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Nephrology
Dialysis
Transplantation

European Best Practice Guidelines 17–18
Adverse effects

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Results

Key points from the EBPG

- Blood pressure may increase in patients receiving epoetin.
- Before starting antihypertensive therapy, re-evaluate dry body weight.

Key findings from ESAM

- 5.3% of the population experienced a vascular access thrombosis. The greatest incidence occurred in the cohort of patients with a synthetic A–V graft. A relationship with the haemoglobin levels has not been shown.
- Nearly 50% of all deaths during the study period were related to cardiovascular causes.
- More than half of the patients who died during the survey were anaemic during each of the 3 months prior to death.
- Differences in mean survival time were significant between those with cardiovascular disease and those without cardiovascular disease.

Figure 45 shows the distribution of patients by type of vascular access in the ESAM sample. Of the total patients studied, 80.3% ($n=9057$) had a native arteriovenous fistula (AVF); 11.9% ($n=1346$) had a synthetic A–V graft and only 7.7% ($n=871$) had catheter access (data for 1847 patients were missing). During the 5 months in which data were collected, a total of 707 patients experienced an AVF thrombosis (Figure 45). By far the greatest incidence of AVF thrombosis occurred in the cohort of patients with a synthetic A–V graft (14.5% experiencing thrombosis during the 5-month period). Those with catheter access had a rate of thrombosis of 5.5%, while only 4.4% of patients with a native AVF had documented thrombosis. Overall, AVF thrombosis rates by achieved haemoglobin categories in month 6 seemed to decrease as haemoglobin increased (Figure 47).

The mortality among patients enrolled in ESAM

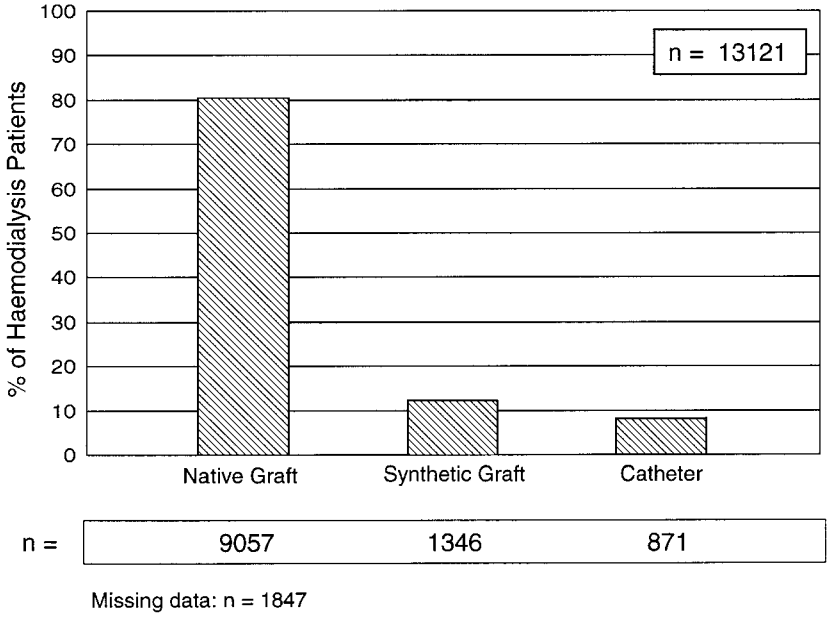

Fig. 45. Vascular access in month 6.

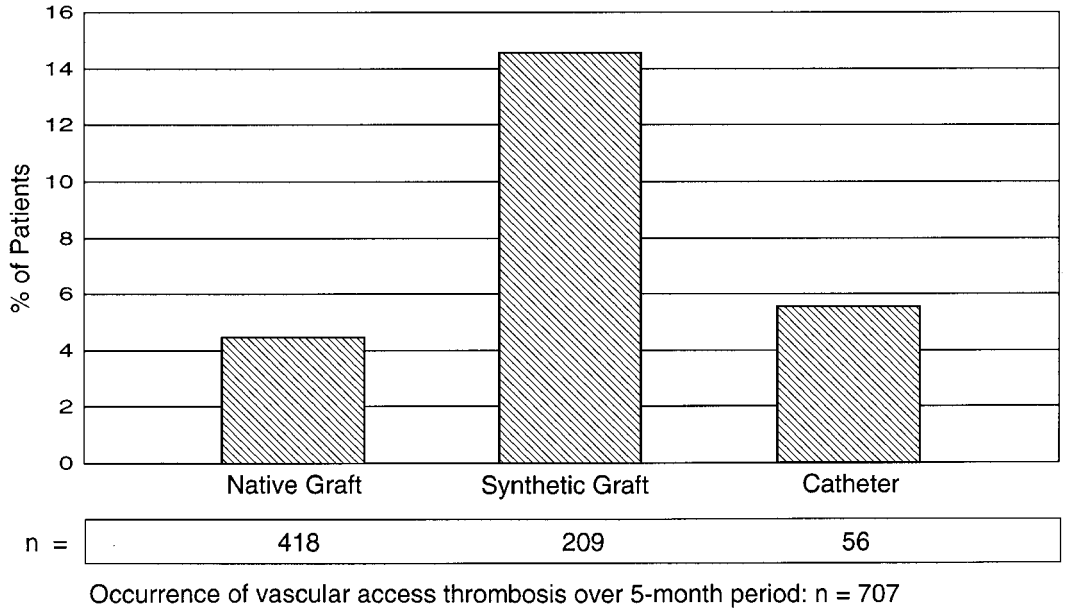

Fig. 46. Percentage of haemodialysis patients with vascular access thrombosis at any month by type of vascular access at month 1.

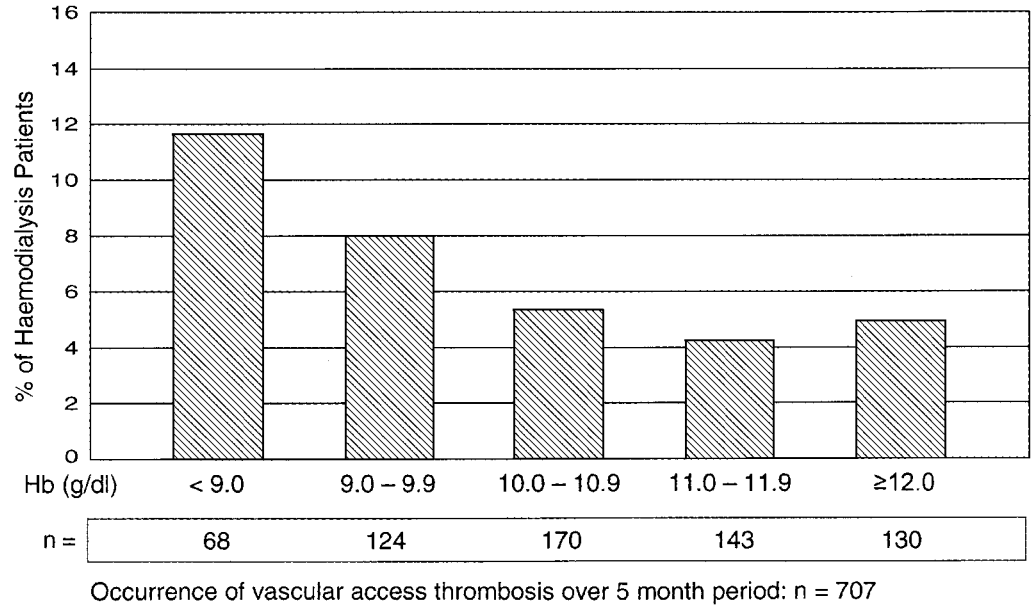

Fig. 47. Percentage of patients with vascular access thrombosis at any month by month 6 achieved Hb.

was documented over the 6-month survey. Table 31 shows the by-month and overall mortality as well as the documented cause of death. Nearly 50% of all deaths during the study period were related to cardiovascular causes. Figure 48 shows the monthly mortality rate for those with cardiovascular disease (CVD) compared with those without CVD. The differences in mortality between the two groups was statistically significant for all months ($P<0.001$ for months 1, 3, 4, 5 and 6; $P<0.05$ for month 2). Figure 48 also reveals the mortality differences between those with a haemoglobin $\geqslant 12$ g/dl in month 1 and those whose haemoglobin was <12 g/dl in month 1.

The last haemoglobin values for patients in the two groups who died differed significantly (mean last Hb for patients with Hb <12 in month 1 = 10.3g/dl; mean last Hb for patients with Hb $\geqslant 12$ in month 1 = 11.7g/dl; $t=-9.99$; df = 635; $P<0.001$). For the purpose of this analysis, haemoglobin was taken for the month of death or, if missing, for the month immediately prior to death. Differences in mortality between the haemoglobin categories are greater within the CVD group; however, no differences were statistically significant in the CVD group. Mortality is analysed further by haemoglobin categories (<9 g/dl, 9–9.9 g/dl, 10–10.9 g/dl, 11–11.9 g/dl and $\geqslant 12$ g/dl) and month

Table 31. Mortality rate in months 2–6 and distribution by cause of death

	Month 2		Month 3		Month 4		Month 5		Month 6		All months	
	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*
Death rate	0.3	41	0.9	130	1.2	174	1.1	156	1.2	162	4.8	663
Causes of death												
Cardiovascular	51.2	21	52.3	68	42.5	74	47.4	74	51.2	83	48.3	320
Infection	26.8	11	7.7	10	20.7	36	16.7	26	17.3	28	15.8	105
Neoplasia	9.8	4	8.5	11	9.2	16	7.7	12	4.3	7	7.5	50
Others	7.3	3	24.6	32	19.5	34	21.8	34	21.0	34	20.7	137
Missing	4.9	2	6.9	9	8.0	14	6.4	10	6.2	10	7.7	51

$n = 14\,527$; missing data = 798.

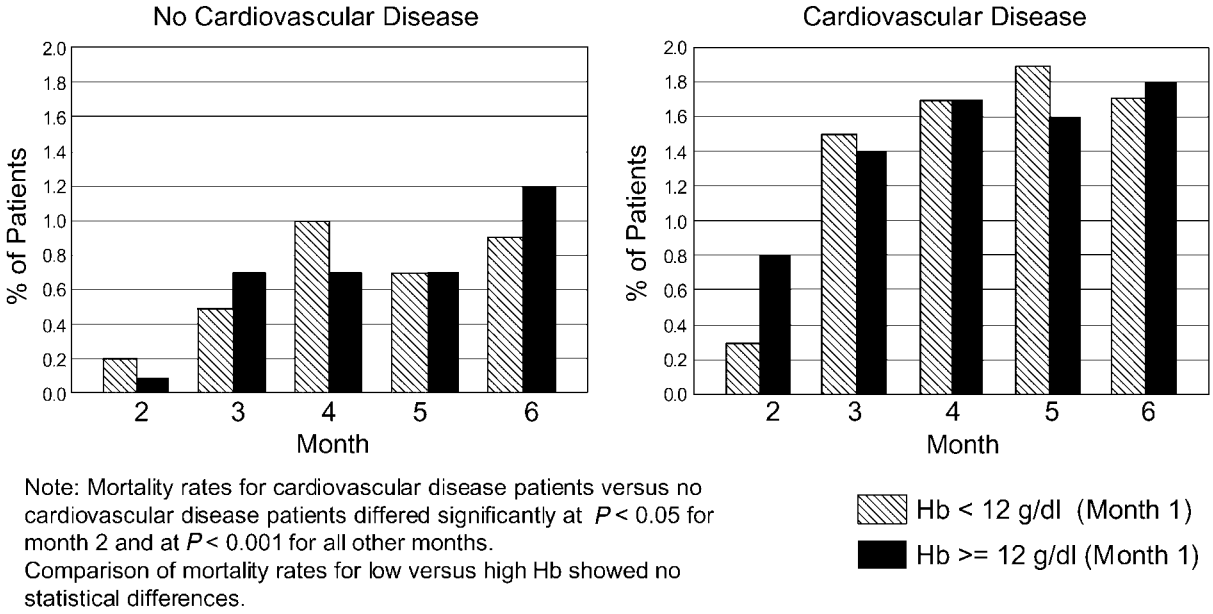

Fig. 48. Mortality rate by cardiovascular disease for patients with month 1 Hb $\geqslant 12$ g/dl *vs* month 1 Hb < 12 g/dl.

of treatment in Figures 49 and 50 for those with no CVD and those with CVD, respectively.

Survival analyses were conducted to determine if differences in length of survival during the 6-month survey exist between patients with and without CVD. CVD is defined as the presence of at least one of three concomitant pathologies: cardiac arrhythmias, coronary artery disease or cardiac failure. The sample was also dichotomized and tested by higher haemoglobin ($\geqslant 12.0$ g/dl) *vs* lower haemoglobin (< 12.0 g/dl) levels. The mean survival time was identical between the two haemoglobin groups (higher haemoglobin group = 5.92 months; lower haemoglobin group = 5.92 months). Differences in mean survival time were significant ($P < 0.001$), however, between those with (5.88 months) and those without CVD (5.95 months) as shown in Figure 51. Differences between those patients with and those without CVD were statistically significant in both the lower haemoglobin group (CVD = 5.89 months; no CVD = 5.95 months; $P < 0.001$) and within the higher haemoglobin group (CVD = 5.87 months; no CVD = 5.95 months; $P < 0.001$) (Figure 52).

Of patients who died during the survey ($n = 663$), haemoglobin values were assessed in the months prior to death. Using 11 g/dl as the threshold for defining anaemia, 54.9% of those patients who died during the observation period were anaemic in the month prior to death. Two months prior to death, 53.5% of patients were anaemic, and 50.1% were anaemic 3 months prior to death. Monthly anaemic rates for patients who did not die during the study period were 50.9% in month 1, 46.6% in month 2, 45.2% in month 3, 44.2% in month 4, 44.5% in month 5 and 46.4% in month 6.

Comments

During the 5-month study period, 4.4% of haemodialysis partients with a native AVF experienced a vascular access thrombosis. Patients with synthetic A–V grafts

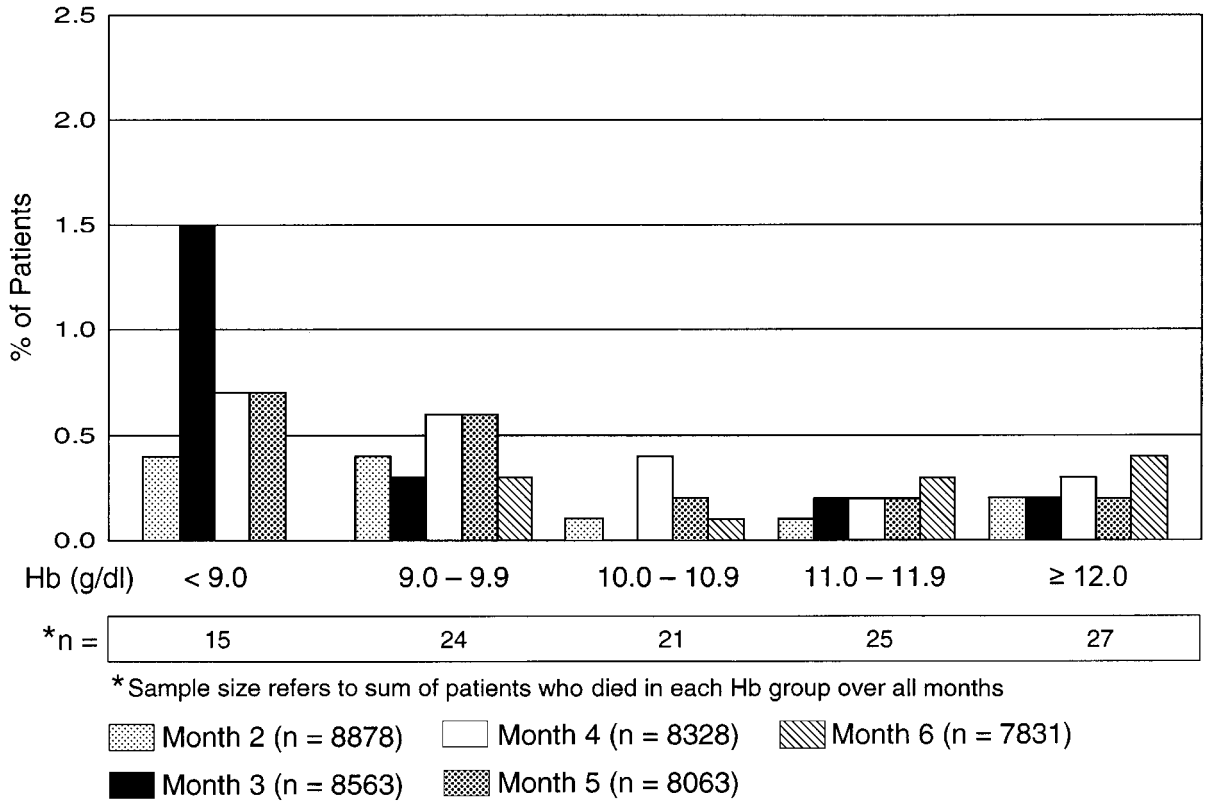

Fig. 49. Mortality rate by Hb group from months 2 to 6 for patients with no cardiovascular disease.

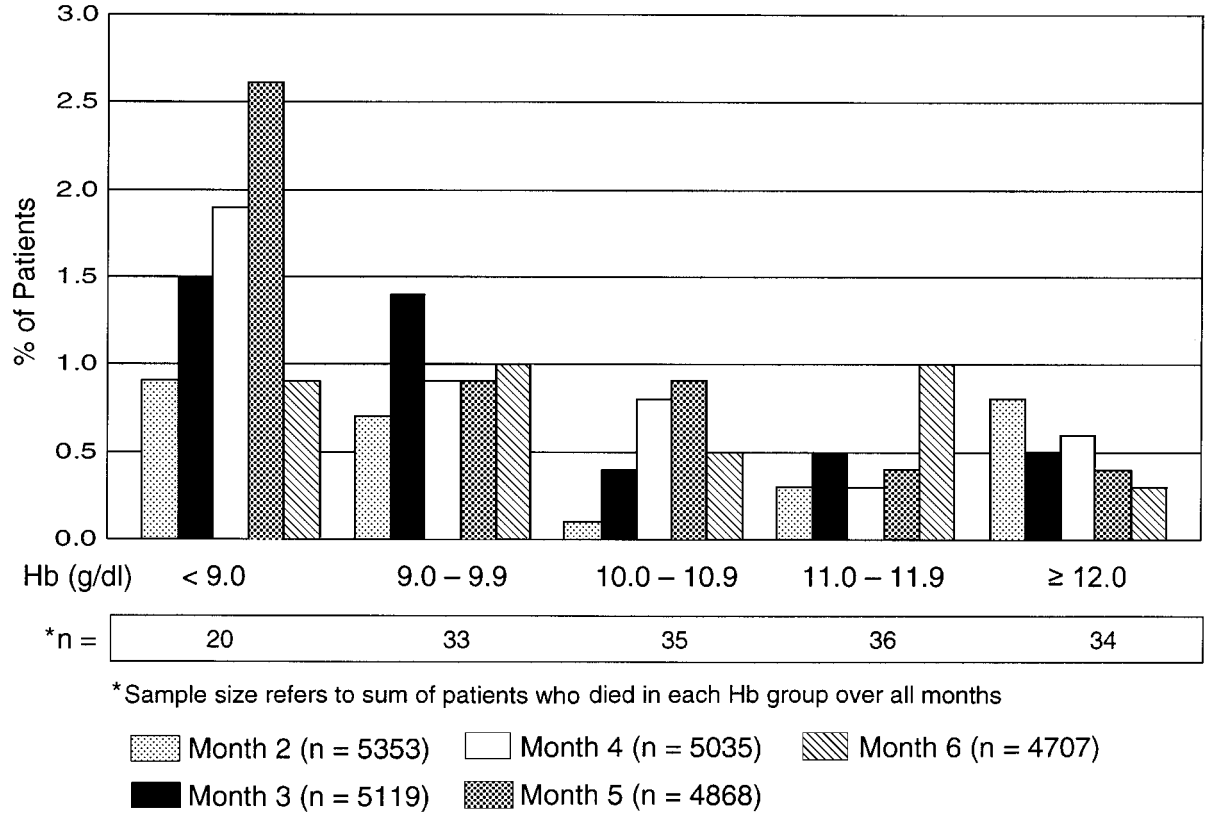

Fig. 50. Mortality rate by Hb group from months 2 to 6 for patients with cardiovascular disease.

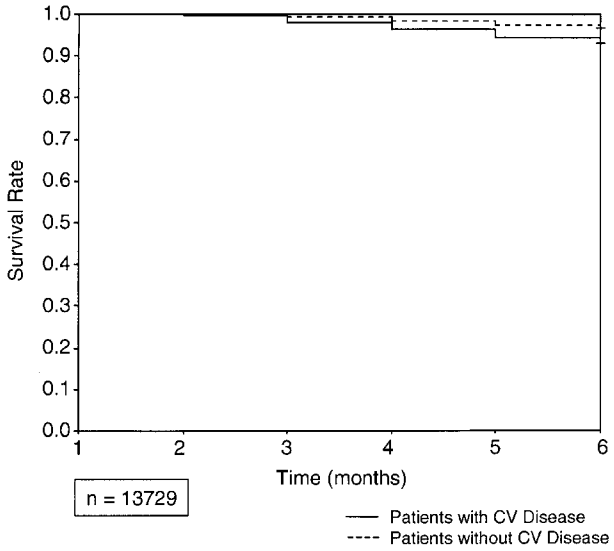

Fig. 51. Survival curve for patients with cardiovascular disease *vs* those without cardiovascular disease.

had a much higher thrombosis rate (14.6%), as did those with catheter access (5.5%) (Figure 45). It has been suggested previously that vascular access thrombosis is linked with access status rather than with haemostatic parameters [1–4].

Paradoxically, the percentage of patients with vascular access thrombosis at any month was highest in the group with the month 6 achieved haemoglobin of <9 g/dl and lowest in the group with haemoglobin levels between 11.0 and 11.9 g/dl (Figure 46). Our interpretation of these results is that the physicians involved in the care of these patients were aware of a risk of vascular access thrombosis and avoided increasing haemoglobin levels above a certain target haemoglobin. Nevertheless, even at a haemoglobin below 9 g/dl, vascular access thrombosis occurrs in high-risk patients. Patients having synthetic polytetrafluoroethylene (PTFE) grafts may be at increased risk of vascular access thrombosis at higher haemoglobin concentrations [5]. In the study of Culp *et al.* [4], there were significant increases in vascular access thrombosis-related risks associated with the placement of a PTFE graft compared with patients with an AVF. However, total heparin dose and epoetin therapy were not associated with an increased risk of thrombosis. The results of the US Normal Hematocrit Cardiac Study [5] showed an increased rate of vascular access thrombosis affecting both native AVFs and synthetic A–V graft access.

Differences in survival time were not significant between haemodialysis patients with a high haemoglobin ($\geqslant 12$ g/dl) and those with a low haemoglobin (<12 g/dl). Differences were significant, however, between haemodialysis patients with and without CVD (Figure 51), and for both the low and the high haemoglobin groups (Figure 52). These findings are important with respect to the data published by Besarab *et al.* [5] showing that haemodialysis patients with congestive heart failure or severe ischaemic cardiac diseases do not benefit from higher haematocrit values (40% *vs* 29%).

In summary, therefore, while vascular access thrombosis is infrequent, it occurs more commonly in patients with a synthetic A–V graft compared to those with a native AVF; this is not related to higher haemoglobin levels. Survival time was significantly better for haemodialysis patients without CVD for both the lower and the higher haemoglobin groups. Higher haemoglobin was not linked to a decrease in survival time.

References

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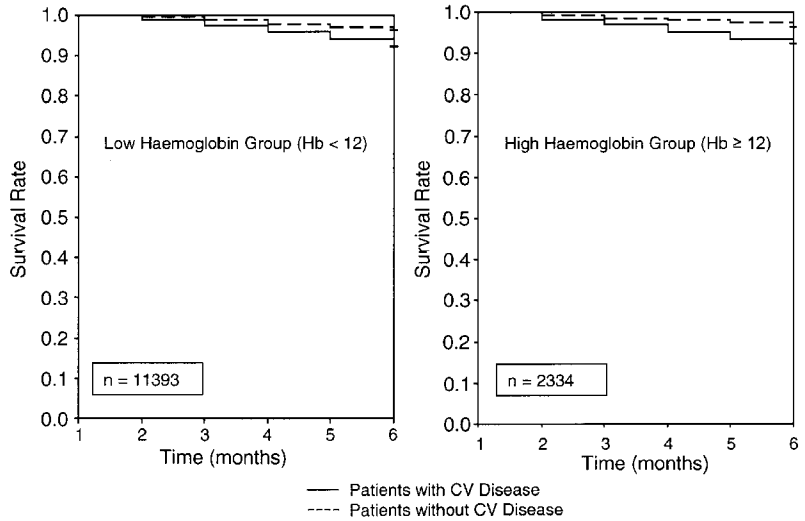

Fig. 52. Survival curves for patients with cardiovascular disease *vs* those without cardiovascular disease by high *vs* low Hb groups.

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