Chapter 6

Optimal duration of treatment with vitamin K antagonists in patients with a first episode of venous thromboembolism: a decision analytic approach


Submitted for publication
Abstract

Objective
To determine the optimal duration of treatment with vitamin K antagonists in several subgroups of patients with a first episode of venous thromboembolism.

Methods
The risk of thromboembolic and treatment-related complications as well as patients’ valuations of health states were incorporated in a Markov decision model. Risk estimates were derived from the literature. Valuations of relevant health states were obtained in a group of 124 patients.

Results
For patients with an increased risk of recurrence (idiopathic first episode), there was an almost nonexistent increase in quality-adjusted life expectancy of 0.03 years when treatment duration was prolonged after six months up to one year and an increase of 0.20 years in case of lifelong treatment. For patients presenting with idiopathic pulmonary embolism the changes were 0.14 and 2.54 years respectively. Sensitivity analysis showed the optimal duration of treatment to be sensitive to the patients’ perceived burden of treatment.

Conclusion
Although prolongation of vitamin K antagonist treatment can be expected to increase longevity, the changes in life expectancy do not always outweigh the downsides of treatment, in particular the burden of therapy. As most changes in quality-adjusted life expectancy will be small and dependent on the patients’ valuations of health states, there is room for individually tailoring the duration of treatment with vitamin K antagonists, for which the proposed decision model might be used.
Introduction

Patients with venous thromboembolism are initially treated with low-molecular-weight heparin or unfractionated heparin for five to ten days [1,2]. Concomitantly, usually within 48 hours, secondary prophylaxis with vitamin K antagonists is started and continued for three to six months in the majority of patients.

It has been shown that prolonging the duration of treatment with vitamin K antagonists results in a decrease of the risk of recurrent thromboembolic events [3]. In some subgroups of patients, especially those with an idiopathic episode of venous thromboembolism and who are therefore at increased risk of recurrent events, there is a trend towards extended secondary prophylaxis [4,5,6]. Yet, in clinical practice there is little consensus about the optimal duration of therapy.

A recent meta-analysis showed that the risk of recurrent venous thromboembolism declined over time in the period after discontinuation of treatment with vitamin K antagonists [7]. Consequently, the benefits of prolonged treatment with vitamin K antagonists will also decrease over time. The decision to extend treatment beyond six months requires a weighing of the absolute reduction in the risk of recurrent venous thromboembolism versus the risk of bleeding and the burden of treatment. It is questionable whether the absolute risk reduction under prolongation of vitamin K antagonist treatment can counterbalance the cumulative burden of treatment and the continuation of and increased risk of bleeding, which will often affect the quality of life for the patient. We constructed a decision model to balance the benefits and disadvantages of continued treatment for several subgroups of patients with a first episode of venous thromboembolism.

Methods

Model design

A Markov model was used for our decision analysis. The natural course of a hypothetical cohort of patients with a first episode of venous thromboembolism was simulated. Several transitory states were defined to accommodate the most important complications that can occur during treatment of venous thromboembolism as well as after discontinuation of treatment. A branch representing these relevant complications following a first episode of venous thromboembolism is depicted in Figure 1.
In this model, patients are at risk for a number of complications. The first to consider is recurrent venous thromboembolism. An episode of recurrent venous thromboembolism can manifest itself as a pulmonary embolism, which can be fatal, or a deep-vein thrombosis. In addition, a possible chronic complication of venous thromboembolism is the post-thrombotic syndrome, which reduces the quality of life [8]. Treatment with vitamin K antagonists reduces the risk of recurrence, but carries an increased risk of haemorrhages. These haemorrhages may be major or minor. An haemorrhagic event in the central nervous system can be fatal. If patients survive major bleeding, they may fully recover or become chronically disabled. The risk of minor haemorrhage was not accounted for. To reflect clinical practice, we incorporated into the model that patients will be treated for one year after a first recurrent episode of venous thromboembolism and lifelong after a second recurrent episode.

The likelihood of various complications may change over time. These changes in risk over time were taken into account by considering a consecutive series of three months episodes, allowing changes in probabilities from episode to episode (Markov cycle length).

**Risk estimates**

We performed extensive literature searches to arrive at valid and precise risk estimates of thromboembolic and therapy-related complications that can occur after a first episode of venous thromboembolism. The different estimates are presented in Table 1.

**Recurrent venous thromboembolism.** A meta-analysis of eighteen studies yielded a summary estimate of the risk of recurrent venous thromboembolism after discontinuation of treatment [7]. The risk of recurrent venous thromboembolism decreases over time and appeared to be stable after one year. This risk of recurrence
Table 1 Estimates for risks of thromboembolic and treatment-related complications, valuations of related health states and plausible ranges used for the sensitivity analyses (references in brackets).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Probability (per 3 months)</th>
<th>Range (95% CI)</th>
<th>Health state Valuation</th>
<th>Range (1st - 3rd quartile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE after discontinuation VKA [7] (time dependent)</td>
<td>(0.036 – 0.013) ‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE [9]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index event DVT</td>
<td>0.29</td>
<td>(0.18 - 0.39)</td>
<td>0.63</td>
<td>(0.36 - 0.86)</td>
</tr>
<tr>
<td>Index event PE</td>
<td>0.86</td>
<td>(0.71 - 0.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT [9]</td>
<td>1-pPE</td>
<td></td>
<td>0.84</td>
<td>(0.64 - 0.96)†</td>
</tr>
<tr>
<td>Fatality of PE [9]</td>
<td>0.303</td>
<td>(0.23 - 0.39)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PTS [10] (time dependent)</td>
<td>(0.078 – 0.001)†</td>
<td></td>
<td>0.82</td>
<td>(0.66 - 0.96) ‡</td>
</tr>
<tr>
<td>Effectiveness of treatment [3] (RR)</td>
<td>0.10</td>
<td>(0.06 - 0.20)</td>
<td>0.92</td>
<td>(0.77 - 0.96) ‡</td>
</tr>
<tr>
<td>Treatment-related major bleeding [11]</td>
<td>0.0025<em>1.57</em>we†</td>
<td>(1.23 - 2.00)</td>
<td>0.71</td>
<td>(0.54 - 0.91)</td>
</tr>
<tr>
<td>CNS bleeding [12, 13]</td>
<td>0.22</td>
<td>(0.08 - 0.38)</td>
<td>0.33</td>
<td>(0.14 - 0.53)</td>
</tr>
<tr>
<td>Fatality of CNS bleeding [14]</td>
<td>0.67</td>
<td>(0.56 - 0.76)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No complete recovery after stroke [14]</td>
<td>0.78</td>
<td>(0.68 - 0.86)</td>
<td>0.33</td>
<td>(0.14 - 0.53)</td>
</tr>
</tbody>
</table>

VKA denotes vitamin K antagonists; VTE venous thromboembolism; DVT deep-vein thrombosis; PE pulmonary embolism; PTS post-thrombotic syndrome; CNS central nervous system. ‡ Risk of recurrence decreases over time after cessation of treatment. After one year the risk is assumed to stabilise at 1.3% per three months [7]. † Risk of PTS is diminishing over time from cessation of treatment to four years. After four years the risk is assumed to stabilise at 0.1% per three months [10]. ‡ The index age = 0 for patients aged 40 (reference age). Every ten years below or above the age of 40 the index is increased or decreased with one unit. ‡ The index age = 0 for patients aged 40 (reference age). Every ten years below or above the age of 40 the index is increased or decreased with one unit. ‡ 0.96 is the median value for the health state "perfect health", therefore in the sensitivity analysis the upper limit for the valuations of other health states did not exceed 0.96.
Optimal duration of treatment with vitamin K antagonists

is based on a heterogeneous population of patients with a first episode of venous thromboembolism. We calculated a relative risk of recurrent venous thromboembolism for several subgroups of patients defined by the presence or absence of a transient or persistent risk factor.

**Pulmonary embolism.** The proportion of patients with pulmonary embolism as the manifestation of a recurrent episode of venous thromboembolism was obtained from a large systematic review by Douketis et al. [9]. This proportion was found to differ conditional on whether the initial event was a case of pulmonary embolism or deep-vein thrombosis. The case-fatality rate of pulmonary embolism was also derived from this review. We did not condition this rate on other patient characteristics.

**Post-thrombotic syndrome.** The risk of the post-thrombotic syndrome was derived from a large follow-up study in which the long term clinical course of patients suffering a first episode of venous thrombosis was investigated [10]. Theoretically, it is possible that a contra-lateral recurrence of venous thrombosis results in another post-thrombotic syndrome. We assumed that patients with a post-thrombotic syndrome who develop a post-thrombotic syndrome in the other leg will not have an additional decrease in quality of life.

**Effectiveness of treatment.** The effectiveness of treatment was derived from a recent meta-analysis which concluded that prolongation of treatment with vitamin K antagonists beyond three months results in a relative recurrence risk reduction of 90% [3].

**Treatment-related major bleeding.** The risk of vitamin K antagonist therapy related bleeding was calculated by means of the Leiden prediction model for bleeding [11]. From the model we derived the formula for patients who were monitored within a target INR-range of 2.0 to 3.0. By using this model we were able to adjust bleeding risk for increasing age during lifetime simulation.

**Major bleeding in the central nervous system (CNS).** The risk of an haemorrhagic event in the CNS in case of major bleeding was derived from a study in which the safety of warfarin was investigated in patients with atrial fibrillation. In that study, oral anticoagulants were given with a target INR between 2.0 and 3.0 [12,13].

**Fatal bleeding in the CNS.** The estimated proportion of fatal CNS-related bleeding was derived from a retrospective cohort study of 79 patients who had suffered an episode of intra-cerebral haemorrhage during treatment with vitamin K antagonists [14].
Unfortunately, the study report provides no data on the intensity of treatment with vitamin K antagonists.

**Recovery after bleeding in the CNS.** The probability of recovery (moderate or complete) from an haemorrhagic stroke was obtained from the same retrospective cohort study [14].

**Background mortality.** The background risk of dying, conditional on age and gender, was derived from Dutch vital statistics data [15].

**Patients' valuations**

To quantify the strength of patients' valuations of the seven health states used in this model, we used the time trade-off method in a group of 124 patients. Of these, 53 patients had experienced an episode of venous thrombosis, 23 patients had experienced a major bleeding event during treatment with vitamin K antagonists and 48 patients had been diagnosed with a post-thrombotic syndrome. Time trade-off method was conducted following standardized protocols with visual aids, as reported elsewhere [16]. With the time trade-off method patients were asked to choose between their remaining life expectancy in a specific health state and a shorter life span in perfect health. The duration of the time $t$ in perfect health $x$ was varied until the patient reported indifference between the two options. The utility of the health state under evaluation was then calculated by dividing $x$ by $t$, producing values in a range from 0 (death) to 1 (perfect health). All patients valued all health states. Differences in health state values were not statistically significantly associated with type of event experienced. In Table 1 the median time trade-off values and their first and third quartiles of the health states are shown.

**Analysis**

We first investigated the effects of prolonged treatment on life expectancy, not using any valuation of health states, for three groups of female patients, all 60 years of age with a first episode of deep-vein thrombosis. The three groups differed in the risk of a recurrent venous thrombosis. The change in life expectancy by prolonging treatment beyond the standard duration of six months was evaluated. Subsequently, the quality-adjusted life expectancy was calculated for these three groups, by weighting each health state by the respective valuations. We explored the quality-adjusted life expectancy in several other subgroups of patients, differing with respect to gender, type of index event (pulmonary embolism or deep-vein thrombosis) and bleeding risk.
To investigate the stability of the results to plausible variation in the parameter estimates we performed multiple sensitivity analyses. The plausible ranges with regard to valuations of health states were based on inter-quartile ranges. The ranges for the risk estimates were based on literature sources and the opinion of clinicians, specialized in treatment of venous thrombosis (Table 1).

### Results

Figure 2A shows the effects of prolonged treatment on life expectancy for three groups of female patients of 60 years, who have an intermediate (overall) risk, low risk (provoked first episode) or high risk (idiopathic first episode) of recurrence. It can be observed that there is a small gain in life expectancy when the duration of treatment with vitamin K antagonists is prolonged from six months to lifelong. Life expectancy increases with 0.91 years for patients with a high recurrence risk. For patients with an intermediate risk of recurrence the gain in life expectancy is 0.54 years. The results for males were similar and these are partly depicted in Table 2. Figure 2B shows the effects of different durations of treatment on the quality-adjusted life expectancy, taking into account patients’ median valuations for treatment, its complications, and the various venous thrombosis-related events. For female patients, aged 60, there is a loss of 0.24 quality-adjusted life years (QALYs) in case of lifelong treatment, compared to the standard duration of six months. This loss is more pronounced in patients with a provoked first episode. Prolongation of treatment would result in a loss of 0.79 QALYs in these patients. For comparable patients with an idiopathic first episode of venous thromboembolism, there is a small gain in quality-adjusted life expectancy of 0.20 QALYs in case of lifelong treatment.
Table 2 Change in quality-adjusted life expectancy when longer duration of treatment is compared to six months of therapy for patients with different characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment duration</th>
<th>Quality-adjusted life expectancy (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 year</td>
<td>2 years</td>
</tr>
<tr>
<td>Base-case†</td>
<td>0.01</td>
<td>0.07</td>
</tr>
<tr>
<td>Male</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Index PE (higher risk of recurrent PE)</td>
<td>0.11</td>
<td>0.35</td>
</tr>
<tr>
<td>Idiopathic DVT (increased risk of recurrence)</td>
<td>0.03</td>
<td>0.12</td>
</tr>
<tr>
<td>Provoked DVT (increased risk of recurrence)</td>
<td>-0.01</td>
<td>-0.01</td>
</tr>
<tr>
<td>Age 50 years</td>
<td>0.04</td>
<td>0.15</td>
</tr>
<tr>
<td>Index PE &amp; Idiopathic</td>
<td>0.14</td>
<td>0.45</td>
</tr>
</tbody>
</table>

DVT denotes deep-vein thrombosis; PE pulmonary embolism. †Base-case patient = female, index DVT, 60 years, intermediate risk of recurrence.

The changes in quality-adjusted life expectancy due to prolongation of treatment up to one, two, five and ten years or lifelong for groups of patients are presented in Table 2. Base-case patients and several subgroups of patients differing from base-case with respect to one or more characteristics are tabulated. For patients with an idiopathic first episode of venous thromboembolism, prolongation of treatment up to five and ten years and lifelong compared to a treatment duration of six months results in a small gain in quality-adjusted life expectancy of 0.21, 0.34 and 0.20 years respectively. For patients with pulmonary embolism, the gain in quality-adjusted life expectancy increases with longer treatment durations compared to six months of therapy. Five years, ten years and lifelong therapy results in a gain in quality-adjusted life expectancy of 0.76, 1.31 and 1.75 years respectively. For patients with a provoked first episode of deep-vein thrombosis every increase in treatment duration above six months results in a decrease of the quality-adjusted life expectancy.

Table 3 presents the results of the sensitivity analyses. Plausible changes in the risk of treatment-related major bleeding have an effect on the change in quality-adjusted life expectancy. Variations in the valuation of treatment have a pronounced effect on the changes in quality-adjusted life expectancy. In the female patient, 60 years of age diagnosed with idiopathic deep-vein thrombosis and for whom the burden of treatment is considerable, prolongation of treatment from six months to lifelong would result in a decrease in quality-adjusted life expectancy of 1.37 years. In those for whom burden of treatment is small there appears to be a slight increase of 0.62 years when treatment duration is extended from six months to lifelong.
Table 3 Results of the sensitivity analysis. Effect of variation of the burden of treatment and the risk of bleeding on change in quality-adjusted live expectancy for patients with different characteristics when lifelong treatment is compared to six months of therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Burden of treatment</th>
<th>Bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Base-case*</td>
<td>0.23</td>
<td>-1.97</td>
</tr>
<tr>
<td>Male</td>
<td>0.08</td>
<td>-1.53</td>
</tr>
<tr>
<td>Index PE (higher risk of recurrent PE)</td>
<td>2.26</td>
<td>-0.18</td>
</tr>
<tr>
<td>Idiopathic DVT (increased risk of recurrence)</td>
<td>0.62</td>
<td>-1.37</td>
</tr>
<tr>
<td>Provoked DVT (increased risk of recurrence)</td>
<td>-0.26</td>
<td>-2.24</td>
</tr>
<tr>
<td>Age 50 years</td>
<td>0.91</td>
<td>-1.86</td>
</tr>
<tr>
<td>Index PE &amp; Idiopathic</td>
<td>3.02</td>
<td>0.72</td>
</tr>
</tbody>
</table>

DVT denotes deep-vein thrombosis; PE pulmonary embolism. *Base-case patient = female, index DVT, 60 years, intermediate risk of recurrence.

Discussion

We investigated the effects of different durations of treatment with vitamin K antagonists on the quality-adjusted life expectancy of patients with a first episode of venous thromboembolism. When median valuations of health states are taken into account, patients with a provoked first episode of venous thromboembolism were found not to benefit from prolongation of treatment beyond six months. In those with an idiopathic episode of deep-vein thrombosis and therefore an increased risk of recurrence, the quality-adjusted life expectancy increases when treatment is extended, but the increase is small. Additional analyses show that in those with an increased risk of pulmonary embolism, lifelong treatment increases the quality-adjusted life expectancy by almost two years. The sensitivity analysis showed that the optimal duration of treatment is quite sensitive to the patients’ perceived burden of treatment.

Some aspects of our study require comment. First, the estimates for the risks of the several complications related to venous thrombosis and treatment with vitamin K antagonists were derived from the literature. Although these data are the best estimates available, the populations they are based on do sometimes differ slightly from our base-case population. In addition, there is limited information available with respect to the long term clinical course in patients who have suffered an episode of venous thrombosis. Our estimates of recurrence are based on a limited time-frame and the recurrence risk beyond one year after cessation of treatment had to
be calculated by extrapolation. Second, we incorporated the risk of treatment-related bleeding events in our model, but did not account for the potential other benefits arising from prolongation of treatment with vitamin K antagonists. It is known that treatment with anticoagulants lowers the risk of coronary artery disease [17]. Since vitamin K antagonist therapy is very effective in the prevention of ischaemic stroke in patients with atrial fibrillation and other cardiac diseases, anticoagulant therapy might reduce the risk of ischaemic stroke in patients with asymptomatic cardiac disorders [18]. The size of this benefit is unknown, but the gain in quality-adjusted life expectancy is slightly underestimated when patients are treated for a prolonged episode. Prolongation of treatment may therefore be somewhat more beneficial than observed in our model.

Until recently the discussion about the optimal duration of treatment with vitamin K antagonists was focused on the balance between efficacy and safety of treatment only. By systematic pooling results of studies with respect to recurrent venous thromboembolism after cessation of therapy we quantified the phenomenon known as “catch up”, which has also been described by others [6, 19]. As far as we know this is the first study which takes both this phenomenon and patients valuations of relevant health states into account in the decision about duration of therapy.

Our model offers potentially important elements for the debate about the optimal duration of treatment with vitamin K antagonists. For the group of patients with low or intermediate risk of recurrence prolonging treatment beyond six months is not beneficial when patient valuations of relevant health states, especially the burden of treatment, are taken into account. This implicates that treatment with vitamin K antagonists for six months is sufficient in patients with a temporary risk factor.

More recently, the debate about optimal treatment duration has become focused more on those with an idiopathic first thromboembolic event and prolongation of treatment up to several years in these patients has been propagated [5, 20]. Our analysis shows that a treatment duration of several years, compared to six months, increases the quality-adjusted life expectancy only slightly for those with idiopathic deep-vein thrombosis. Although the optimal treatment duration will depend on many factors, including the costs of treatment, this small increase will make it difficult to justify prolongation of treatment in this group.

Our analysis showed that the perceived burden of treatment has a significant effect on the optimal duration of treatment. Our model may also offer an aid in individual decision making. For example, a female patient, 50 years of age, with a provoked first
event of deep-vein thrombosis will not benefit from prolongation of treatment if this is experienced as a real burden. Yet, her quality-adjusted life expectancy increases with a clinically significant amount if therapy poses no problem for her.

The findings of our study will support the tendency to tailor treatment duration to individual patient characteristics and preferences. Our model offers potentially important elements for the determination of a more optimal duration of treatment and therefore prevents patients and the society from over- and undertreatment.

References


