Management of antithrombotic therapy in venous and arterial thromboembolism

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ABSTRACT

Background: The optimal duration of oral anticoagulant therapy for patients with a first episode of deep vein thrombosis is still a matter of debate. However, according to the ACCP consensus strategy a limited stratification in treatment duration is advocated, i.e., 3 months for patients with a transient risk factor and one year or longer for patients with recurrent disease or a consistent risk factor like thrombophilia or cancer. This consensus strategy is founded on the mean optimal duration of therapy obtained in large cohorts of patients and is mainly based on the risk of recurrent venous thromboembolism, with only minimal consideration for the patient’s bleeding risk.

Objectives: The aim of this study is to optimise the anticoagulant treatment strategy with vitamin K antagonists for the individual patient with deep vein thrombosis.

Methods: Based on an extensive literature study, a mathematical model was constructed to balance the risk of recurrent venous thromboembolism against the risk of major hemorrhagic complications. The following parameters are incorporated in the model: baseline estimates and risk factors for recurrent VTE and bleeding, clinical course of DVT and efficacy of treatment with vitamin K antagonists. With the use of these parameters, the risk for a recurrent VTE and a bleeding episode can be calculated for the individual patient. The optimal duration of anticoagulant therapy can be defined as the time point at which the benefit of treatment (i.e prevention of VTE) is counterbalanced by its risk (i.e. bleeding).

Results/Conclusion: How long a patient should receive anticoagulant treatment is a matter of balancing the benefits and risks of treatment. The model shows that the optimal treatment duration varies greatly from patient to patient according to the patient’s unique bleeding and recurrence risk.
INTRODUCTION

Deep vein thrombosis of the lower extremity is a frequently occurring disorder, with an estimated incidence of 2 per 1000 persons per year\(^1\). The primary objectives of treating patients with venous thromboembolism (VTE) are to prevent death from pulmonary embolism and to reduce the risk for recurrent thromboembolic events. For this purpose, patient are treated with an initial course of heparin followed by a second phase of vitamin K antagonists\(^2\)\(^-\)\(^4\). According to the ACCP consensus strategy a limited stratification in treatment duration is advocated, i.e., 3 months for patients with a transient risk factor and one year or longer for patients with recurrent disease or a consistent risk factor like thrombophilia or cancer\(^5\). This consensus is founded on the mean optimal duration of therapy obtained in large cohorts of patients and mainly based on the risk of recurrent venous thromboembolism, with only minimal consideration for the patient's bleeding risk\(^6\)\(^-\)\(^8\). It is a well documented fact that the cumulative risk of bleeding complications is determined by various risk factors. Major determinants are the length of therapy and patients characteristics\(^9\)\(^-\)\(^10\). Therefore, the consensus strategy has two major limitations. First, by not taking into account the bleeding risk, a balanced decision on the duration of anticoagulant therapy can not be made adequately. Second, decisions based on large cohorts neglect the fact that the risk for bleeding and recurrent VTE are dependent on individual characteristics\(^11\)\(^-\)\(^12\). Thus, rational decisions on the optimal duration of anticoagulant therapy for the individual patient require knowledge of the risk of recurrence after discontinuation of treatment and the risk of bleeding during anticoagulant therapy. Ideally, treatment should be continued until the benefits of treatment (i.e. prevention of recurrent VTE events) are offset by the risks (i.e. major bleeding), considering that each patient has an individual spectrum of risk factors for recurrent events and bleeding.

Sarasin et al published their decision model in 1994\(^13\). They compared risk-benefit tradeoffs for treatment durations between 6 weeks and 6 months. However, in the last decade several new risk factors for recurrent VTE have been identified and new insights in the risk for bleeding have become available. Therefore, we constructed a mathematical model based on recent literature which can be easily applied to individual patients and which balances the risk of recurrent venous thromboembolic events against the risk of haemorrhagic complications.
METHODS

To construct a model for the individual patient, that balances the risk for recurrent venous thromboembolic events against the risk for major haemorrhagic complications, several parameters have to be taken into consideration, i.e. (1) baseline estimates for recurrent VTE (2) risk factors for recurrent VTE and their risk estimate (3) clinical course of DVT (4) baseline estimates for haemorrhage and their risk estimate (5) risk factors for haemorrhage during anticoagulant therapy (6) efficacy of anticoagulant therapy in preventing recurrent VTE. For this purpose, a systematic review of the literature was performed using a computer-assisted search in Medline and Embase database over the period 1966 to 2002. The keywords and textwords used for the search were: thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, risk factor, warfarin, oral anticoagulants, bleeding, haemorrhage, thrombophilia, recurrence, treatment, therapy. The reference lists of all retrieved articles were screened to identify additional papers.

To obtain a solid baseline estimate for the incidence of recurrent VTE, studies were considered eligible when they included a cohort of patients in which all known thrombophilic conditions were excluded. To obtain baseline estimates for major haemorrhage during oral anticoagulant therapy, studies which made reference to the incidence of major bleeding in the thromboembolic population were evaluated. For the identification of significant risk factors for recurrent VTE as well as bleeding during anticoagulant therapy, articles that assessed the relative risk of such a risk factor were analysed. Odds ratios for patients with a specific risk factor were calculated separately and, when appropriate, pooled using the Mantel-Haenszel method. To obtain estimates on efficacy of vitamin K antagonist therapy, data were derived from studies, which reported on the incidence of recurrent VTE during vitamin K antagonist therapy. The efficacy was expressed as relative risk reduction for a thromboembolic event, as compared to no treatment. Finally, the clinical course of DVT was assessed by evaluation of clinical studies, which included long term follow-up.

All eligible studies were weighted for methodological strength, according to Sackett et al. In order to obtain high quality data, only those articles with the strongest methodology were selected for construction of the mathematical model.

In order to answer the question of how to balance the adverse events of antithrombotic management strategies, i.e. bleeding complications as a result of anticoagulant therapy and recurrent VTE as manifestation of withholding anticoagulant therapy, we sent out a questionnaire to 30 thrombosis-experts in the Netherlands.

The structure of the model is described in the section below. The parameters are summarized in Table I.
Table I. Estimates used in the decision model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rates (95% CI)</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factor for haemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (every 10 year above 40)</td>
<td>1.5 (1.2-1.8)</td>
<td>39:42</td>
</tr>
<tr>
<td>Cancer</td>
<td>2.0 *</td>
<td>12:43:44</td>
</tr>
<tr>
<td><strong>Risk factor for recurrent VTE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin mutation</td>
<td>1.4 (0.9-2.0)</td>
<td>18:22</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>1.3 (1.0-1.7)</td>
<td>16:18:19:23:26</td>
</tr>
<tr>
<td>Elevated levels of factor VIII (&gt;200 IU/dl)</td>
<td>1.8 (1.0-3.3)</td>
<td>27:28</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>2.5 *</td>
<td>33:34</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>2.5 *</td>
<td>8:18:31:32</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>2.5 *</td>
<td>18:29:30</td>
</tr>
<tr>
<td>Protein C &amp; Protein S deficiency</td>
<td>2.5 *</td>
<td>18:29:30</td>
</tr>
<tr>
<td>Cancer</td>
<td>2.0-4.0 *</td>
<td>11:35:37</td>
</tr>
<tr>
<td>Transient risk factor (surgery, immobilisation)</td>
<td>0.5 *</td>
<td>4:35:3b</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>1.5 *</td>
<td>(assumption)</td>
</tr>
<tr>
<td>Baseline estimate for major hemorrhage</td>
<td>P_{bleeding} = 0.083</td>
<td>39</td>
</tr>
<tr>
<td>Baseline estimate for DVT</td>
<td>P_{recur} = 1.2 x e^{-14/14} + 0.1</td>
<td>16:17</td>
</tr>
<tr>
<td>Efficacy of treatment</td>
<td>90% (86%-97%)</td>
<td>4:6:8</td>
</tr>
<tr>
<td>Risk for pulmonary embolism in DVT</td>
<td>20%</td>
<td>38</td>
</tr>
</tbody>
</table>

95% CI = 95% confidence interval; VTE = venous thromboembolism; DVT = deep vein thrombosis

* = no confidence interval available. Relative risks are estimates

**RESULTS**

*Baseline estimates for recurrent VTE*

To determine the baseline estimates for recurrent VTE in patients without oral anticoagulant therapy two studies were identified in which all known thrombophilic conditions were excluded in a subset of patients^{16,17}. Since the methodology of both studies was comparable, both studies were combined to calculate the absolute recurrence rate. As expected, the rate of recurrent events in this population declines exponentially as a function of time. This decline is represented by the formula: \( P_{recurrence} = 1.2 \times e^{-14/14} + 0.1 \)
Risk factors for recurrent VTE

The incidence of recurrent VTE in patients with the prothrombin G20210A mutation was reported in five studies. The pooled odds ratio, using the Mantel-Haenszel method, is 1.4 (95% CI 0.9-2.0).

Eight studies have been published which report on the incidence of recurrent venous thromboembolism in patients with the Factor V Leiden mutation. In one prospective study, the only decreased risk for recurrent VTE (odds ratio 0.5) was observed, however data needed for the Mantel-Haenszel method could not be extracted from this study. The calculated pooled odds ratio for the other 7 studies, using the Mantel-Haenszel method, is 1.3 (95% CI 1.0-1.7).

Several studies reported on an increased risk of a first episode of venous thromboembolism in patients with elevated plasma levels of factor VIII, however studies reporting on the risk of recurrence are scarce. We have reported on a dose-dependent relative risk for recurrent VTE, which was confirmed in another study. An odds ratio for the risk of recurrence, using the Mantel-Haenszel method, was calculated for factor VIII levels exceeding 200 IU/dl. This common odds ratio is 1.8 (95% CI 1.0-3.3).

Three retrospective studies have assessed the risk for recurrent VTE in patients with antithrombin, protein S or protein C deficiency. No prospective studies on the risk of recurrence in untreated patients with antithrombin, protein C or S deficiency are available. Data needed for the Mantel-Haenszel method could not be extracted. The estimated relative risk for a recurrent event based on these retrospective studies is 2.5.

The risk of recurrent VTE in patients with antiphospholipid antibodies has been studied in one retrospective and three prospective studies. Since the original data did not provide sufficient information for the Mantel-Haenszel method, we estimated the overall risk to be 2.5.

Two studies have shown an increased risk for recurrent events in patients with high levels of homocysteine. In a prospective study, the relative risk was 2.6. In a case-control study, an odds ratio of 3.1 was found. By combining the results taking into account that case-control studies tend to overestimate the results, the relative risk was estimated to be 2.5.

Cancer is generally considered to increase the risk of recurrent VTE. In two prospective cohort studies the relative risk for a recurrent event in cancer patients was 1.7 and 2.2 respectively. A higher rate of recurrence was observed in a retrospective study (relative risk = 3.2). Interestingly, the association with VTE seems to be cancer-specific. The types of malignancy most commonly associated with venous thromboembolism are: pancreatic, ovarian, lung and mucin-secreting gastrointestinal carcinoma. Therefore, we varied the relative risk depending on the kind of cancer. The relative risk for high-risk cancer is estimated to be 4, whereas for the other types of cancer a relative risk of 2 is used.
Three well-conducted studies (two prospective cohort studies\textsuperscript{35,36} and one randomised trial\textsuperscript{4}) evaluated the incidence of recurrent VTE in patients with a transient risk factor (e.g. surgery, trauma, immobilisation). The authors reported on relative risks varying between 0.3 to 0.7. Thus, these patients are at reduced risk for a recurrence as compared with patients with idiopathic thrombosis, with a mean relative risk of 0.5.

In the absence of data from the literature, it is assumed that recurrent VTE without any underlying thrombophilic disorder is associated with a relative risk of 1.5.

Finally, other potential risk factors (for example elevated levels of factor XI, renal insufficiency, hypertension, smoking, obesity) were excluded from analysis, due to lack of data to estimate the risk of recurrent VTE.

**Multiplying the baseline risk**

Studies comparing the risk for recurrent VTE in patients with a thrombofilitic factor to the risk in patients without a thrombofilitic abnormality (our baseline population) show that the exponential decline of VTE-events, as described above, is identical for patients with and without a thrombofilitic factor\textsuperscript{16,31,33}. This means that at any time elapsed since the event, the difference in risk of recurrence between the two groups of patients is represented by a constant factor, i.e. the relative risk for the specific thrombofilitic condition. Therefore the absolute risk of recurrent VTE at any specific time-point for the individual patient with a certain thrombofilitic abnormality is obtained by multiplying the relative risk for this thrombofilitic condition with the baseline risk for recurrent VTE at this time-point; \( P_{\text{recurrence}} = (1.2 \times e^{-t/14} + 0.1) \times RR_{\text{recurrence}} \).

We assumed that the relative risk is constant at any time elapsed since the first event, and that in the presence of two or more risk factors for recurrent VTE, the risk ratios should be multiplied.

**Clinical course of DVT and efficacy of treatment**

In patients with DVT, approximately 20\% of all recurrent events will be symptomatic PE\textsuperscript{38}. Thus, in order to achieve a curve representing the risk for developing PE following DVT, the baseline curve should be multiplied with 0.2.

To obtain the efficacy of treatment with vitamin K antagonists, a meta-analysis of four randomised trials was performed\textsuperscript{4,6,8}, which showed an efficacy (i.e. a relative risk reduction of the occurrence of VTE during oral anticoagulant treatment) of 93\% (CI 86 to 97 \%). We assumed that the efficacy of treatment remains stable at 90\%. In conclusion, the risk for the individual patient to develop a PE following DVT after stopping anticoagulant treatment can be written as a function of baseline risk for DVT multiplied by the relative risk obtained by a given risk factor and two constant factors (the risk for developing PE after DVT (0.2) and the efficacy of treatment (0.9)); \( P_{\text{recurrence PE}} = 0.2 \times 0.9 \times (1.2 \times e^{-t/14} + 0.1) \times RR_{\text{recurrence}} \).
Baseline estimates for major haemorrhage

To determine the baseline estimate for major bleeding during anticoagulant therapy, we identified one study in which in unselected patients using oral anticoagulants no selection was made and the long-term follow-up was performed. In this study\(^3^9\) the patients were categorised according to age, which was shown to be a major risk factor for bleeding during oral anticoagulant therapy. The baseline estimate of haemorrhage was therefore assessed by evaluating the risk of haemorrhage in the youngest category. For this patient category, the baseline risk of major bleeding is consistent over time with an incidence of 1% per year (= 0.083%/month); \(P_{\text{bleeding}} = 0.083\). As an assumption, we ignored the potentially higher risk of bleeding in the period when treatment with anticoagulants is being initiated.

Risk factors for major bleeding

We identified two risk factors for major haemorrhage: increasing age and the presence of cancer. In addition, other risk factors for major haemorrhage such as a history of gastrointestinal bleeding or cerebrovascular accident should be considered, but the quantitative contribution of these factors to the bleeding risk is still unknown. In a study by Van der Meer et al\(^3^9\), a relative risk of 1.5 for every 10 years increase in age above the age of 40 years was observed for major bleeding. An odds ratio of 3.2 for an age above 65 was found in another cohort study\(^4^0\), which is comparable with the relative risk in the study of Van der Meer et al for this age category. Two other articles with a lower methodological strength show identical results of elevated bleeding risks with increasing age\(^4^1^4^2\). Three cohort studies reported on the risk for major bleeding in patients with malignant disease\(^1^2^4^3^4^4\). The mean odds ratio for malignancy is approximately 2.0. Whether there is a type of cancer specific odds ratio for bleeding cannot be inferred from the available literature. The individual risk for major haemorrhage can be defined as a function of the baseline risk for developing a major bleeding and the presence of a relative risk factor; \(P_{\text{bleeding}} = R R_{\text{bleeding}} \times 0.083\), and is assumed to be constant over time, except for the fact that ageing is a risk factor which should be corrected for. In the presence of two risk factors for major bleeding, the risk ratios should be multiplied.

The questionnaire

The results of the questionnaire among thrombosis-experts show that DVT is rated equally to minor bleeding, non-fatal pulmonary embolism as a manifestation of a recurrent VTE is rated equally to major bleeding, and death due to PE is rated equally to death due to major bleeding (original data not shown). In our model, the risk for major bleeding is outweighed against the risk for a PE as recurrent event.
**Figure I.** The sloping curve depicts the risk per month to develop a PE as a manifestation of recurrent VTE. The horizontal curve represents the bleeding risk and is expressed as percentage per month.

**Integration of recurrence risk and bleeding risk**

Oral anticoagulant treatment should ultimately be stopped at the time point at which the benefit of treatment (i.e., prevention of recurrent VTE) is counterbalanced by its risk (i.e., bleeding). Regarding the individual risk curves for both recurrent VTE and bleeding, the time point at which the risk of bleeding is equal to the risk of recurrent VTE is represented by the intersection of these curves (Figure I). Mathematically the time-point of the ultimate duration of anticoagulant therapy can be calculated by the equalisation of the formulas for recurrent VTE and major bleeding: \( RR_{\text{bleeding}} \times 0.083 = 0.2 \times 0.9 \times (1.2 \times e^{-t/14} + 0.1) \times RR_{\text{recurrence}} \). A simple conversion leads to the overall formula: \( t = -\frac{14}{0.39} \ln \left(\frac{RR_{\text{bleeding}}}{RR_{\text{recurrence}}}\right) \times 1/12 \), where \( t \) is defined as the optimal individual duration of anticoagulant therapy.

With use of the formula, the optimal time-point can be calculated for each individual patient, since the relative risks for recurrent VTE and major bleeding are incorporated. The exact position of the point of intersection of the two curves, and therefore the optimal treatment duration, depends on the presence and quantity of the odds ratios. When the patient is treated longer than his calculated optimal treatment
duration, the risk of PE is exceeded by the bleeding risk and the oral anticoagulant treatment could be harmful.

To avoid complex calculations and potential calculation errors, we designed a simple nomogram for daily clinical practice (Table II), by which the optimal treatment duration in months can be easily determined with use of the risk factors for both recurrent VTE and bleeding.

To illustrate the clinical usefulness of the nomogram, three common clinical scenarios are presented (Table III). Patient A, a 23-year-old woman, had an episode of spontaneous deep vein thrombosis. She carries the factor V Leiden mutation (heterozygous). There are no risk factors present for bleeding. Therefore, the advocated duration of treatment with oral anticoagulant treatment using our method is 24 months. Patient B is a 58-year-old man who developed a deep vein thrombosis after surgery and subsequent immobilisation. Due to the advanced age, there is a 2.25 (1.5 x 1.5) times higher risk for developing a bleeding as compared to the baseline bleeding risk of a person less than 40 years of age. Since his DVT was secondary to a transient event the relative risk for a recurrent VTE is 0.5. Therefore, the advocated treatment duration in this patient is 1 month. Patient C is a 49-year-old man who has pancreatic carcinoma. He had an episode of spontaneous deep vein thrombosis. The active cancer contributes to a 4-fold higher risk for recurrent VTE. Due to his age and the presence of cancer, the bleeding risk is 3.0 (1.5 x 2.0). The advocated treatment duration according to the nomogram is, therefore, 22 months.
Table II. Nomogram for clinical practice

<table>
<thead>
<tr>
<th>RR for major bleeding</th>
<th>RR for VTE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>1.4</td>
<td>(0.9-2.0)</td>
</tr>
<tr>
<td>1.5</td>
<td>1.3</td>
<td>(1.0-1.7)</td>
</tr>
<tr>
<td>2.0</td>
<td>1.8</td>
<td>(1.0-3.3)</td>
</tr>
<tr>
<td>2.5</td>
<td>2.5</td>
<td>na</td>
</tr>
<tr>
<td>3.0</td>
<td>2.5</td>
<td>na</td>
</tr>
<tr>
<td>4.0</td>
<td>2.0-4.0</td>
<td>na</td>
</tr>
<tr>
<td>5.0</td>
<td>1.5</td>
<td>na</td>
</tr>
<tr>
<td>6.0</td>
<td>0.5</td>
<td>na</td>
</tr>
<tr>
<td>8.0</td>
<td>1.5</td>
<td>na</td>
</tr>
</tbody>
</table>

DETERMINATION OF THE OPTIMAL TREATMENT DURATION
1. Determine the relative risk for developing a recurrent VTE. In presence of 2 or more risk factors for recurrent VTE, the risk ratios should be multiplied.
2. Determine the risk for developing a major bleeding. In presence of 2 risk factors for major bleeding, the risk ratios should be multiplied.
3. The calculated RR's should be rounded down to the nearest stratum.
4. Read the corresponding treatment duration (in months) in the table.

FORMULA: $t = -14 \ln (0.39 \times (RR_{\text{nomogram}} / RR_{\text{recurring}}) - 1/12)$

Table III. Patient scenarios

<table>
<thead>
<tr>
<th>Patient A</th>
<th>Patient B</th>
<th>Patient C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, age</td>
<td>23 years</td>
<td>58 years</td>
</tr>
<tr>
<td>Risk factor and relative risk for recurrent VTE</td>
<td>Factor V Leiden</td>
<td>Surgery, immobilisation</td>
</tr>
<tr>
<td>RR for VTE</td>
<td>1.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Risk factor and relative risk for bleeding</td>
<td>None</td>
<td>Age</td>
</tr>
<tr>
<td>RR for bleeding</td>
<td>1.0</td>
<td>2.25 (1.5 x 1.5)</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>24 months</td>
<td>1 month</td>
</tr>
</tbody>
</table>

RR = relative risk

**DISCUSSION**

In the ACCP guidelines for antithrombotic therapy, stratification in the treatment duration is recommended. According to this consensus, patients with a reversible risk factor should be treated for at least three months, patients with a first episode of
idiopathic VTE for at least 6 months and patients with recurrent VTE or continuing risk factors for at least one year or longer. Two major disadvantages of this strategy are the fact that this strategy is less based on the risk of bleeding and, secondly, that this stratification in only 3 or 4 groups is quite arbitrary and generalising for a large subset of patients. We here present a model in which the individual risk for a recurrent VTE is more precisely counterbalanced against the individual risk for bleeding. With the use of this model a rational and literature-based decision on the optimal duration of anticoagulant therapy can be made for each individual patient. How long a patient should receive oral anticoagulant therapy is a matter of balancing the benefits of treatment, in terms of reduced incidence of thromboembolic recurrences, and the risks, in terms of increased incidence of major haemorrhages. Patients with a thrombophilic defect and therefore a higher risk for a recurrent event will benefit from a prolonged duration of therapy. On the other hand, for patients with an increased risk of an anticoagulant-related bleeding, this prolonged duration could be harmful.

Several decision analyses on the optimal duration of anticoagulant treatment in venous thromboembolic disease have been published. Sarasin et al\textsuperscript{45}, suggest in their decision analysis that prolonged duration of treatment among factor V carriers, at least beyond one year, results in more risks (haemorrhages) than benefits (prevention of pulmonary embolism). Van de Belt et al\textsuperscript{46}, performed a decision analysis for patients with an antithrombin, protein C or S deficiency, yielding recommendations for the duration of treatment varying from 6 months to 3 years of treatment, considering age, type of initial event and time elapsed since the event. Although these decision analyses also address the question of duration, their analyses only demonstrate a utility in a small subset of patients with a defined thrombophilic factor, whereas our model is applicable for the majority of patients with DVT.

The limitations, in general, of decision analyses are that they are based on data derived from literature. The baseline estimate for major bleeding is a critical element of the model and it is supported by a single study. Indeed more studies are available which evaluated the risk of bleeding during anticoagulant therapy, but these studies included patients with increasing age, whereas no adjustment for this considerable risk factor for bleeding was performed. The incidence of recurrent thromboembolic events, one of the other key parameters in our model, is difficult to assess since only a limited number of studies are available. However, a recently published meta-analysis confirmed that the risk of recurrence decreases over time\textsuperscript{47}. Some studies that evaluated the relative risk of recurrence in patients with a thrombophilic factor, especially carriers of the factor V Leiden mutation, show conflicting results and are confined to relatively small number of patients. However, we have included studies with a sound methodology only in our analysis.
Furthermore, in this model we rated pulmonary embolism (as manifestation of a recurrence) equal to major bleeding. Ideally, the patient’s perception of the impact of the non-fatal events and the quality of life associated with long-term anticoagulant therapy should also be considered. In some patients, stopping treatment affects quality of life negatively because of a strong fear of a recurrent episode, whereas others experience anticoagulant treatment and its monitoring as a burden. This subjective estimation of quality of life will probably have a great impact on the patient orientated optimal duration of treatment. Unfortunately, no reliable estimates of these variables are available yet.

One of the assumptions of the model is that in the presence of two or more risk factors for recurrent VTE or major bleeding, these risk ratios should be multiplied. This is in correspondence with Emmerich et al\textsuperscript{48}, who described a complete multiplicative effect of the combined Factor V Leiden and prothrombin mutation for the risk of a first episode of VTE. Odds ratios were 4.9 and 3.8 for the factor V Leiden and prothrombin mutation, respectively. The odds ratio for VTE in double heterozygotes was 20.0. Also for recurrent VTE a multiplicative effect of a double mutation was observed\textsuperscript{18}. This multiplicative effect of risk factors is also described by several others\textsuperscript{49,50}. We are aware of the fact that this assumption could induce an estimating simplification of reality for some additive instead of multiplicative combinations of risk factors. However, due to the fact that in our model, the number of risk factors for bleeding are outnumbered by the risk factors for VTE, the optimal duration of VKA-therapy is more likely to be calculated too long than too short, which is in line with the current ACCP consensus strategy.

Recently, two new factors for the prediction of a recurrent VTE are described. First, in patients with persistent residual thrombosis confirmed by ultrasonography, recurrent disease is more frequent as compared to patients with early recanalization\textsuperscript{51}. Second, Palareti et al showed that the presence of increased D-dimer after discontinuation of oral anticoagulant therapy was associated with a higher risk for recurrent VTE\textsuperscript{52}. However, more evidence is needed before these elements can be incorporated into the model.

Several developments in therapeutic quality control have improved the safety and efficacy of oral anticoagulant therapy. Monitoring of anticoagulant therapy by a specialized anticoagulation clinic reduce the bleeding and thromboembolic event rates\textsuperscript{53}. More recently, home testing of the coagulation status by means of a portable coagulometer that performs an INR on a single drop of capillary blood have become available. INR home testing appears to be a safe and efficient anticoagulation control method which results in a higher percentage of target range values compared to the conventional laboratory-based testing regimen\textsuperscript{54-56}. 

125
The limitations of this kind of approach thus include the absence of hard data from management trials in which the proposed guidelines have been proven safe and effective, the danger of propagating uncertainty, and the difficulty of assigning individual patients to categories of risk. All these limitations are valid and attempts should be undertaken in the future to reduce them.

In conclusion, since each patient has his own unique bleeding and thrombosis risk, decisions about the duration of treatment should preferably be based on the individual risk of recurrent thromboembolic events and the individual bleeding risk, rather than a predefined treatment duration which is uniform for a large subset of patients and is based primarily on the risk of recurrent VTE and doesn't take the patients bleeding risk into account. Application of an individual approach results in a balanced duration of treatment for each patient. Theoretically, this will lead to a lower incidence of recurrent DVT and bleeding complications. To verify this statement, a prospective clinical study should be initiated to validate the model.

**REFERENCE LIST**


