

Blood Coagulation, Fibrinolysis and Cellular Haemostasis

Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences

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Summary

Determining the optimal duration of vitamin K antagonist (VKA) therapy for patients with venous thromboembolism (VTE) requires a weighting of the benefits and risks of treatment. The objectives of our study were to investigate patient variability in health state valuations associated with VKA therapy and treatment preferences, and to investigate the extent to which valuations and treatment preferences are associated with prior experience with these health states and other patient characteristics. Valuations of outcomes after VTE scaled from 0 (tantamount to death) to 1 (tantamount to perfect health) were elicited from 53 patients who had experienced VTE, 23 patients who had experienced major bleeding during treatment, and 48 patients with the post-thrombotic syndrome. In

addition, patients' treatment preferences were evaluated using treatment trade-off questions. Median health state valuations ranged from 0.33 for 'non-fatal haemorrhagic stroke' to 0.96 for 'no VKA treatment'. Variability between patients was substantial. Patients' treatment preferences also varied: 25% of patients chose cessation of treatment, regardless of the probability of recurrent VTE presented, whereas 23% of patients were never willing to choose cessation of treatment. Differences in valuations and treatment preferences were not associated with type of event experienced. Due to the substantial and unpredictable variability in valuations and treatment preferences, recommendations regarding treatment duration should be tailored to patients' specific values and concerns.

Keywords

Venous thromboembolism, health state valuations, treatment preferences

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Introduction

The clinical effectiveness of treatment with vitamin K antagonists in the prevention of recurrent venous thromboembolism has been well established. However, during vitamin K antago-

nist therapy patients have a tendency to bruise and bleed more readily, they have an increased risk of major bleeding, and frequent blood tests are needed to allow laboratory testing and subsequent dose-adjustments. Determining the optimal duration of treatment requires a weighting of both the effec-

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tiveness of treatment as well as the risks and the burden to patients.

Explicit, quantitative expressions of patients' valuations of all health states related to venous thromboembolism and its treatment with vitamin K antagonists can help in making balanced decisions on the duration of treatment. These valuations can be incorporated into a formal decision analysis to evaluate whether the effectiveness of treatment outweighs the risks and burden of treatment. Alternatively, one can ask patients directly and explicitly to make a trade-off between the benefits and risks of a specified treatment duration. This approach is also known as the treatment trade-off method. The treatment trade-off method may offer a more realistic reflection of the actual decision dilemma than health valuation methods, and could be more useful for individual patient decision making (1).

Valuations for outcomes associated with vitamin K antagonist therapy have been assessed in several studies (2-7). Studies in patients with atrial fibrillation have shown that differences in patients' valuations for health states associated with vitamin K antagonists can have a large impact on decisions regarding treatment (2-4, 8). In addition, treatment preferences have been shown to vary considerably between physicians and patients at risk for atrial fibrillation (9). These findings emphasise the importance of taking patients' views into account when deciding on the optimal duration of treatment with vitamin K antagonists after venous thromboembolism. Health state valuations of patients with venous thromboembolism have been assessed in only one study: O'Meara et al. (6) obtained valuations for central nervous system bleeding and the post-thrombotic syndrome in patients with deep vein thrombosis. To our knowledge, treatment preferences have never been assessed in patients with venous thromboembolism.

Based on studies in patients with atrial fibrillation (2-4,5), we expect state of health valuations and treatment preferences to differ in patients with venous thromboembolism. If so, and if the magnitude of these differences is substantial, the construction of clear and simple recommendations for all patients may not be possible. In that case, recommendations have to be tailored according to the patient's actual valuations or treatment preferences.

The objectives of this study were to investigate patient variability in state of health valuations and treatment preferences associated with venous thromboembolism, and to investigate the extent to which valuations and treatment preferences can be associated with prior experience with these health states and patient characteristics. We obtained health state valuations and treatment preferences from patients with prior experience with venous thromboembolism, treatment with vitamin K antagonists, as well as patients who had experienced some of the potential downsides of treatment.

Materials and methods

Patients

Three groups of eligible patients were recruited between October 2000 and June 2002: (a) Newly diagnosed patients with a first or second episode of venous thromboembolism for whom treatment with vitamin K antagonists had been started; (b) patients who had experienced an episode of major bleeding during treatment with vitamin K antagonists in the previous year; (c) patients with a post-thrombotic syndrome, diagnosed at least one year after an episode of deep vein thrombosis, who had been treated with vitamin K antagonists for at least three months.

The diagnosis of deep vein thrombosis was established using compression ultrasonography or venography. The diagnosis of a pulmonary embolism was established by either perfusion-ventilation lung scan or pulmonary angiography. Major bleeding was defined as: bleeding leading to a fall in the haemoglobin level of at least 1.25 mM, bleeding that required a blood transfusion or hospital admission, and bleeding leading to residual complaints. For the diagnosis of the post-thrombotic syndrome we applied the criteria used by Brandjes et al. (10). Excluded were patients younger than 18 years, patients with cancer or other serious co-morbidity, as well as patients with an insufficient knowledge of the Dutch language. The study was performed in three academic centres: the Academic Medical Centre in Amsterdam, the University Hospital of Groningen and the University Hospital of Maastricht. In each centre, the study had been approved by the institutional review board.

Procedure

Patients were invited to the study by a physician or research nurse, who explained the purpose of the study and provided written information. After written informed consent had been obtained, arrangements were made for an interview. Since we wanted patients to have experienced treatment with vitamin K antagonists at the time of the interview, patients with an episode of venous thromboembolism were interviewed approximately three months after inclusion. Patients who had experienced a major bleeding event and patients with a post-thrombotic syndrome had been treated with vitamin K antagonists, and were therefore contacted a few days after inclusion, to schedule an interview appointment. All patients were interviewed by one of four trained interviewers. On average, the interview lasted 62 minutes (range 32-130).

Health state descriptions

Written descriptions of eight health states associated with venous thromboembolism and its treatment with vitamin K antagonists were developed, based on information provided by clinical experts in the field. In addition, patients were asked to value their 'own current health', so a total of nine health states

were evaluated. The four chronic health states were 'non-fatal haemorrhagic stroke', 'post-thrombotic syndrome', 'no treatment with vitamin K antagonists', and patients' 'own current health'. The five temporary health states were 'deep vein thrombosis', 'pulmonary embolism', 'gastro-intestinal bleeding', 'muscular bleeding', and 'treatment with vitamin K antagonists'. Each scenario was labelled, written in the third person, and described outcomes on physical, psychological, and social dimensions. Separate versions were used for men and women. As an example, health state descriptions for 'treatment with vitamin K antagonists', 'deep vein thrombosis', and 'non-fatal haemorrhagic stroke' are provided in appendix A.

Health state valuations

Rank ordering procedure

Patients were first asked to rank all health states from least to most preferred. Next, they were asked to value the health states with the direct rating method and the time trade-off method.

The direct rating method and the time trade-off method are procedures which enable patients to give quantitative expressions of their valuations for health outcomes. These valuations range between 0 (tantamount to death) and 1 (tantamount to perfect health).

Direct rating

Patients rated all health states by marking a horizontal rating scale anchored at the ends with the states death (0) and perfect health (100). These values were then rescaled to from 0 to 1.

Time trade-off

With the time trade-off method patients were asked to choose between their remaining life expectancy (t) in a specific health state, and a shorter life span in perfect health. The duration of the time in perfect health (x) was varied until the patient reported indifference between the two options. The value for the health state under evaluation was calculated by dividing x by t , and ranged from 0 (tantamount to death) and 1 (tantamount to perfect health). We used the time trade-off for the chronic health states. Since temporary health states are, by definition, not followed by death, the time trade-off constitutes an unrealistic choice for these health states. Several adaptations of the time trade-off have been proposed for the evaluation of temporary health states (2, 11-13). In this study, we converted the values of the nine health states obtained with the rating scale to time trade-off values, using the following power function (14):

$$TTO = 1 - (1 - R)^\alpha,$$

where R stands for values obtained with direct rating to be converted to time trade-off values, TTO . The power function was fitted for chronic health states, to match the values obtained with the direct rating method to values obtained with the time

trade-off. The value of α was calculated, based on the original values for chronic health states obtained with the time trade-off, using non-linear regression analysis. The converted values, ranging from 0 (tantamount to death) and 1 (tantamount to perfect health) will be reported here.

Treatment preferences

Patients' treatment preferences were evaluated using treatment trade-off questions. Patients were presented with a written hypothetical scenario. They were asked to advise a close friend, treated with vitamin K antagonists for three months after an episode of venous thromboembolism, on the following two choices: continuation of treatment for another two years or cessation of treatment. Continuation of treatment would involve regular blood tests, a tendency to bruise and bleed more readily, a 3% chance of a major bleeding event, and a 2% chance of a recurrent episode of venous thromboembolism in the next 2 years. Cessation of treatment was associated with a specific probability of a recurrent episode of venous thromboembolism. Four values were presented in random order: 3%, 5%, 10% and 15%. For each of these four probabilities of recurrent venous thromboembolism, patients were asked to choose between continuation and cessation of treatment with vitamin K antagonists. The treatment threshold was defined as the smallest risk of recurrent venous thromboembolism a patient was willing to take during cessation of treatment.

Additional measures

The presence of a family history of venous thromboembolism was registered at inclusion. In addition, all patients were handed over a questionnaire which included questions on marital status, educational level (i.e. low, medium or high) and employment status.

Analyses

To test if health state values and treatment preferences differed among patients after an episode of venous thromboembolism, a major bleeding event, or after the diagnosis of the post-thrombotic syndrome, Kruskal-Wallis tests were performed. To determine whether patient characteristics (gender, age, marital status, educational level, employment status and family history of venous thromboembolism) were related to health state values and treatment preferences, Somers' d tests were performed (15). P-values < 0.05 were considered statistically significant.

Results

Patients

Of 159 eligible patients, 129 (81%) gave consent. Five patients died before the interview could take place, so 124 (96%) patients were interviewed: 53 (43%) patients after an episode

Health state	Median ranking	Median valuation (IQR)
No VKA treatment	9	0.96 (0.82-1.00)
Own current health	9	0.95 (0.81-1.00)
VKA treatment	7	0.92 (0.77-0.98)
Post-thrombotic syndrome	6	0.82 (0.66-0.97)
Deep vein thrombosis	5	0.84 (0.64-0.98)
Muscular bleeding	4	0.76 (0.59-0.95)
Gastro-intestinal bleeding	3	0.65 (0.49-0.86)
Pulmonary embolism	3	0.63 (0.36-0.86)
Non-fatal haemorrhagic stroke	1	0.33 (0.14-0.53)

IQR = inter-quartile range
A higher valuation score or ranking indicates better health status

Table 1: Rankings and valuations for own current health and health states associated with venous thromboembolism and its treatment with vitamin K antagonists (VKA).

of venous thromboembolism (deep vein thrombosis n = 38; pulmonary embolism n = 15), 23 (18%) patients after a major bleeding event, and 48 (39%) patients with the post-thrombotic syndrome. Their average age was 53 (range 21-85), approximately half of patients were female (53%), married (55%) and unemployed (49%). Most patients had a medium educational level (40%). In 104 patients, it was known whether the patient had a family history of venous thromboembolism or not. Of these patients, 35% had one or more relative with venous thromboembolism. The average time between inclusion and the interview was 13 weeks for patients in the venous thromboembolism group, 6 weeks for patients in the major bleeding group, and 4 weeks for patients in the post-thrombotic syndrome group.

Health state valuations

A separate power function was fitted for each patient and the median α (1.996) was used in the final transformations. The rankings and values of the nine health states are shown in Table 1. There was substantial variability among patients with

the largest inter-quartile range for pulmonary embolism (0.50). Median rankings were equal for 'no treatment with vitamin K antagonists' and 'own current health', and also for 'gastro-intestinal bleeding' and 'pulmonary embolism'. Compared to the median rankings of 'post-thrombotic syndrome' and 'deep vein thrombosis', the rank order of the median time trade-off scores was reversed. With the rank ordering procedure, patients valued 'post-thrombotic syndrome' as a better health state than 'deep vein thrombosis', whereas with the time trade-off patients valued 'deep vein thrombosis' as a better health state than 'post-thrombotic syndrome'.

Kruskal-Wallis test statistics indicated that the health state values did not differ significantly among patients after an episode of venous thromboembolism, a major bleeding event or after the diagnosis of the post-thrombotic syndrome. Of the patient characteristics, marital status and family history were significantly associated with the health state values. Married patients had higher scores for 'deep vein thrombosis' (p = 0.02), 'pulmonary embolism' (p = 0.02) and 'non-fatal stroke' (p = 0.02). Patients with a family history of venous thromboembolism had lower scores for 'no treatment with vitamin K antagonists' (p = 0.01).

Table 2: Treatment preferences.

Treatment threshold [§]	N (%)
Always cessation of treatment [†]	30 (25)
Stop at 5% risk of VTE	25 (21)
Stop at 10% risk of VTE	27 (23)
Stop at 15% risk of VTE	9 (8)
Always continue treatment [†]	27 (23)
Total	118 (100)

[§]Treatment threshold: the smallest risk of recurrent venous thromboembolism a patient is willing to accept during cessation of treatment
[†]Regardless of the probability presented

Treatment preferences

In table 2 patients' treatment preferences are reported. Treatment preferences did not differ significantly among patients after an episode of venous thromboembolism, a major bleeding event or after the diagnosis of the post-thrombotic syndrome. Of the patient characteristics, gender (p = 0.01) and educational level (p < 0.01) were significantly associated with the risk patients were willing to take regarding recurrent venous thromboembolism. Men were willing to take higher risks during cessation of treatment than women. Patients with a low educational level were more willing to choose for continuation of treatment, regardless of the risk of venous thromboembolism, than patients with a medium or high educational level.

Discussion

This study showed that patients were able to assign values to health states related to venous thromboembolism and its treatment with vitamin K antagonists, and to state their treatment preferences, balancing the downsides of treatment versus a risk of recurrent venous thromboembolism. Health state values varied substantially among patients, as did the reported recurrence-risk thresholds for accepting further treatment with vitamin K antagonists. Health state values and treatment preferences did not differ significantly among patients after an episode of venous thromboembolism, a major bleeding event or after the diagnosis of the post-thrombotic syndrome.

The duration of interviews varied between 32 and 130 minutes. This rather wide range can be explained by the fact that patients who were not willing or able to come to the hospital were interviewed at home. On average, the duration of interviews held at home was longer than interviews held at the hospital. Additional analyses show that the duration of interviews was not associated with health state valuations or treatment preferences.

The valuations patients provided for 'treatment with vitamin K antagonists' were of similar magnitude as valuations found in previous studies (2-4, 5). Health state values for different types of major bleeding events and the post-thrombotic syndrome, however, differed from previously reported values. Thomson et al. (4) reported a value of 0.88 for gastro-intestinal bleeding in patients with atrial fibrillation, which is substantially higher than the median value of 0.65 we found in this study. The value for major stroke was estimated at 0.26 and for minor stroke at 0.55 in a systematic review (16), whereas we found a value of 0.33 for 'non-fatal haemorrhagic stroke'. For 'post-thrombotic syndrome' we found a median value 0.82 whereas O'Meara et al. (6) found a mean score of 0.98 for severe post-thrombotic syndrome, and a mean score of 1.00 for mild post-thrombotic syndrome. Lenert and Soetikno (7) found a median value of 0.95 for severe post-thrombotic syndrome and a median value of 1.00 for mild post-thrombotic syndrome. Differences between the valuations found in previous studies and the values found in this study can be explained by a difference in methods (17). We obtained health state values with the time trade-off, whereas in several of the other studies values were obtained with the standard gamble method. In addition, differences between valuations could be caused by differences in definitions of the health states (16).

Previous experience with venous thromboembolism, major bleeding, and the post-thrombotic syndrome did not significantly influence patient valuations. A study by Dolan and Roberts has shown that age, sex and marital status can be important determinants of respondents' health state valuations (18). In our study, of the patient characteristics, only marital status and a family history of venous thromboembolism were associated

with health state values. We can speculate that single patients may find being dependent on others for their activities of daily life to be worse than married patients. Future research, in which patients are asked to explain their valuations, might provide more insight into the relationship between patients' marital status and health state valuations. Patients with a family history of venous thromboembolism may perceive the risk of a recurrent episode of venous thromboembolism as higher than patients with no family history of venous thromboembolism. This could explain the lower health state values that patients with a family history assign to 'no treatment with vitamin K antagonists'.

Not all participants were themselves facing the decision dilemmas that were the topic of the treatment trade-off questions. Furthermore, we wanted to evade issues of regret and dissonance reduction. For this reason, we phrased the questions as advice to a close friend. A similar procedure has been used in other studies (19).

Treatment preferences were not significantly influenced by type of event experienced. Of the patient characteristics, gender and educational level were associated with the risk of recurrent venous thromboembolism that patients were willing to take during cessation of treatment. Men were willing to take higher risks after cessation of treatment than women, which is consistent with studies assessing risk-taking behaviour (20, 21). Patients with a lower educational level were more willing to choose continuation of treatment, regardless of the risk of venous thromboembolism, than patients with a medium or high educational level. This could indicate that patients with a lower educational level found it more difficult to balance the benefits and risks associated with treatment than patients with a medium or high educational level.

Health state values and treatment preferences varied substantially between patients, without a significant association with type of event previously experienced. Other factors such as personality characteristics, attitudes, subjective illness perceptions and medication beliefs might be more important determinants of valuations and treatment preferences (22, 23). Qualitative research in patients with atrial fibrillation has shown that patients' health beliefs can determine decisions regarding vitamin K antagonist therapy (24). The thromboembolic threat for patients with atrial fibrillation may be greater than for patients with venous thromboembolism, and this may significantly alter patients' valuations and treatment preferences. Future studies could focus on the relationship between valuations and treatment preferences on the one hand, and, on the other hand, health beliefs in patients with venous thromboembolism treated with vitamin K antagonists.

The substantial variability in valuations and treatment preferences among patients suggests that no general guidelines can be made, and that recommendations regarding treatment duration have to be tailored to patients' specific values and concerns. As treatment trade-off questions may offer a more realistic and

simple reflection of the actual decision dilemma, and are less time consuming than the assessment of health state values for outcomes after venous thromboembolism, we suggest that the treatment trade-off method can be transformed into a suitable decision aid to guide patient-physician decision-making in clinical practice.

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Appendix A

Health state descriptions for 'treatment with vitamin K antagonists', 'deep vein thrombosis' and 'non-fatal haemorrhagic stroke' (male version).

Treatment with vitamin K antagonists

Physical functioning. The patient has a tendency to bruise and bleed easily.
Social functioning. Family and leisure activities are somewhat limited because the patient is not able to do certain sports. It is difficult to plan holidays due to appointments at the thrombosis service.

Psychological functioning. The patient is somewhat worried about a recurrent deep vein thrombosis or pulmonary embolism in the future. In addition, he worries about possible bleeding events.

Deep vein thrombosis

Physical functioning. The patient is admitted to the hospital for one day. His leg hurts and his calf is swollen. He has difficulties walking short distances. He is not able to walk long distances. The patient is partly dependent upon others for his daily care. After a couple of days the patient recovers.

Social functioning. Work, family and leisure activities are limited for approximately four weeks, due to pain in the leg.

Psychological functioning. The patient is somewhat anxious due to his condition. He is also somewhat worried about a recurrent deep vein thrombosis in the future.

Non-fatal haemorrhagic stroke

Physical functioning. The patient has limited strength in the right side of his body. People find it hard to understand what he is saying. The patient has problems processing information and he has difficulties concentrating. He walks short distances with a walker. He is not able to walk long distances. The patient is partly dependent upon others for his daily care.

Social functioning. The patient is not able to work. Family and leisure activities are limited due to the reduced strength in his body, the problems people have understanding him, and his difficulties with the processing of information.

Psychological functioning. The patient is very worried about a recurrent stroke in the future. He is depressed.

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