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Nephrology
Dialysis
Transplantation

European Best Practice Guidelines 9–13
Anaemia management

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Results

Key points from the EBPG

- A starting dose of 50–150 IU/kg/week epoetin, preferably given subcutaneously, is appropriate for almost all chronic renal failure (CRF) patients; the target is to increase haemoglobin (Hb) at a rate of 1–2 g/dl/month.
- Monitor Hb regularly during epoetin treatment (correction phase: every 1–2 weeks; maintenance phase: every 4–6 weeks).

Key results from ESAM

- The mean epoetin dose administered in month 3 of the study (107.8 IU/kg/week) remained within the EBPG recommendation.
- Intravenous (i.v.) administration is used slightly more often than the subcutaneous (s.c.) route for haemodialysis patients; s.c. administration is preferred for peritoneal dialysis patients.
- Two-thirds of the patients receiving i.v. epoetin had three injections per week. In contrast, one-quarter of the patients receiving s.c. epoetin were treated with one injection per week and one-third of patients received two injections weekly.
- 53.6% of patients achieved Hb levels of at least 11 g/dl at month 6 of the study, well below the 85% standard recommended by the EBPG.

According to the EBPG, target haemoglobin concentrations for a given patient should be reached within 2–4 months of initiating treatment. The initial dose of epoetin should be 50–150 IU/kg/week (typically 4000–8000 IU/week) (EBPG 10A). The median maintenance dose of epoetin in a population of patients given s.c. epoetin will usually be <125 IU/kg/week, with $>90\%$ of patients receiving <300 IU/kg/week ($\sim 20\,000$ IU/week) (EBPG 12D) (for the definition of correction and maintenance phases used in this survey, see Figure 28). Failure to attain the target haemoglobin concentration while receiving >300 IU/kg/week of epoetin s.c., or a continued need for such dosage to maintain the target, indicates 'resistance' to epoetin (EBPG 14A).

Table 20 shows aggregate and by-country epoetin dose and achieved haemoglobin for month 3. Mean month 3 epoetin doses range from a low of 93.1 IU/kg/week in Germany to a high of 161.2 IU/kg/week in Sweden. Achieved mean haemoglobin ranges from a low of 10.8 g/dl in France to a high of 12.0 g/dl in Sweden. Tables 21 and 22 present statistics for month 3 doses and haemoglobin for the aggregate ESAM sample and by-country samples for haemodialysis patients and peritoneal dialysis patients, respectively.

Table 23 shows the distribution of epoetin dose (in groupings of 100 IU/kg/week) by injection route for haemodialysis and peritoneal dialysis patients in the maintenance phase. Figures 29 and 30 show the distribution of injection route by epoetin dose in month 1 for haemodialysis and peritoneal dialysis patients. The relationship between dose, administration route and epoetin treatment phase (correction *vs* maintenance dose) is summarized in Figure 31. Note the differences in range of dose for patients in the correction and the maintenance phases, yet also the larger standard deviation for patients in the correction phase receiving epoetin i.v.

Data on the number of injections per week used to administer epoetin in relation to administration route and treatment phase are presented in Figures 32 and 33. For month 1 data, there were 316 i.v. and 412 s.c. patients in the correction phase compared with 5431 i.v. and 6365 s.c. patients in the maintenance phase. Among the patients in the correction phase using the i.v. route, 76.3% of patients received three injections per week, whereas among patients in the correction phase using the s.c. route, 47.5% had three injections per week and 37.6% had two injections per week. For patients in the maintenance phase receiving i.v. epoetin, 65.6% had three injections a week compared with 37.4% for s.c. patients. Of patients receiving i.v. epoetin in the maintenance phase, 22.6% received two injections per week, and only 11.1% of patients used one injection per week. This is in contrast to the group of patients using s.c. in the maintenance phase, in whom 36.4% had twice-weekly injections and 25.7% had once-weekly injections.

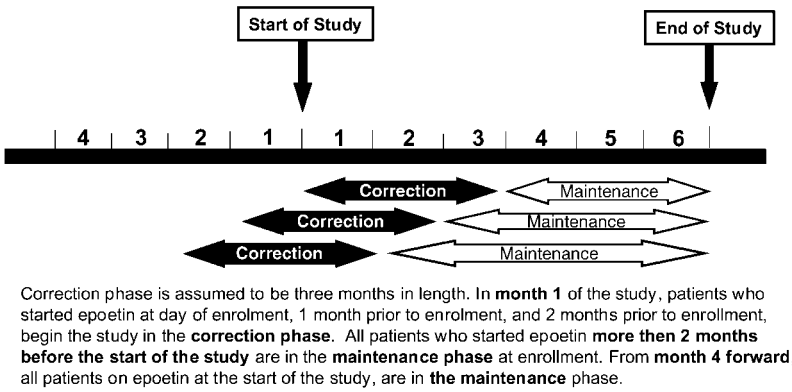


Fig. 28. Operational definition of correction and maintenance phases.

Table 20. Epoetin dosage at month 3 and achieved Hb at month 3: all patients

	Epoetin dose at month 3				Achieved Hb at month 3			
	n	Mean	Median	SD	*n*	Mean	Median	SD
Austria (686)	632	159.5	125.0	128.9	660	11.2	11.2	1.4
Belgium and Luxembourg (1095)	1032	142.1	114.5	108.8	1048	11.4	11.3	1.3
Denmark (221)	202	101.0	82.0	75.5	199	11.4	11.4	1.3
Finland (321)	283	122.6	103.0	86.9	283	11.4	11.6	1.5
France (3934)	3710	94.6	80.0	68.5	3809	10.8	10.8	1.3
Germany (4384)	4035	93.1	76.0	75.8	4028	11.1	11.1	1.2
Greece (1351)	1279	116.4	94.0	82.2	1315	10.9	11.0	1.3
Italy (369)	327	94.1	69.0	90.3	341	11.0	11.1	1.6
Netherlands (427)	346	104.4	89.0	68.1	353	11.5	11.4	1.4
Norway (162)	147	109.2	90.0	86.4	154	11.5	11.5	1.6
Spain (692)	669	116.5	95.0	100.3	678	11.1	11.1	1.4
Sweden (556)	515	161.2	127.0	118.0	509	12.0	12.1	1.5
Switzerland (329)	321	104.8	84.0	77.0	313	11.4	11.6	1.4
Total (14 527)	13 498	107.8	86.0	87.1	13 690	11.1	11.1	1.3

Table 21. Epoetin dosage at month 3 and achieved Hb at month 3: haemodialysis patients

	Epoetin dose at month 3				Achieved Hb at month 3			
	n	Mean	Median	SD	*n*	Mean	Median	SD
Austria (614)	571	162.4	127.0	130.6	593	11.2	11.1	1.4
Belgium and Luxembourg (1044)	986	144.6	119.0	109.0	1004	11.3	11.3	1.3
Denmark (153)	148	108.3	85.5	77.9	145	11.3	11.3	1.2
Finland (243)	223	132.7	116.0	91.4	223	11.3	11.4	1.5
France (3561)	3363	96.8	82.0	69.4	3467	10.7	10.7	1.2
Germany (4366)	4019	93.2	76.0	75.8	4011	11.1	11.1	1.2
Greece (1298)	1229	118.3	96.0	82.5	1264	10.9	11.0	1.3
Italy (8)	8	123.4	41.5	186.8	8	11.4	11.5	1.1
Netherlands (304)	235	111.5	97.0	71.3	243	11.4	11.3	1.3
Norway (140)	129	112.4	92.0	88.8	134	11.6	11.5	1.6
Spain (657)	635	119.4	99.0	102.0	644	11.1	11.1	1.4
Sweden (445)	411	177.9	143.0	121.5	415	11.9	12.0	1.5
Switzerland (288)	281	108.9	87.0	79.3	277	11.4	11.6	1.4
Total (13 121)	12 238	110.1	88.0	88.2	12 428	11.0	11.0	1.3

Changes were noted in the number of injections from month 1 to month 6 (without consideration of administration route or treatment phase). Of the 6234 patients receiving $\geqslant 3$ injections per week in month 1, the majority (79.9%) were still on the same regimen at month 6, yet 13.8% had decreased to twice-weekly and 6.3% to once-weekly dosing. Of the 3470 patients with a twice-weekly injection frequency at month 1, 62.0%

Table 22. Epoetin dosage at month 3 and achieved Hb at month 3: peritoneal dialysis patients

	Epoetin dose at month 3				Achieved Hb at month 3			
	n	Mean	Median	SD	*n*	Mean	Median	SD
Austria (72)	61	132.5	110.0	109.4	67	11.6	11.7	1.5
Belgium and Luxembourg (51)	46	88.2	64.0	88.6	44	11.8	11.8	1.6
Denmark (68)	54	81.1	62.0	65.1	54	11.8	11.9	1.4
Finland (78)	60	85.0	69.5	53.6	60	12.0	12.0	1.4
France (373)	347	73.1	60.0	54.0	342	11.2	11.1	1.5
Germany (18)	16	88.1	64.5	73.8	17	10.7	10.7	2.3
Greece (53)	50	68.6	56.0	58.8	51	10.7	11.0	1.3
Italy (361)	319	93.3	69.0	87.0	333	11.0	11.1	1.6
Netherlands (123)	111	89.5	80.0	58.2	110	11.6	11.8	1.6
Norway (22)	18	86.2	68.5	64.6	20	11.5	11.2	1.5
Spain (35)	34	62.4	60.0	23.1	34	11.3	11.3	1.0
Sweden (111)	104	95.1	74.0	71.8	94	12.5	12.6	1.4
Switzerland (41)	40	75.8	62.0	50.3	36	11.6	11.5	1.7
Total (1406)	1260	85.8	66.0	71.7	1262	11.4	11.4	1.6

Table 23. Distribution of administration route by epoetin dosage

Dose (IU/kg/week)	Haemodialysis maintenance		Peritoneal dialysis maintenance	
	i.v. % (*n*)	s.c. % (*n*)	i.v. % (*n*)[a]	s.c. % (*n*)
0–100	57.3 (3144)	60.9 (3236)	50.0 (3)	73.3 (850)
101–200	31.2 (1712)	30.7 (1632)	16.7 (1)	21.9 (254)
201–300	8.0 (441)	5.9 (314)	0 (0)	3.2 (37)
301–400	2.1 (113)	1.3 (67)	0 (0)	1.0 (12)
>400	1.5 (80)	1.2 (64)	33.3 (2)	0.5 (6)

[a]Note the very small number of patients for this group.

Table 24. Distribution of haemoglobin at month 6 by country

Country (*n*)	% of patients <11 g/dl	% of patients ⩾11 g/dl
Austria (588)	44.6	55.4
Belgium and Luxembourg (952)	39.0	61.0
Denmark (177)	41.2	58.8
Finland (225)	35.6	64.4
France (3473)	56.3	43.7
Germany (3897)	45.7	54.3
Greece (1253)	45.8	54.2
Italy (261)	49.4	50.6
Netherlands (301)	35.5	64.5
Norway (123)	26.8	73.2
Spain (585)	47.2	52.8
Sweden (451)	22.2	77.8
Switzerland (261)	29.5	70.5
Total (12 547)	46.4	53.6

maintained this regimen at month 6, and 15.5% changed to once-weekly dosing. However, 22.5% received ⩾3 injections per week at month 6.

As shown in Figure 34, 53.6% of the 12 547 patients for whom both month 1 and month 6 haemoglobin levels were available achieved haemoglobin levels of 11.0 g/dl or more at the completion of the survey. Further, 49.1% of these 12 547 patients already had haemoglobin levels of ⩾11.0 g/dl and 20.8% had levels of ⩾12.0 g/dl in the first month of the survey. Interestingly, 44.1% of patients showed a decrease in haemoglobin from month 1 to month 6, 3.8% had identical values, and in 52.1% an increase was noted. Mean haemoglobin levels were 10.9 g/dl (median = 10.9, SD = 1.3) at month 1 and 11.0 g/dl (median = 11.0, SD = 1.3) at month 6, a statistically significant change ($t = -11.828$; df = 12546; $P < 0.001$).

We examined the subset of patients whose epoetin therapy was initiated >6 months before the start of the ESAM study ($n = 9338$) (Figure 35). Of these patients, 53.8% achieved haemoglobin levels of ⩾11.0 g/dl and 24.2% levels of ⩾12.0 g/dl at month 6 (mean = 11.0 g/dl, median = 11.0 g/dl, SD = 1.3); compared with 50.1% of patients starting at or above 11.0 g/dl and 21.3% at or above 12.0 g/dl (mean = 10.9 g/dl, median = 11.0 g/dl, SD = 1.3). In this cohort, 22.9% showed increases of >1.0 g/dl, 20.9% decreased by 1.0 g/dl or more, and the remaining 56.2% were observed to be stable (±1.0 g/dl).

We also performed an analysis of only correction phase patients (i.e. patients who at month 1 of the ESAM study had been on epoetin for 3 months or less) for whom both month 1 and month 6 data were available ($n = 634$; Figure 36). Only 6.0% of these patients had haemoglobin levels of 11.0 g/dl or greater

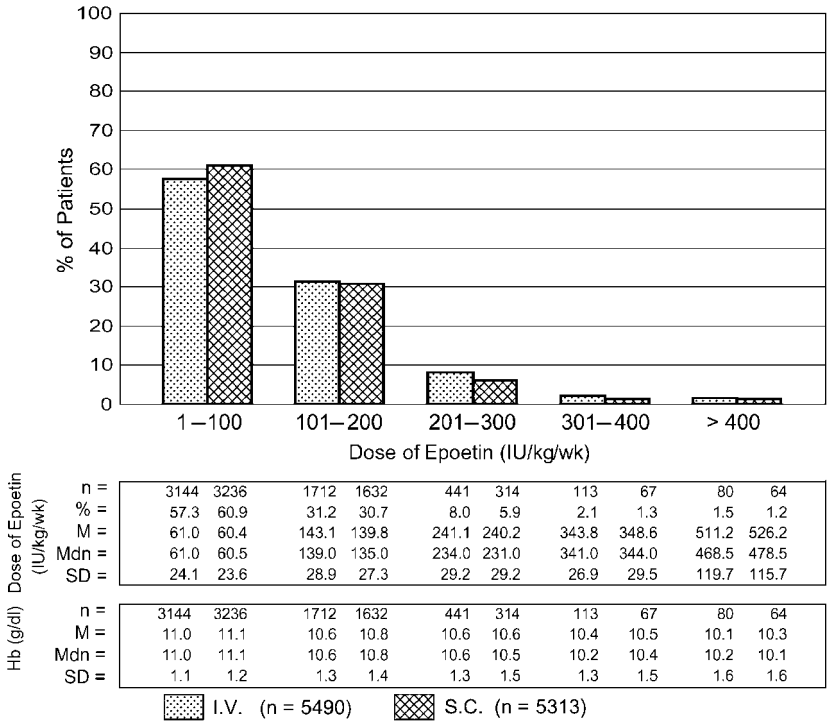


Fig. 29. Distribution of injection route by epoetin dose for haemodialysis patients in the maintenance phase (month 1).

when starting epoetin therapy (1.0% at $\geqslant$12.0 g/dl). At month 1 of the survey (i.e. up to $\sim$90 days from the start of epoetin therapy), 26.3% had haemoglobin levels $\geqslant$11.0 g/dl and 9.5% were $\geqslant$12.0 g/dl. This increased to 53.9 and 25.1%, respectively, at month 6. Note that 10.9% showed a decrease in haemoglobin of $\geqslant$1.0 g/dl from month 1 to month 6, 49.7% increased by $\geqslant$1.0 g/dl and 39.4% stayed within $\pm$1.0 g/dl. The mean haemoglobin levels were 9.0 g/dl (median = 8.9, SD = 1.2) at the start of epoetin therapy, 10.0 g/dl (median = 10.0 g/dl, SD = 1.4) at month 1 and 11.1 g/dl (median = 11.0 g/dl SD = 1.34) at month 6.

Figure 37 reviews the relationship between haemoglobin and epoetin dose at month 1 for maintenance phase patients (n = 12 093) (these are 'same-month' data and therefore do not imply a dose–effect relationship). Note the wide distribution of the scatter plot co-ordinates at levels of dosing and across the various treatment response categories. A very weak but statistically significant negative correlation was observed ($r = -0.16$, $P < 0.001$), yet this statistical significance may be attributed to the large sample size. Note that the variance explained is minimal (2.7%). These findings were consistent across all months.

Although we discovered that patients with increasing haemoglobin levels were offset by patients with decreasing haemoglobin levels (see above), we examined the haemoglobin–epoetin dose relationship association for those patients in the maintenance phase with a haemoglobin level at month 1 of $\leqslant$11.0 g/dl and an epoetin dose of $\leqslant$300 IU/kg/week (Figure 38). Of 2501 patients with a suboptimal response at month 1, 10.2% achieved haemoglobin levels of $\geqslant$12.0 g/dl at month 6, 20.3% improved to the within-guidelines level, 31.0% showed a minimal response, 37.7% remained in the suboptimal range and 0.8% changed to an inadequate response. Among 2985 patients with a minimal response at month 1, 13.4% improved to a haemoglobin level of $\geqslant$12.0 g/dl, 30.1% attained the within-guidelines response level and 35.3% remained at the same level. However, 20.6% decreased to the suboptimal response category, and 0.6% showed inadequate response at month 6. Thus, 61.5% of suboptimal response patients improved by one or two categories, including the 30.1% who achieved EBPG-recommended levels. In contrast, 56.7% of minimal response patients showed either a decline (21.2%) of one or two categories or no change in response level (35.3%). These shifts were statistically significant at the omnibus level ($\chi^2 = 210.58$, df = 4, $P < 0.001$), which should be considered within the bi-directional improvement/decline patterns within this cohort of patients.

Comments

The maintenance dose of epoetin administered to the total sample of patients enrolled in this 6-month study was fairly constant (107.0 $\pm$ 80.5 IU/kg/week at month 2 and 109.1 $\pm$ 85.2 IU/kg/week at month 6). These dose requirements are lower than those recorded in large US studies conducted over the last decade, despite achieving very similar haemoglobin levels [1,2].

There was no difference in maintenance doses between i.v. and s.c. administration in haemodialysis patients at all dose levels.

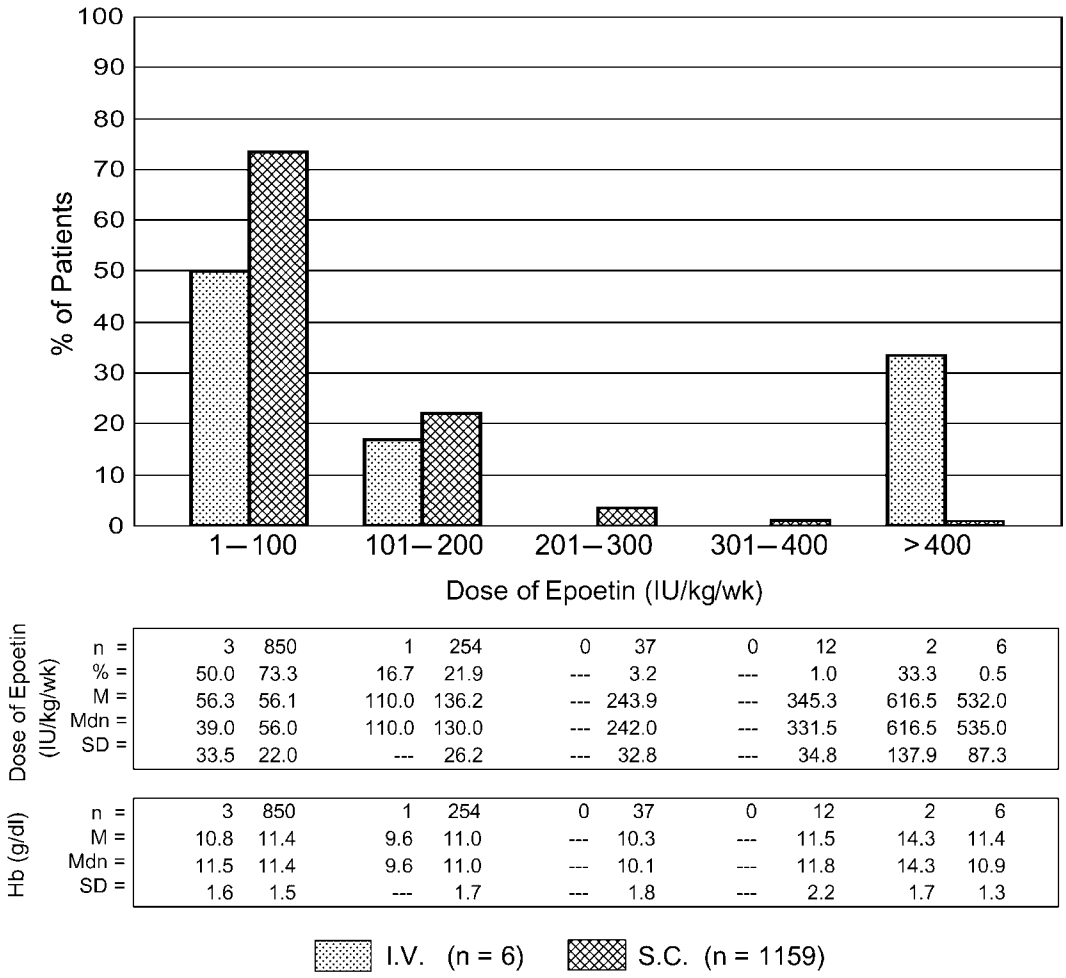


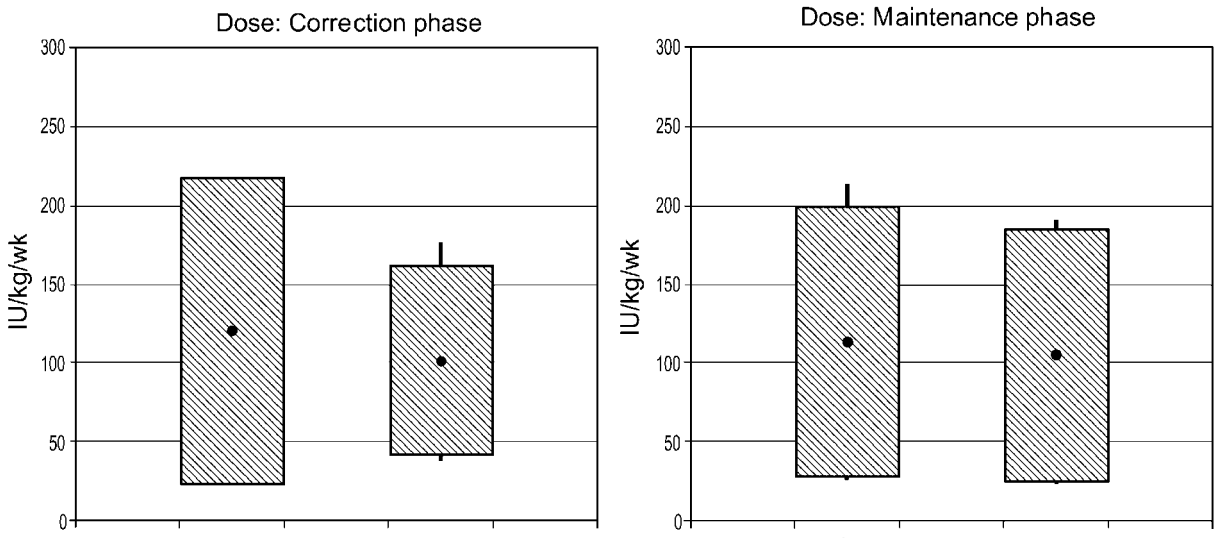
Fig. 30. Distribution of injection route by epoetin dose for peritoneal dialysis patients in the maintenance phase (month 1).

While no significant difference in epoetin dose and response was found between i.v. and s.c administration in haemodialysis patients [3–5], some studies suggest substantially less epoetin if it is given s.c. [6,7]. This latter finding has formed the basis of the recommendations in DOQI [8] and EBPG guidelines [9]. Intraperitoneal administration of epoetin does not seem to have been used in peritoneal dialysis patients in this survey. Pharmacokinetic [10] as well as clinical studies [11] have, however, shown that the intra-peritoneal route may be a suitable alternative for some patients receiving peritoneal dialysis. The dose requirements are, however, greater for maintaining the same haematocrit target range, the bioavailability of epoetin being improved by instilling the drug into a peritoneal cavity maintained empty for a prolonged period [10].

During the correction phase, 76.3% of the patients who received epoetin i.v. were on a thrice-weekly regimen, whereas only 47.8% of those receiving s.c. epoetin used twice-weekly dosing. During the maintenance phase, 66.3% of the patients receiving i.v. epoetin were injected thrice-weekly, whereas 37.9% received thrice-weekly s.c. epoetin. One injection per week was considered adequate for 11.1% of the i.v.-treated patients, but was used more often for patients receiving s.c. epoetin (25.7%). Whether the frequency of administration of a given total weekly dose of epoetin plays a significant role in achieving a desired haemoglobin concentration remains debatable, similar responses being reported with once- or thrice-weekly regimens [12,13]. It has also been shown that in well-nourished, iron-replete patients, thrice-weekly i.v. or s.c. administration of epoetin gives comparable results [14].

At the end of the ESAM, only 53.6% of the entire cohort of patients for whom both month 1 and month 6 haemoglobin levels were available achieved haemoglobin levels of 11 g/dl or more (see Figure 34). Only 53.6% achieved levels of $\geqslant$11 g/dl, well below the 85% considered as appropriate by the EBPG recommendations [9]. In addition, the proportion of patients achieving a haemoglobin level of $\geqslant$11 g/dl at the completion of the ESAM survey was 4.7 percentage points higher than 6 months earlier (at the start of the study). Both the intrinsic effect of epoetin and the fact that the patients were enrolled into an investigation protocol (and not studied at random) could readily account for this result.

The wide gap that separates the target haemoglobin



	i.v.	S.C.		i.v.	S.C.
n=	318	318	Dose of Epoetin (IU/kg/wk)	5490	5313
M=	120.1	101.2		113.5	104.7
Mdn=	94.5	90.0		90.0	86.0
SD=	97.2	60.5		86.2	79.6
n=	318	318	Hb (g/dl)	5490	5313
M=	10.2	9.7		10.8	10.9
Mdn=	10.2	9.5		10.9	11.0
SD=	1.3	1.4		1.2	1.3

Note: Graphs indicate mean (central point in box), standard deviation (top and bottom boundaries of box), and 90th and 10th percentiles (extent of line behind box).

Fig. 31. Epoetin dose for haemodialysis patients by injection route (month 1).

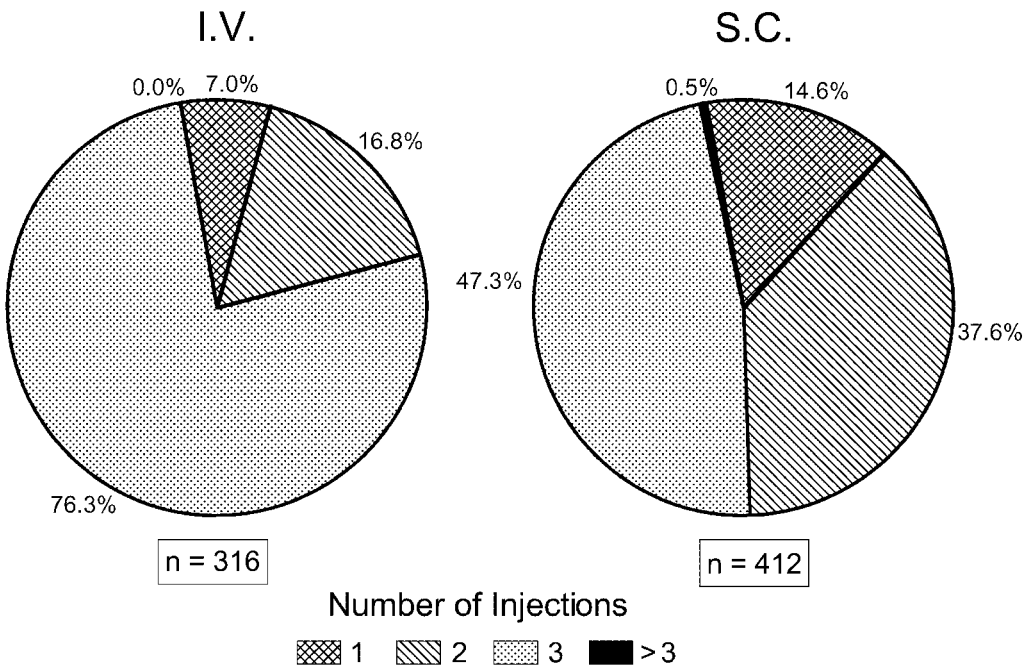


Fig. 32. Distribution of number of epoetin injections (correction phase).

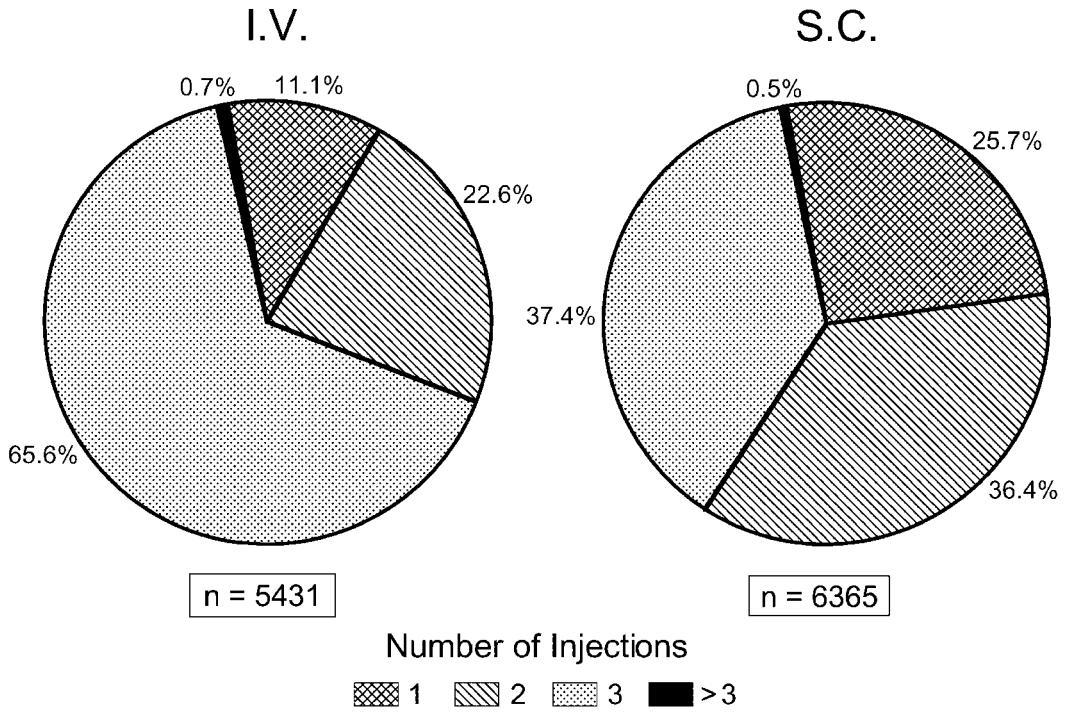


Fig. 33. Distribution of number of epoetin injections (maintenance phase).

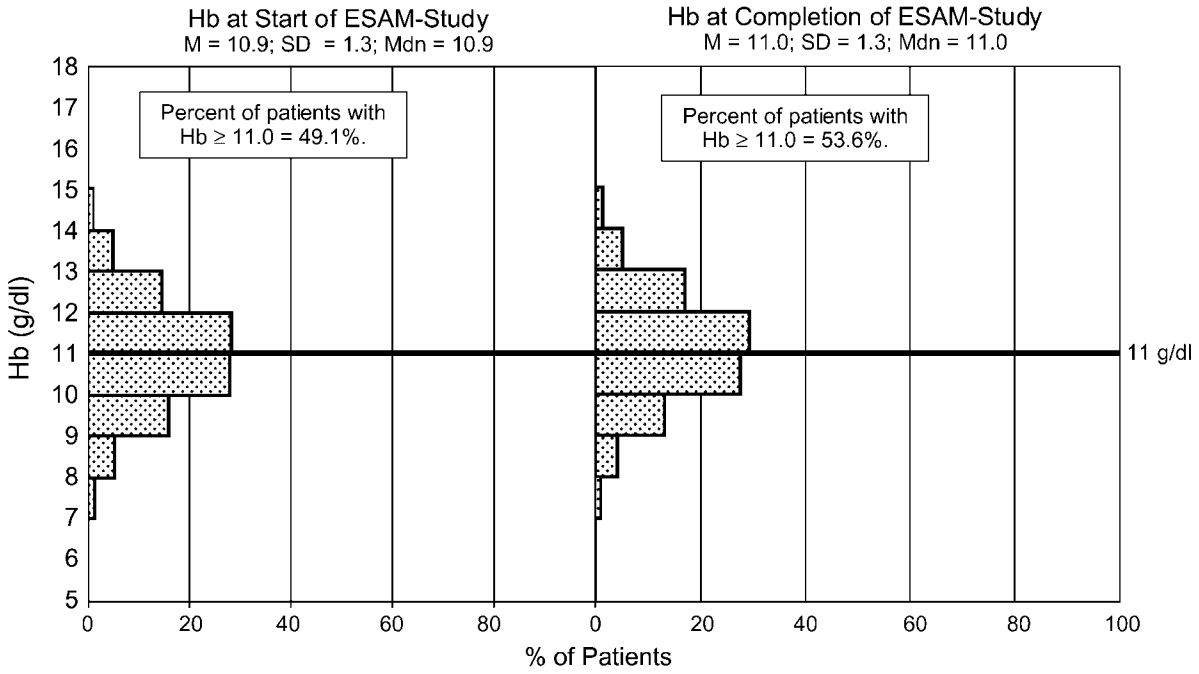


Fig. 34. Achieved Hb (months 1 and 6) for cohort with valid months 1 and 6 data ($n = 12\,547$).

recommended in published guidelines from the results actually observed in the dialysis populations is well documented in several large studies. Over a 7-year period (1990–1996), only 'modest increases' in haematocrit have been recorded in several thousands of US haemodialysis patients despite substantial increases of epoetin doses administered during this period [1]. Uncertainty about the optimal target haemoglobin, inadequate iron supplementation and inadequate management of epoetin resistance, associated with limiting effects of reimbursement policies, were the main factors proposed to explain these disappointing results. Among 4991 adult haemodialysis patients investigated in the USA from October to December 1996, the mean

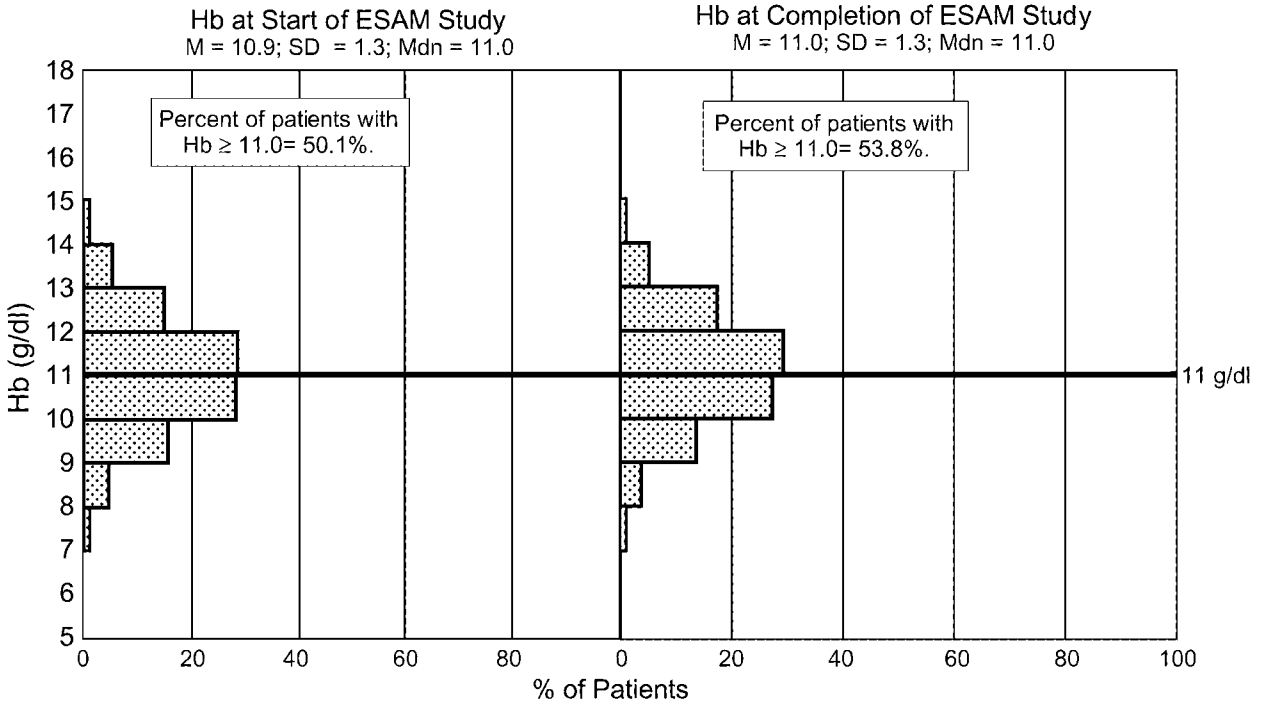


Fig. 35. Achieved Hb (months 1 and 6) for cohort with valid months 1 and 6 data who started epoetin therapy prior to 6 months before the ESAM study ($n=9338$).

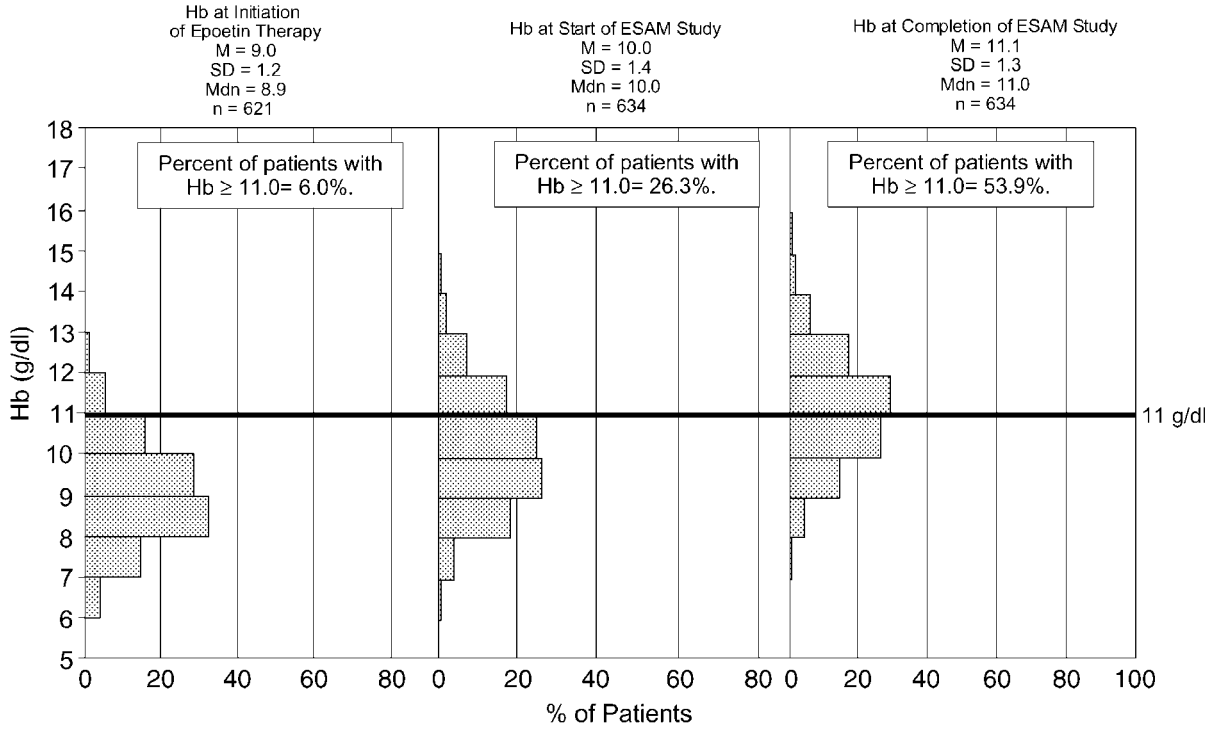


Fig. 36. Initial and achieved Hb level (months 1 and 6) for cohort with valid months 1 and 6 data who started epoetin therapy within 3 months prior to ESAM study.

haematocrit was 32.6±3.5%; 42% of the patients had haematocrit values between 33 and 36% (as advised in the DOQI guidelines). However, 28% of the patients did not achieve a haematocrit of 30%, and 10% remained severely anaemic with a haematocrit <28% [2]. The average weekly dose of epoetin received by these patients (202.4±137.2 IU/kg) was much greater than that in the ESAM study patients (107.0±80.5

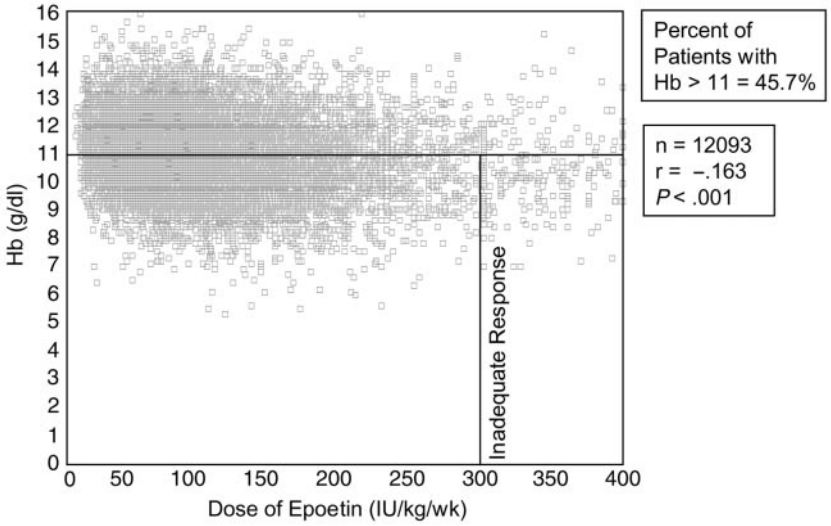


Fig. 37. Distribution of Hb by epoetin dose, month 1 (maintenance phase).

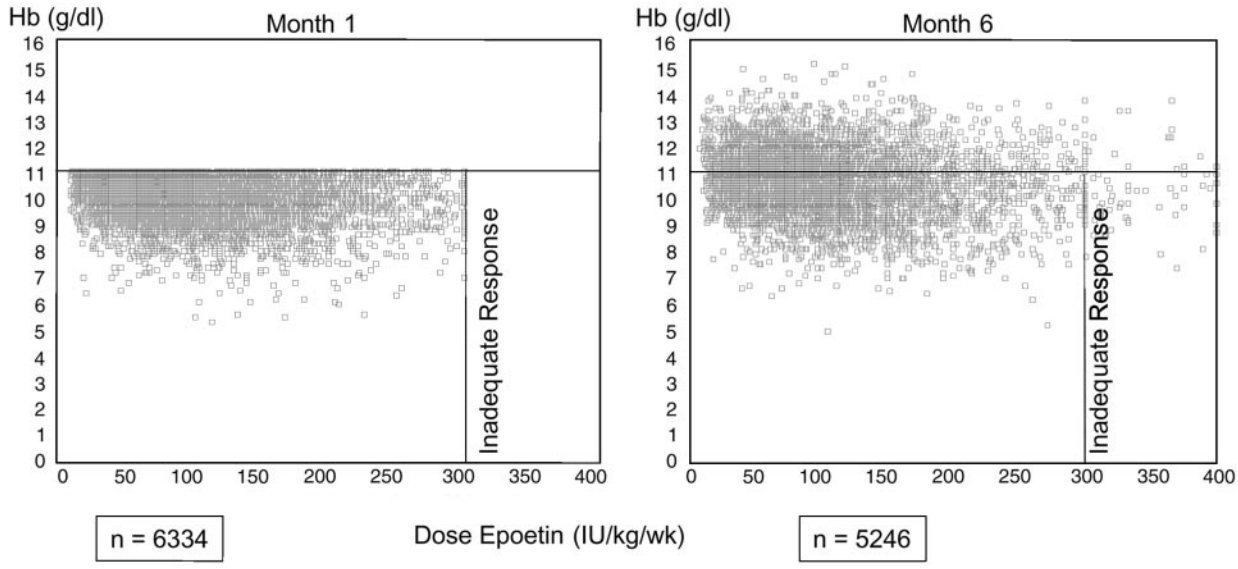


Fig. 38. Distribution of Hb by epoetin maintenance dose at month 6 for patients whose month 1 Hb was $\leqslant$11 g/dl and epoetin dose was $\leqslant$300 IU/kg/wk.

IU/kg). Only 6% of these US haemodialysis patients received epoetin s.c. Within the cohort of patients with haematocrit values $<$36%, an inverse relationship existed between prescribed epoetin alfa and haematocrit values, with smaller doses being associated with higher haematocrit values. In the ESAM study, no association between haemoglobin levels and epoetin dose was found.

While inadequate delivery of haemodialysis dose (Kt/V $<$1.2) and poor nutritional status (based on low serum albumin concentrations) were identified in the 1997 ESRD Core Indicators Project as having a negative impact on the correction of anaemia with epoetin [2], iron deficiency (whether absolute or functional) was clearly shown to be the most important factor accounting for the lack of response to epoetin therapy. In this nationally representative database of US haemodialysis patients, 25% received no iron supplementation [2]. In the 27% of patients with overt iron deficiency, defined as a transferrin saturation $<$20% ($\sim$1350 patients), a quarter of them ($\sim$340 patients) did not receive iron supplementation, and 50% did not receive parenteral iron.

Among the haemodialysis patients in the ESAM study for whom data were available at month 1, 21.6% were considered as having absolute iron deficiency (serum ferritin $<$100 µg/l). This proportion decreased to 18% at month 3 and to 15.3% at month 6. Functional iron deficiency (serum ferritin $>$100 µg/l and transferrin saturation $<$20%) was reported for 21.3, 20.5 and 21.0% of the patients surveyed at months 1, 3 and 6, respectively, while adequate iron status (serum ferritin

$>100\,\mu g/l$ and transferrin saturation $>20\%$) were reported for only 57.0, 61.5 and 63.4% of the patients at the same time points. The lowest epoetin dose was received by patients with adequate iron status, while those with functional iron deficiency received the highest dose. Haemodialysis patients with adequate iron status had significantly higher mean haemoglobin levels at all three time points, while patients with absolute iron deficiency had higher haemoglobin levels than those with functional iron deficiency. Results for peritoneal dialysis patients were more difficult to interpret as, surprisingly, patients with absolute or functional iron deficiency had higher haemoglobin values than did those with adequate iron status. The reason for this unexpected finding remains unclear.

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