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Treatment of Venous Thromboembolism with Vitamin K antagonists: Patients’ Utilities and Treatment Trade-offs

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Submitted for publication
Abstract
Determining the optimal duration of vitamin K antagonist therapy for patients with venous thromboembolism (VTE) requires a weighing of both the long-term effectiveness of treatment and the risks and burden for patients. We elicited utilities for health states related to VTE and treatment with vitamin K antagonists from 53 patients who had experienced an episode of VTE, 23 patients who had experienced a major bleeding event during treatment, and 48 patients with the post-thrombotic syndrome, using the time trade-off method and direct rating. We also evaluated patients' preferences for either continuation or cessation of treatment after three months of therapy using treatment trade-off questions. We found that median utilities ranged from 0.33 for ‘non-fatal haemorrhagic stroke’ to 0.96 for ‘no VKA treatment’. There was substantial variability between patients, with the largest inter-quartile range for pulmonary embolism (0.50). Patients also varied in the reported threshold for accepting further treatment: 25% of patients were not willing to accept any risk of recurrent VTE after cessation of treatment, whereas 23% of patients chose for cessation of treatment, regardless the probability presented for recurrent VTE. Differences in utilities and treatment trade-off were not associated with type of event experienced. We conclude that patients are able to value health states related to VTE and vitamin K antagonist therapy and to balance the benefits and risks associated with treatment. Due to the substantial and unpredictable variability between patients, recommendations regarding treatment duration should be tailored to a patient’s specific values and concerns.
Introduction

The clinical effectiveness of treatment with vitamin K antagonists in the prevention of recurrent venous thromboembolism (VTE) has been well established. However, during vitamin K antagonist 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 weighing of both the effectiveness of treatment as well as the risks and the burden to patients.

Explicit, quantitative expressions of patients’ valuations – or utilities – of all health states related to VTE and its treatment with vitamin K antagonists can help in making balanced decisions on the duration of treatment. Patient utilities 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. Such treatment trade-off questions may offer a more realistic reflection of the actual decision dilemma, and could be more useful for individual patient decision making.

Previous studies in patients with atrial fibrillation have shown that differences in patient utilities can substantially alter the optimal duration of treatment for specific patient groups. In addition, the assessment of treatment trade-offs has shown to improve patients’ understanding of the benefits and risks associated with vitamin K antagonist therapy, which may help them make definitive choices about treatment duration. Treatment trade-offs have also been shown to vary considerably between physicians and patients at risk for atrial fibrillation. These findings emphasise the importance of taking patients’ views into account when deciding on the optimal duration of treatment after VTE.

It is an open question whether utilities and treatment trade-offs for scenarios related to VTE and its treatment differ between patients. 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 utilities or treatment trade-offs.

The objectives of this study were to assess patients’ utilities for health states related to VTE and its treatment with vitamin K antagonists, as well as patients’ treatment trade-offs for either continuation or cessation of treatment after three months of vitamin K antagonist therapy. We wanted to determine the level of variability in these utilities and treatment trade-offs, as well as the extent to which utilities and
treatment trade-offs can be associated with prior experience with these health states and patient characteristics.

Methods

Patients

Three groups of eligible patients were recruited between October 2000 and June 2002: (1) newly diagnosed patients with a first or second episode of VTE for whom treatment with vitamin K antagonists had been started; (2) patients who had experienced an episode of major bleeding during treatment with vitamin K antagonists in the previous year; (3) 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. We selected these three different groups because we wanted to obtain valuations and preferences from patients with prior experience with VTE, treatment with vitamin K antagonists, as well as patients who had experienced some of the potential downsides of treatment.

The diagnosis of deep venous 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 mmol/L, 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. 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 Center 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.

Interview

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 VTE 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. For quality control, each interviewer audio-taped three of the ten first interviews and received detailed feedback. On average, the interview lasted 62 minutes (range 32-130).

Health State Descriptions

Written descriptions of eight health states associated with VTE 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 venous thrombosis’, and ‘non-fatal haemorrhagic stroke’ are provided in the appendix.

Utility Assessment

*Rank ordering procedure*. Patients were first asked to rank order the health states from least to most preferred. Next, they were asked to assign utilities to the health state descriptions with the direct rating method and the time trade-off method.

*Direct rating*. Patients rated the health states by marking a horizontal visual analogue scale anchored at the ends with the states death (0) and perfect health (100). We used direct rating as it is easy to understand although some feel that the scores produced cannot be regarded as true utilities, as there is no trade-off involved.

*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 reports indifference between the two options. The value for the health state under evaluation was calculated by dividing x by t. 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. 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:

\[ TTO = 1 - (1 - R)^{a,13} \]

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 \( a \) 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 will be referred to as utilities.

**Treatment Trade-off**

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 VTE, 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 VTE in the next 2 years. Cessation of treatment was associated with a specific probability of a recurrent episode of VTE. Four values were presented in random order: 3%, 5%, 10% and 15%. For each of these four probabilities of recurrent VTE, 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 VTE a patient was willing to take after cessation of treatment.

**Additional Measures**

The presence of a family history of VTE was registered at inclusion. In addition, all patients received a questionnaire a few days after inclusion, which included questions on marital status, educational level, and employment status (i.e. low, medium or high).

**Statistical Analyses**

To test if utilities and treatment preferences differed among patients after an episode of VTE, 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 VTE) were related to utilities and treatment preferences, Somers’ d tests were performed. 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 of VTE (deep venous 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 VTE or not. Of these patients 35% had one or more relatives with VTE. The average time between inclusion and the interview was 13 weeks for patients in the VTE group, 6 weeks for patients in the major bleeding group, and 4 weeks for patients in the post-thrombotic syndrome group.

Utilities
A separate power function was fitted for each patient and the median a (1.996) was used in the final transformations. The rankings and utilities of the nine health states are shown in Table 1. There was substantial variability among patients, with 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 venous thrombosis’, the rank order of the median time trade-off scores was reversed. Kruskal-Wallis test statistics indicated that utilities did not differ significantly among patients after an episode of VTE, 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 utility scores. Married patients had higher scores for ‘deep venous thrombosis’ (p = 0.02), ‘pulmonary embolism’ (p = 0.02) and ‘non-fatal stroke’ (p = 0.02). Patients with a family history of VTE had lower scores for ‘no treatment with vitamin K antagonists’ (p = 0.01).
Table 1: Ranking and median time trade-off scores for own current health and the health states associated with VTE and its treatment with vitamin K antagonists (VKA).

<table>
<thead>
<tr>
<th>Health state</th>
<th>Rank median</th>
<th>Time trade-off median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No VKA treatment</td>
<td>1</td>
<td>0.96 (0.82-1.00)</td>
</tr>
<tr>
<td>Own current health</td>
<td>2</td>
<td>0.95 (0.81-1.00)</td>
</tr>
<tr>
<td>VKA treatment</td>
<td>3</td>
<td>0.92 (0.77-0.98)</td>
</tr>
<tr>
<td>Post-thrombotic syndrome</td>
<td>4</td>
<td>0.82 (0.66-0.97)</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>2</td>
<td>0.84 (0.64-0.98)</td>
</tr>
<tr>
<td>Muscular bleeding</td>
<td>3</td>
<td>0.76 (0.59-0.93)</td>
</tr>
<tr>
<td>Gastro-intestinal bleeding</td>
<td>6</td>
<td>0.65 (0.49-0.86)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>6</td>
<td>0.63 (0.36-0.86)</td>
</tr>
<tr>
<td>Non-fatal haemorrhagic stroke</td>
<td>8</td>
<td>0.33 (0.14-0.53)</td>
</tr>
</tbody>
</table>

# IQR inter-quartile range

Treatment Trade-off

In table 2 patients’ answers to the treatment trade-off questions are reported. Sixty-nine percent of patients chose for cessation of treatment if the risk of recurrent VTE did not exceed 10%. Twenty-five percent of patients opted for continuation of treatment and 23% of patients chose for cessation of treatment, regardless of the probability presented. Treatment preferences did not differ significantly among patients after an episode of VTE, 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 of recurrent VTE patients were willing to take. Men were willing to take higher risks after 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 VTE, than patients with a medium or high educational level.

Table 2: Treatment trade-off.

<table>
<thead>
<tr>
<th>Treatment threshold</th>
<th>N  (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always continue treatment</td>
<td>30 (25)</td>
</tr>
<tr>
<td>Stop at &gt;5% risk of VTE</td>
<td>25 (21)</td>
</tr>
<tr>
<td>Stop at 10% risk of VTE</td>
<td>27 (23)</td>
</tr>
<tr>
<td>Stop at 15% risk of VTE</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Always cessation of treatment</td>
<td>27 (23)</td>
</tr>
<tr>
<td>Total</td>
<td>118 (100)</td>
</tr>
</tbody>
</table>

*Treatment threshold: the smallest risk of recurrent VTE a patient is willing to accept after cessation of treatment. *Regardless of the probability presented.
Discussion

This study showed that patients were able to assign utilities to health states related to VTE and its treatment with vitamin K antagonists, as well as to make treatment trade-offs, balancing the downsides of treatment versus a risk of recurrent VTE. Utilities varied substantially among patients, as did the reported recurrence risk thresholds for accepting further treatment with vitamin K antagonists. Utilities and treatment thresholds did not differ significantly among patients after an episode of VTE, a major bleeding event or after the diagnosis of the post-thrombotic syndrome.

The valuations patients provided for ‘treatment with vitamin K antagonists’ were of similar magnitude as the utilities found in previous studies. Utilities for different types of major bleeding events, however, differed from previously reported utilities: Thomson et al. reported a median standard gamble score of 0.88 for gastro-intestinal bleeding in patients with atrial fibrillation, which is substantially higher than the median time trade-off score of 0.65 found in this study. The difference between these valuations could be explained by the different health state valuation methods used. In general, standard gamble scores are higher than time trade-off scores. In a systematic review, the time trade-off score for major stroke was estimated at 0.26 and for minor stroke at 0.55, whereas we found a utility of 0.33 for ‘non-fatal haemorrhagic stroke’. Post and colleagues argued that the variation between time trade-off utilities may be caused by differences in definitions of the health states. Two studies assessed valuations of the post-thrombotic syndrome. O’Meara et al. found a mean standard gamble score of 0.98 for severe post-thrombotic syndrome, and a mean standard gamble score of 1.00 for mild post-thrombotic syndrome. Lenert and Soetikno also used the standard gamble technique. They found a median utility of 0.95 for severe post-thrombotic syndrome and a median utility of 1.00 for mild post-thrombotic syndrome. We found a median utility of 0.82 for ‘post-thrombotic syndrome’. Differences between the utilities for the post-thrombotic syndrome found in previous studies and the utilities found in this study, could be explained by a method effect. We obtained health state values with the time trade-off whereas the other studies obtained standard gamble scores.

Previous experience with VTE, major bleeding, and the post-thrombotic syndrome did not significantly influence the utility scores. Of the patient characteristics, only marital status and family history were associated with the utilities. We can speculate that single patients may find being dependent on others for their activities of daily living to be worse than married patients, although we
did not ask patients to explain their valuations. This could explain the lower utilities single patients assigned to ‘deep venous thrombosis’, ‘pulmonary embolism’ and ‘non-fatal stroke’. However, being single was not associated with lower values for ‘gastro-intestinal bleeding’ and ‘muscular bleeding’, although these health states also involved being dependent on others for daily care. Patients with a family history of VTE may perceive the risk of a recurrent episode of VTE as higher than patients with no family history of VTE. This could explain the lower utilities patients with a family history assign to ‘no treatment with vitamin K antagonists’.

Answers to the treatment trade-off questions were not influenced by type of event experienced, which could be explained by the fact that we randomly varied the probability of a recurrent episode of VTE. It is likely that patients based their decisions on the probability presented, and not on their own perceived risk of a recurrence. Of the patient characteristics, gender and educational level were associated with the risk of recurrent VTE 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. Patients with a lower educational level were more willing to choose for continuation of treatment, regardless of the risk of VTE, 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.

In conclusion, utilities and treatment trade-offs varied substantially between patients, without a significant association with type of event previously experienced. The substantial variability among patients suggests that no general guidelines can be made, and that recommendations regarding treatment duration have to be tailored to a patient’s 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 utilities for all health states related to VTE and its treatment, 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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Gran tt  Suppor t
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References
Appendix

Health state descriptions for 'treatment with vitamin K antagonists', 'deep venous 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 venous thrombosis or pulmonary embolism in the future. In addition, he worries about possible bleeding events.

Deep venous 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 venous 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.