

Blood Coagulation, Fibrinolysis and Cellular Haemostasis

Quality of life and the duration of treatment with vitamin K antagonists in patients with deep venous thrombosis

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Summary

In clinical practice, decisions on the duration of treatment with vitamin K antagonists are usually based on the presence of persistent risk factors, the risk of bleeding and centre policy. Little is known about the influence of patients' experienced quality of life. The objectives of this study were: 1) to explore the course of quality of life in patients with venous thrombosis treated for 3 months versus patients treated for 6 months with vitamin K antagonists; 2) to investigate the factors that were associated with the duration of treatment with vitamin K antagonists. The study sample comprised patients participating in a multi-centre clinical trial. Quality of life was assessed at study entry, after 10-14 days, 3 and 6 months in 360 patients. Overall, no dif-

ferences in quality of life were found between the 2 patient groups. An interaction effect between group and time was found for physical functioning. Regression analyses indicated that the presence of one or more permanent risk factors, duration of hospitalisation, mobility prior to deep-vein thrombosis and study centre were associated with the duration of treatment with vitamin K antagonists. Interestingly, quality of life was not associated with treatment duration. Since study centre was the most important factor associated with treatment duration, local policy appears to have a great influence on decisions regarding the duration of treatment with vitamin K antagonists.

Keywords

Vitamin K antagonists, quality of life, duration of treatment

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Introduction

It is current practice to treat patients with acute deep venous thrombosis with an initial course of heparin. Vitamin K antagonist therapy is commonly started concomitantly and continued for at least 3 months (1). To maintain a therapeutic level of anticoagulation, frequent venipunctures are required to allow laboratory testing and subsequent dose-adjustments. The frequency of these venipunctures is largely determined by the degree of stability of the patient's international normalised ratio (INR), which is used for monitoring (2).

In the absence of a definitive guideline, providing optimal duration of treatment, decisions on the duration of treatment with vitamin K antagonists in clinical practice are usually based on the presence of persistent risk factors, the risk of bleeding and centre policy. Little is known about the influence of patients' experienced quality of life on these decisions. The results of studies assessing quality of life in patients treated with vitamin K antagonists are conflicting. Studies comparing the self-management of vitamin K antagonist therapy with management by an anticoagulation clinic find lower levels of treatment-related quality of life in patients in the latter group, indicating

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that standard treatment with vitamin K antagonists affects quality of life adversely (3-5). In other studies, however, standard treatment with vitamin K antagonists is not associated with limitations in lifestyle or decreased levels of quality of life (6, 7).

We used the dataset of a large clinical trial in patients with venous thrombosis in whom quality of life was assessed prospectively both before treatment and during a 6 month follow up period. We were interested in the extent to which quality of life was affected adversely by treatment with vitamin K antagonist and, in return, whether the duration of treatment was influenced by patients' quality of life. We therefore compared the course of quality of life in patients treated for 3 months, with those treated for 6 months with vitamin K antagonists. In addition, we examined the extent to which demographic, clinical and quality of life factors were associated with the duration of treatment with vitamin K antagonists.

Materials and methods

Patients

Patients who took part in the Tasman trial between October 1992 and September 1994 comprised the study population. Briefly, the study evaluated the efficacy, safety and cost-effectiveness of in-patient treatment with intravenous unfractionated heparin versus outpatient treatment with subcutaneous low-molecular-weight heparin, in patients with deep-vein thrombosis (8). In all patients, treatment with vitamin K antagonists was initiated on the first or second day, and continued for a period of 3 months or longer. We compared patients who were treated with vitamin K antagonists for a period of 3 months with those whose treatment was continued until at least 6 months. To be eligible for our analyses, patients had to be treated with vitamin K antagonists for at least 3 months. If duration of treatment was discontinued earlier, patients were excluded.

Demographic and clinical factors

Demographic and clinical factors included: age, gender, the patients' ability to return home (on the basis of physicians' opinion before randomisation), initial treatment (standard heparin versus low-molecular-weight heparin), duration of hospitalisation, documented femoral or more proximal thrombosis, presence of permanent risk factors (i.e., previous deep-vein thrombosis or pulmonary embolism, known cancer, deficiencies of natural anticoagulants, and presence of a lupus anticoagulant), mobility prior to deep-vein thrombosis (i.e., mobile without assistance, mobile with some assistance, mobile with much assistance, and bedridden), and treatment centre (i.e., Academic Hospital Groningen, Groningen, the Netherlands; Academic Medical Centre, Amsterdam, the Netherlands; Auckland Hospital, Auckland, New Zealand; Flinders Medical Centre, Adelaide, Australia; Hôpital Clamart, Paris, France; Prince of

Wales Hospital, Sydney, Australia; Slotervaart Hospital, Amsterdam, the Netherlands; University Hospital Padua, Padua, Italy; University Hospital Pavia, Pavia, Italy).

Quality of life

Overall quality of life was assessed by a 10 cm visual analogue scale, anchored by lowest quality of life (0) and highest quality of life (100). The Medical Outcome Study Short Form-20 (MOS-SF-20), a generic quality of life measure, was used to assess physical functioning, role functioning, social functioning, mental health, health perception and pain (9,10).

The Rotterdam Symptom Checklist (RSCL), originally developed for cancer patients (11), was adapted for use in patients with deep-vein thrombosis. Three experts in thrombosis treatment were asked whether items in the scale were relevant. If their opinion was consistently negative, the item was omitted. A total of 20 items were deleted. The following symptoms specific to thrombosis were added to the checklist on the basis of these experts' opinions: pain in the calf, pain in the thigh, swelling of the leg, and a heavy feeling in the leg. A principal component analysis of the revised RSCL, containing 23 items, yielded three sub-scales measuring psychological distress, fatigue, and thrombosis complaints. Internal consistency of these sub-scales at baseline and the first measurement after initial treatment (Cronbachs' alpha) was satisfactory to good, ranging from 0.70 to 0.91 (12).

Effort needed to cope with illness and treatment was assessed with a 10 cm visual analogue scale, ranging from 0, no effort at all to 100, a great deal of effort (13). Valid versions were available in English and Dutch for the MOS-SF-20, in English, Dutch and French for the RSCL, and in English, French and Italian for the effort to cope scale. The remaining language versions were translated according to standard forward-backward translation procedures. The timeframe employed for all measures was the previous week.

Procedure

Clinical and demographic data were assessed by a clinical investigator at study entry, except for duration of hospitalisation, which was assessed when the patient was discharged from the hospital. Quality of life and coping were assessed at the outpatient department at four points in time: at entry (T1), after 1-2 weeks (T2), after 3 months (T3), and after 6 months (T4). A nurse was available to help patients complete the questionnaires if required. The nurse was instructed not to influence the patients' responses.

Analysis

Differences in demographic and clinical factors between patients treated for 3 months and patients treated for 6 months with vitamin K antagonists were tested using Mann Whitney U tests and Chi square tests. Differences in the course of quality of

life over time were determined by repeated measures analysis of variance. To examine whether patients reported different levels of quality of life after treatment with oral anticoagulants was either continued or stopped, 95% confidence intervals were calculated for the average changes scores (T4-T3) of patients treated for 3 months and for 6 months with vitamin K antagonists. For missing items in the quality of life data, mean scale-scores

of the remaining items were imputed when at least 50% of the scale-items was completed.

Based on these analyses, demographic, clinical and quality of life factors differing between patients treated for 3 months, and patients treated for 6 months with vitamin K antagonists were included in a stepwise multivariate logistic regression analysis ($p < 0.10$). Mobility prior to deep-vein thrombosis was

Table 1: Demographic and clinical characteristics of patients treated for 3 months and patients treated for 6 months with vitamin K antagonists (VKA).

Characteristic	VKA = 3 months (N = 216)	VKA = 6 months (N = 144)	p value
Mean (\pm SD) age (yr)	59 \pm 17	60 \pm 16	.735 [†]
Male sex	108 (50)	76 (53)	.683 [‡]
Able to return home	176 (81)	115 (80)	.806 [‡]
Initial treatment			.089 [‡]
Standard Heparin	96 (44)	78 (54)	
Low-Molecular-Weight Heparin	120 (56)	66 (46)	
Mean (\pm SD) duration of hospitalisation (days)	5 \pm 4.4	6 \pm 4.9	.036 [†]
Femoral or more proximal deep-vein thrombosis	146 (68)	109 (76)	.124 [‡]
Permanent risk factors			
Previous deep-vein thrombosis	26 (12)	44 (31)	< .001 [‡]
Previous pulmonary embolism	10 (5)	9 (6)	.413 [‡]
Known cancer	24 (11)	32 (22)	.017 [‡]
Deficiencies of natural anticoagulants	1 (1)	3 (2)	N.T.
Presence of lupus anticoagulant	1 (1)	3 (2)	N.T.
\geq 1 of these	48 (22)	75 (52)	< .001 [‡]
Mobility prior to deep-vein thrombosis			.03 ^{‡§}
Mobile without assistance	163 (76)	104 (72)	
Mobile with some assistance	39 (18)	19 (13)	
Mobile with much assistance	14 (7)	12 (8)	
Bedridden	0 (0)	9 (6)	
Centre			< .001 ^{¶¶}
Auckland Hospital, New Zealand	47 (22)	8 (6)	
Prince of Wales Hospital, Australia	5 (2)	1 (1)	
University Hospital Pavia, Italy	40 (19)	14 (10)	
Academic Medical Centre, Holland	40 (19)	17 (12)	
Slotervaart Hospital, Holland	25 (12)	17 (12)	
University Hospital Padua, Italy	36 (17)	32 (22)	
Academic Hospital Groningen, Holland	17 (8)	17 (12)	
Hôpital Clamart, France	5 (2)	13 (9)	
Flinders Medical Centre, Australia	1 (1)	25 (17)	

^{||} Data are presented as numbers and percentages, unless noted otherwise.

[†] Mann Whitney U test.

[‡] Chi square test.

[§] The categories 'mobile with much assistance' and 'bedridden' were combined for the Chi square test.

^{¶¶} The overall category 'centre' was grouped into the centres that mainly continued treatment with vitamin K antagonists ($> 50\%$; Hôpital Clamart and Flinders Medical Centre) versus the remaining centres for the Chi square test.

N.T.: not tested due to the small number of patients.

dichotomised into mobile with or without some assistance versus mobile with much assistance or being bedridden. The variable study centre was grouped into the centres that mainly continued treatment with vitamin K antagonists (> 50%; Hôpital Clamart and Flinders Medical Centre) versus the remaining centres. Duration of hospitalisation, health perception and physical functioning were dichotomised at the median. The final multivariate logistic regression model was constructed using both forward and backward selection. All reported p values ($p < 0.05$) are two-sided.

Results

Patients

Of the 400 randomised patients, 360 were eligible for our analyses. Two hundred and sixteen of these patients were treated for 3 months and 144 patients were treated for 6 months. Forty patients were ineligible, since their treatment with vitamin K antagonists was discontinued or interrupted before the 3 month period had passed. Reasons for discontinuation or interruption were thrombotic events ($n = 9$), bleeding events ($n = 8$), other

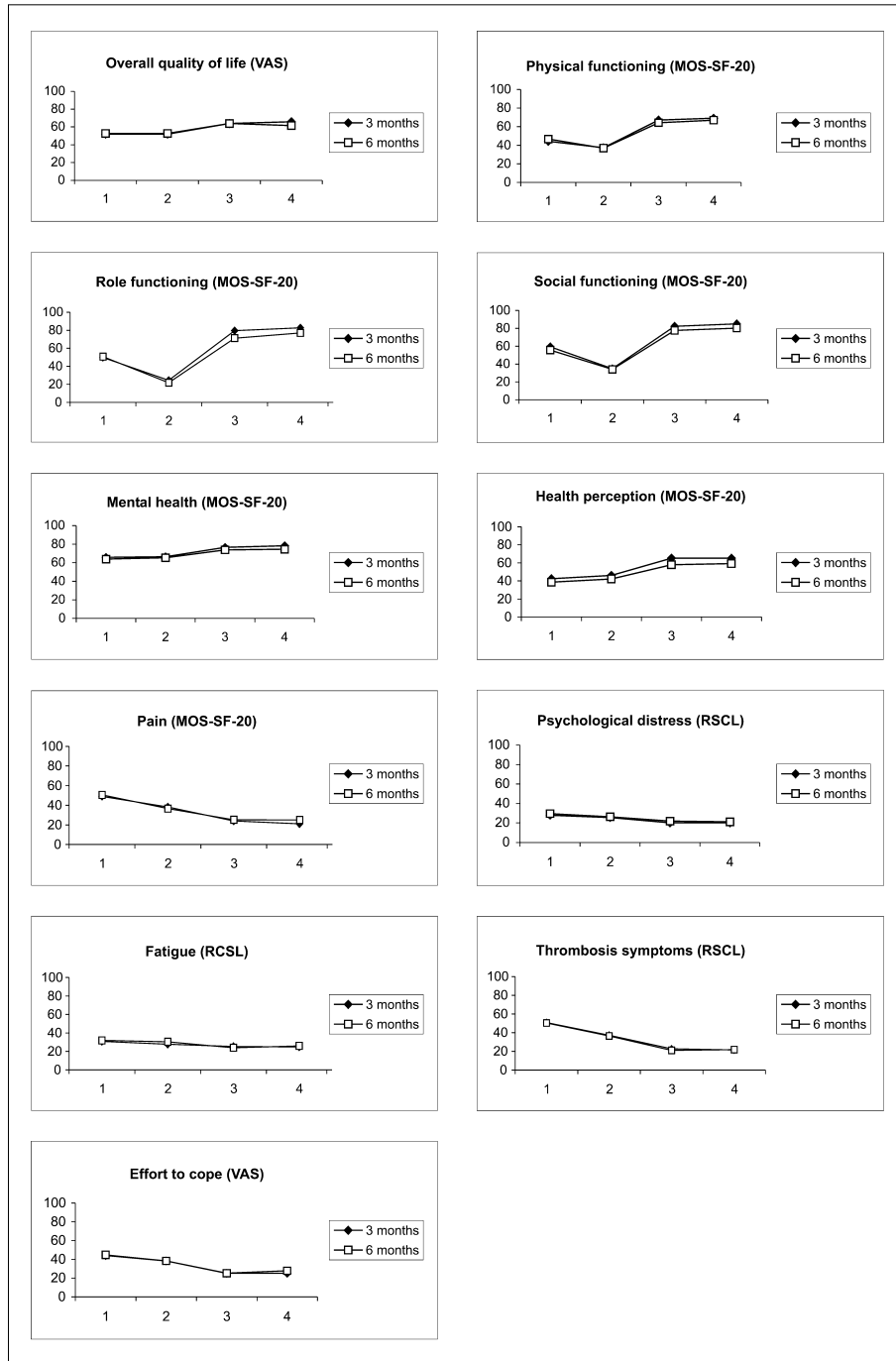


Figure 1: Course of quality of life. All scale results are transformed to a 0-100 scale value, with higher scores indicating higher function or impairment on the attribute measured: better overall quality of life, better physical functioning, better role functioning, and better social and mental functioning, better health perception, more pain, fatigue, thrombosis symptoms, more effort to cope with the illness and treatment. 1: study entry ($N = 343$); 2: 10-14 days ($N = 334$); 3: 3 months ($N = 329$); 4: 6 months ($N = 308$). VAS: Visual Analogue Scale; MOS-SF-20: Medical Outcome Study Short Form-20; RSCL: Rotterdam Symptom Checklist.

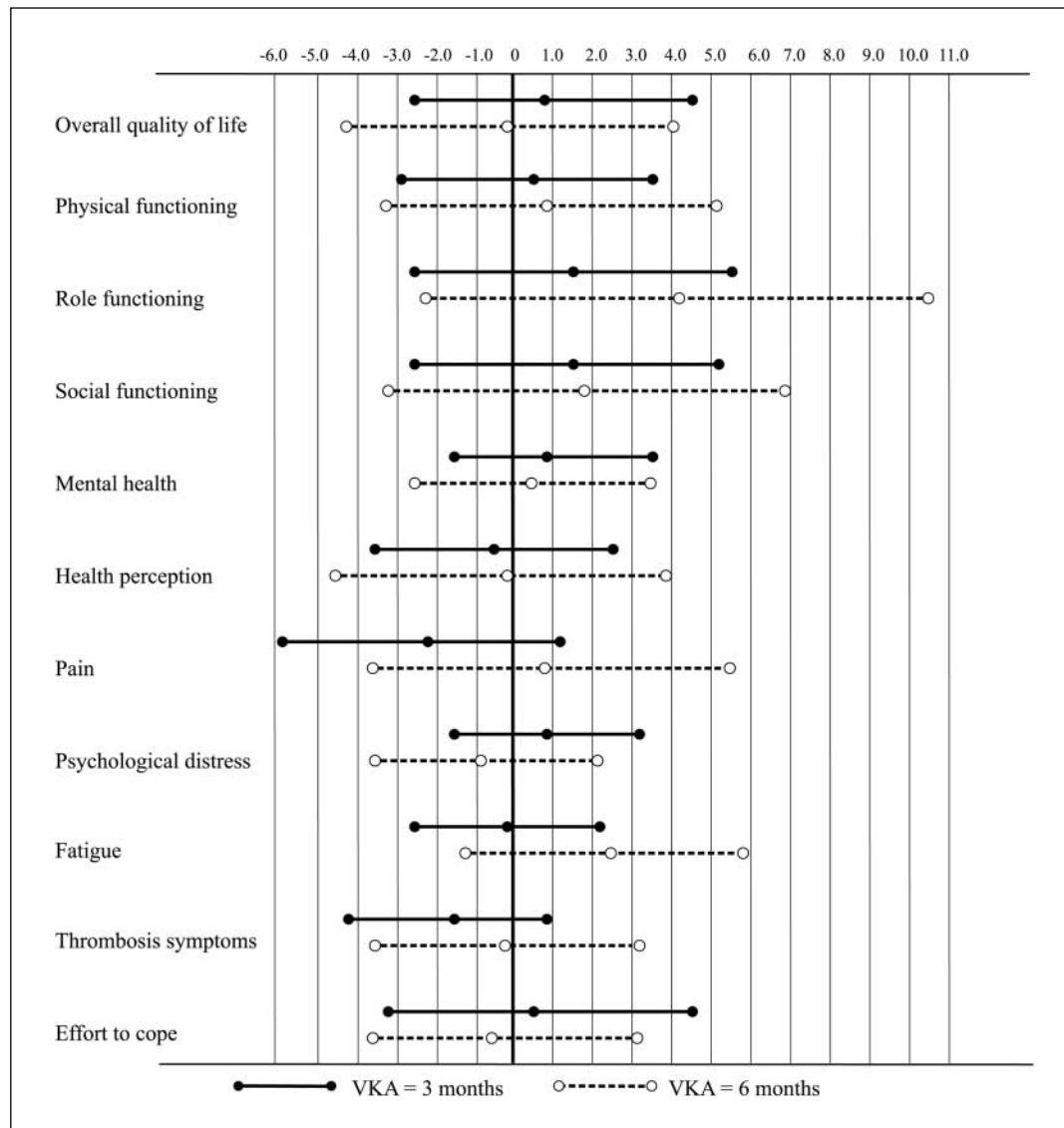


Figure 2: Change scores on quality of life (T4-T3).

Horizontal bars denote 95% confidence intervals around mean change scores on quality of life. Positive change scores indicate higher function or impairment on the attribute measured over time: better overall quality of life, better physical functioning, better role functioning, and better social and mental functioning, better health perception, more pain, fatigue, thrombosis symptoms, more effort to cope with the illness and treatment. If a bar does not cross zero, there is a significant difference between quality of life scores at 3 months and 6 months. Sample sizes at 3 months and 6 months were 207 and 193 respectively for patients treated for 3 months, and 122 and 115 respectively for patients treated for 6 months with vitamin K antagonists. T3: 3 months. T4: 6 months.

adverse events (n = 5), death (n = 7), patients' or physicians' refusal to continue study treatment (n = 4), and discontinuation for other reasons (n = 7).

Demographic and clinical factors

Demographic and clinical characteristics of eligible patients are detailed in Table 1. In comparison to patients treated for 3 months, patients treated for 6 months were more likely to be treated with standard unfractionated heparin, to have stayed in the hospital for a longer period of time, to have had previous

deep-vein thrombosis, to have known cancer, to have 1 or more permanent risk factors for venous thromboembolism, to be immobile prior to the deep vein thrombosis, and to be treated in Hôpital Clamart, or Flinders Medical Centre.

The course of quality of life over time

The course of quality of life over time was visualised by plotting mean scale scores at the four measurement moments of patients treated for 3 months and of those treated for 6 months

Variable	OR for VKA = 6 months	95% CI	p value
Hôpital Clamart/Flinders Medical Centre	16.87	5.71-49.87	< .001
≥ 1 Permanent risk factors	4.72	2.61- 8.54	< .001
Longer duration of hospitalisation	2.58	1.43- 4.66	.002
Poor mobility prior to DVT	3.67	1.47- 9.23	.006

Table 2: Multivariate logistic regression analysis on duration of treatment with vitamin K antagonists (VKA), N = 360.

(Fig. 1). Patients treated for 3 months were treated with vitamin K antagonists at time point 1, 2 and 3 whereas patients treated for 6 months were treated at all 4 measurement moments. Of the 216 patients treated for 3 months, 96% completed the quality of life questionnaires at 3 months and 89% completed the questionnaires at 6 months. These proportions were 85% and 80% respectively for the 144 patients treated for 6 months. Repeated measures analyses of variance indicated time effects, with improvement in all quality of life scales ($p < 0.001$). Group effects were not significant, indicating insignificant differences in quality of life scores between patients treated for 3 months and patients treated for 6 months. All p values were above 0.20, except for health perception ($p = 0.099$). An interaction effect between group and time was found for physical functioning ($p = 0.028$). We did not find statistically significant differences between the two groups with respect to the change scores of the quality of life scales at 3 months and 6 months (Fig. 2).

Factors associated with duration of treatment

Demographic, clinical and quality of life factors that differed between patients treated for 3 months, and patients treated for 6 months with vitamin K antagonists were included in a stepwise multivariate logistic regression analysis ($p < 0.10$). Variables included in the regression analysis were: initial treatment, duration of hospitalisation, previous deep-vein thrombosis, known cancer, presence of 1 or more permanent risk factors, mobility prior to deep-vein thrombosis, study centre, and health perception and physical functioning at study entry, 10-14 days and 3 months. The resulting multivariate logistic regression model included study centre, presence of 1 or more risk factors, duration of hospitalisation and mobility prior to deep-vein thrombosis (Table 2). The model indicated that patients treated for 6 months were more likely to be treated in Hôpital Clamart, or Flinders Medical Centre, to have 1 or more permanent risk factors for venous thromboembolism, to have stayed in the hospital for a longer period of time, and to be immobile prior to the deep-vein thrombosis. Forward and backward selection of variables produced the same model.

Discussion

We compared the course of quality of life in patients with deep-vein thrombosis treated for 3 months with vitamin K antagonists, and patients treated for 6 months. Quality of life improved over time, irrespective of duration of treatment. The changes in quality of life were similar when treatment with vitamin K antagonists was either continued or stopped at 3 months. No differences with respect to the change scores of quality of life at 3 months and 6 months were found between patients treated for 3 months and patients treated for 6 months. A number of clinical factors, and none of the demographic or quality of life factors were found to be associated with duration of treatment.

Prior to interpreting our findings, some methodological aspects should be considered. First, we expected patients who were treated for 6 months to have more thrombosis-related physical complaints, and lower scores on physical aspects of quality of life than patients whose treatment lasted for only 3 months. However, such differences were not found. This may, in part, be explained by bias introduced by the different compliance rates at 3 months and 6 months, which could be related to poorer health status. The selective patient attrition may have mitigated the observed difference. No bleeding complications occurred in the group treated for 6 months. The differential attrition rates can, therefore, not be ascribed to poorer health status due to bleeding events.

Second, we hypothesised that patients whose treatment was not extended after 3 months, needed more effort to cope with their illness and treatment at entry, 10-14 days and 3 months compared to patients treated for 6 months, and might therefore have more psychological distress and lower levels of mental health at these points in time. Such differences were not found. Although the quality of life questionnaires were reliable and responsive over time (9-13), it should be noted that the scales effort to cope, mental health and psychological distress were general scales. Patients with major co-morbidity could therefore have answered the items of these scales with regard to the consequences of other conditions than thrombosis. Since the group treated for 6 months comprised significantly more patients with major co-morbidity (i.e., immobile patients and patients with known cancer) we repeated the analyses with exclusion of all

patients with major co-morbidity. Again, no differences in quality of life or coping were found between patients treated for 3 months, and patients treated for 6 months. Hence, the absence of a difference between the 2 groups of patients can not be attributed to the different prevalence of co-morbidity.

Third, our results suggest that treatment with vitamin K antagonists has no adverse effects on quality of life. However, patients were not randomly allocated to different treatment durations. Therefore, this finding should be interpreted with caution. While the effect of different treatment durations with vitamin K antagonists has been examined in randomised trials, none of them assessed patients' quality of life (14-17).

Fourth, we investigated patients enrolled in a large multi-centre trial, in 5 different countries, involving 4 different languages. While use could be made of established translated versions, some of the quality of life questionnaires had to be translated into 1 or more languages. The psychometric performance of the translated questionnaires is unknown.

In the multivariate logistic regression analysis, study centre was found to be the most important factor associated with treatment duration. This indicates that centre policy has a great influence on decisions regarding the duration of treatment with vitamin K antagonists. Quality of life was not associated with the length of treatment, which could indicate that patients' perceived burden of treatment does not influence decisions regard-

ing treatment duration. In a clinical decision analysis, however, van den Belt et al demonstrated that small variations in perceived burden of treatment with vitamin K antagonists, expressed as utilities, have a major impact on decisions regarding treatment duration, especially in young patients without co-morbidity (18). Since empirical data on patients' utilities for health states associated with vitamin K antagonist treatment is not available, it is difficult for physicians to take perceived burden of treatment into account when deciding on the duration of treatment. To make adequate decisions on the treatment length in patients with venous thrombosis, a clinical decision model would be needed, including the risk for recurrent venous thromboembolism, the risk of bleeding complications and patients' utilities for health states associated with treatment with vitamin K antagonists.

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Abbreviations

VAS, visual analogue scale; MOS-SF-20, Medical Outcome Study Short Form-20; INR, International Normalised Ratio; RSCL, Rotterdam Symptom Checklist; VKA, vitamin K antagonists; DVT, deep vein thrombosis

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