used for treating patients with left ventricular dysfunction or diabetic nephropathy. Consistent with ESAM data, the dose or duration of ACE inhibitor therapy did not affect haemoglobin or haematocrit level in the study of Charytan *et al.* [19]. The authors concluded that ACE inhibitor therapy

Table 29. Target and achieved haemoglobin, and epoetin dosage of patients receiving enalapril

		Target Hb (g/dl)			Achieved Hb (g/dl)			Epoetin dose (IU/kg/week)		
		Mean	SD	Sample size (*n*)	Mean	SD	Sample size (*n*)	Mean	SD	Sample size (*n*)
Month 1 Enalapril	5 mg/day	11.5	0.87	177	10.6	1.33	193	108.8	69.35	193
	20 mg/day	11.5	0.88	140	11.1	1.34	151	110.6	74.91	151
Month 2 Enalapril	5 mg/day	11.4	0.84	167	11.0	1.43	183	107.8	67.10	183
	20 mg/day	11.6	0.91	133	11.0	1.31	138	112.7	75.73	138
Month 3 Enalapril	5 mg/day	11.4	0.81	169	10.8	1.36	183	110.5	88.92	183
	20 mg/day	11.5	0.91	126	11.1	1.35	131	115.5	80.14	131
Month 4 Enalapril	5 mg/day	11.4	0.80	169	10.9	1.18	184	110.1	83.46	184
	20 mg/day	11.4	0.91	126	11.1	1.42	131	112.9	76.72	131
Month 5 Enalapril	5 mg/day	11.4	0.84	173	11.0	1.19	185	101.9	77.29	185
	20 mg/day	11.5	0.90	115	11.1	1.29	120	107.7	66.72	120
Month 6 Enalapril	5 mg/day	11.4	0.86	168	11.0	1.24	186	109.1	81.37	186
	20 mg/day	11.5	0.91	124	11.1	1.34	130	114.5	75.95	130

does not appear to affect the response to epoetin in chronic dialysis patients.

Because ESAM is a prospective survey and not an interventional trial, we cannot consider these results as absolute proof of the non-interference of ACE inhibitors with haemoglobin and epoetin dose. However, we can conclude that in this large population no obvious differences were found. This does not, however, exclude the possibility that individual patients may need more epoetin during ACE inhibitor therapy or that haemoglobin levels may increase after withdrawal of the ACE inhibitor.

Supplementation with L-carnitine is recommended to achieve maximal erythropoiesis [20–25]. High plasma iPTH concentrations have been associated with resistance to epoetin, but treatment with active forms of vitamin D may counteract this [26–30]. Vitamin C may act as a synergist to epoetin, but the risks of oxalate deposition from the large doses required may reduce its potential use [31,32]. Tarng and Huang (33) treated 12 epoetin-resistant, iron-overloaded patients with ascorbic acid (300 mg i.v. post-dialysis three times weekly). After 8 weeks of treatment, the haematocrit increased significantly, with a concomitant rise in transferrin saturation, and a decrease in zinc protoporphyrin. Monthly doses of epoetin were also significantly reduced. Possible explanations for this effect of ascorbic acid include increased iron absorption, mobilization of iron from inert tissue stores and increased iron utilization in the erythron [34].

Folic acid and vitamin B_{12} deficiencies are known to cause a macrocytic anaemia, and supplementation of these agents is recommended. There is also a suggestion that the anti-oxidant effects of vitamin E supplementation might enhance the epoetin response [35]. There is considerable variability of supplementation across countries, particularly with regard to vitamin B_{12}, vitamin C and L-carnitine (Table 30).

In conclusion, absolute and functional iron deficiency as well as elevated CRP levels were associated with an inadequate response to epoetin treatment. Peritoneal dialysis patients displayed differences in epoetin dose for ACE inhibitor users *vs* non-users; haemodialysis patients showed no such difference in epoetin dose levels. Considerable variability exists with regard to vitamin B_{12}, vitamin C and L-carnitine supplementation across Europe.

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Table 30. Month 3 supplementation by country

	Vitamin B_{12}		Vitamin E		Vitamin C		Vitamin D		Folic acid		L-Carnitine		Vitamin B_{12} + folic acid	
	% patients	Sample size (*n*)	% patients	Sample size (*n*)	% patients	Sample size (*n*)	% patients	Sample size (*n*)	% patients	Sample size (*n*)	% patients	Sample size (*n*)	% patients	Sample size (*n*)
Austria	25.4	650	0.2	603	39.7	652	44.6	659	29.1	612	1.5	682	12.7	608
Belgium and Luxembourg	38.6	1045	6.0	1026	24.4	1040	38.0	1039	41.0	1026	0.7	1088	23.3	1020
Denmark	18.5	205	0.5	201	75.1	209	45.9	209	48.0	204	0.9	221	2.5	201
Finland	6.5	293	0.4	280	95.3	301	51.2	293	11.4	280	0.3	321	2.2	275
France	4.7	3716	2.6	3551	3.4	3711	36.9	3734	19.1	3575	3.7	3885	3.0	3546
Germany	17.9	4196	0.8	3862	46.1	4249	53.8	4220	45.4	3948	11.3	4365	15.4	3890
Greece	48.7	1072	4.5	847	1.3	871	40.0	314	60.8	1032	15.6	1346	35.7	988
Italy	6.8	308	31.2	369	0.7	303	45.2	323	12.5	263	0.6	348	5.8	259
Netherlands	42.6	310	17.1	315	88.5	356	55.0	338	65.1	350	1.6	373	22.8	303
Norway	18.3	153	3.4	149	25.5	153	81.0	153	17.3	150	0.0	162	8.7	150
Spain	46.5	648	0.9	580	33.3	651	40.2	652	48.3	611	6.8	690	36.0	592
Sweden	19.5	517	3.4	507	65.3	524	54.1	523	43.7	508	0.2	556	13.7	502
Switzerland	13.5	267	23.4	252	41.4	295	39.5	299	49.8	291	5.2	327	8.2	245
Total	18.5	13 380	2.5	12 427	30.7	13 315	45.4	13 479	37.2	12 850	6.5	14 362	14.2	12 579

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