Clinical scores to predict recurrence risk of venous thromboembolism

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Summary
Venous thromboembolism (VTE) is a common and chronic disease with a considerable risk of recurrence. Patients with unprovoked (in the absence of a transient risk factor) VTE have a recurrence risk as high as 30% within five years after cessation of anticoagulation. Depending on patient selection the case-fatality rate of recurrence ranges between 3.6%-10%. Thus, indefinite anticoagulation treatment should be considered in these patients. However, anticoagulation confers a considerable risk of bleeding (fatal bleedings 0.1%-0.5%/year). It is therefore of utmost clinical importance to identify those patients, who will not benefit from indefinite anticoagulation, i.e. patients, in whom the bleeding risk during anticoagulant treatment is higher than the risk of recurrence. Several attempts to discriminate patients with a high from those with a low risk of recurrence including screening for acquired and inherited thrombotic risk factors or measurement of coagulation activation markers have either failed (thrombophilia screening) or were of moderate success (stratification according to D-dimer only). A novel approach for assessing risk of recurrent VTE consists of linking clinical patient characteristics with laboratory testing. Several such scoring models which can be used to assess the risk of recurrent VTE have been developed and await prospective validation before they can be applied in daily routine care. The aim of this report is to describe currently available scoring systems in more detail.

Keywords
Venous thrombosis, recurrence risk, prediction model

Introduction
Venous thromboembolism (VTE), i.e. deep-vein thrombosis (DVT) with or without pulmonary embolism (PE), is common with an annual incidence of 1–2 per 1,000 persons (1). A serious complication of VTE is recurrence, which is fatal in 3.6% to 10% of patients (2, 3). To prevent recurrence patients are given antithrombotic therapy, which consists of a short course of heparin followed by vitamin K antagonists (VKA) for at least three months (4). Anticoagulation is very effective as recurrent VTE is rarely encountered during this time (5). However, the price for effective secondary thromboprophylaxis is bleeding. The annual incidence of fatal bleeding during VKA therapy depends upon the presence of various patient characteristics and ranges between 0.1 and 0.5% (2, 6, 7). The rate of major bleeding during VKA therapy in VTE patients is approximately 3% during the first three months (8). Data on the bleeding risk thereafter are sparse. Depending on the risk profile, the estimated annual risk of major bleeding ranges between 0.8% and more than 6% (8). Outside of clinical studies in unselected patients receiving usual care the bleeding risk associated with VKA treatment is markedly higher (9). The case fatality rate of bleeding exceeds 10% (2, 6). Hence, in order to establish the optimal duration of anticoagulation for an individual patient, the physician has to balance bleeding risk during anticoagulation against risk of recurrent VTE when anticoagulant treatment is discontinued. At the time being no bleeding risk score exists, which can be applied for VTE patients.

Patients in whom VTE occurs in association with a transient risk factor including surgery, trauma, or pregnancy, have a low risk of recurrence and will not benefit from anticoagulation longer than three months (8). In contrast, patients with unprovoked VTE, i.e. with an event that cannot be explained by a transient triggering event, may have an annual recurrence risk of as high as 10% (10). Current guidelines recommend indefinite anticoagulant treatment for all patients with unprovoked proximal DVT and/or PE provided the risk of bleeding is low or moderate and good coagulation monitoring is achievable (8). Despite an overall high recurrence risk the majority of patients with a first unprovoked VTE, however, will stay recurrence free but is exposed to a risk of bleeding when these guidelines are applied. It is therefore important to develop strategies to stratify patients according to their recurrence risk, i.e. to discriminate between patients in need of long-term thromboprophylaxis from those in whom a short course of anticoagulation is sufficient.
Screening for single laboratory abnormalities (thrombophilia screening)

Various genetic defects and biochemical abnormalities the presence of which is associated with an increased recurrence risk have been identified (see [10] for review). There has also been demonstrated that the two most frequent mutations in the coagulation system, factor V Leiden and prothrombin G20210A, are not associated with a risk of recurrence high enough to justify for prolonged extended anticoagulation (11–14). The notion that patients with a natural inhibitor deficiency or phospholipids antibodies are at high recurrence risk stems mainly from retrospective studies with heterogeneous populations and small patient numbers, and is meanwhile questioned. In the Leiden Thrombophilia Study, for instance, the risk of recurrent VTE among patients with a coagulation inhibitor deficiency was only less than two-fold increased (15).

In a large prospective study from Great Britain, testing for heritable thrombophilia did not allow prediction of recurrent VTE in the first two years after anticoagulant therapy (16). In a study from the Netherlands, the risk of recurrence was similar in patients with and without thrombophilia (15). In a case-control study testing for inherited thrombophilia was not associated with a reduced rate of recurrent VTE (17).

Although some defects in the coagulation system may influence the risk of recurrent VTE, we recently proposed that routine screening for a single thrombophilic risk factor is futile and should be abandoned (10) for the following reasons: i) trials that have assessed the benefits of testing for thrombophilia are absent; ii) many patients have more than one abnormality and the effect of combined defects on the recurrence risk is unknown; iii) testing may lead to over-treatment; iv) testing may cause unnecessary concern; v) a third of patients with recurrent unprovoked VTE have a normal test result and a negative finding may result in a false sense of safety.

Clinical characteristics and conditions

The risk of recurrence is particularly high among patients in whom the initial VTE occurred in the absence of a temporary triggering factor (such as surgery, trauma, pregnancy, female hormone use). Recurrence risk can be predicted by patient characteristics including the patient’s sex (18), as well as clinical conditions including location of VTE (for review see [10]).

The usefulness of residual vein thrombosis as a predictor of recurrence is under debate. In a systematic review and meta-analysis residual vein thrombosis was associated with a modestly increased risk of recurrent VTE in patients with DVT. However, residual vein thrombosis was not a predictor of recurrent VTE in patients with unprovoked DVT (19). Moreover, association with recurrence risk is strongly dependent on how residual vein thrombosis is defined (20). Thus, it is premature to make clinical decisions on the basis of residual vein thrombosis measurement results.

D-dimer

VTE is a multicausal disease driven by the interaction of various genetic and acquired risk factors. It is, therefore, intriguing to measure global markers of coagulation, the levels of which might reflect multifactorial thrombophilia. Among several markers including thrombin generation and the activated partial thromboplastin time, D-dimer is the most promising. With regard to recurrent VTE, measurement of D-dimer allows discrimination into groups of high and low risk of recurrence. D-dimer measured one month after discontinuation of oral anticoagulation has a high negative predictive value for recurrence regardless of the presence or absence of hereditary thrombophilia (21). In an Italian study patients with a low D-dimer after withdrawal of anticoagulation have a low risk of recurrence (4.4 recurrences/100 patient years). Patients with high D-dimer in whom anticoagulation was stopped after six months had a five-fold higher risk of recurrence than those who received anticoagulation for a longer period of time (10.9 vs. 2.0 recurrences/100 patient years) (22). We found that patients with a first unprovoked VTE and D-dimer levels less than 250 ng/ml had a 60% lower recurrence rate than those with higher levels (23). In a Canadian study, the cut-off of 250 ng/ml proved to be particularly useful to identify women at low recurrence risk (24).

Scoring models of recurrent VTE

Thus far, three scoring models have been developed that assess the risk of recurrent VTE by linking clinical patient characteristics with laboratory testing (Table 1). In a multicentre prospective cohort study from Canada, 646 participants with a first, unprovoked VTE were followed for a mean of approximately 18 months. A total of 69 potential clinical and laboratory predictors of recurrent VTE were collected while patients were taking oral anticoagulation therapy (24). After discontinuing anticoagulant therapy, 91 episodes of recurrent VTE were recorded (annual risk of recurrent VTE 9.3%; 95% confidence interval [CI] 7.7%–11.3%). Consequently, a multivariable analysis of predictor variables (p < 0.10) with high inter-observer reliability was performed in order to derive a clinical decision rule. None of the combination of predictors satisfied the criteria for identifying a low-risk subgroup of men. Women with less than two certain patient characteristics (hyperpigmentation, oedema or redness of either leg; D-dimer ≥250 µg/l while taking warfarin; body mass index [BMI] ≥30 kg/m²; age ≥65 years) had an annual risk of recurrent VTE of 1.6% (95% CI 0.3%–4.6%), whereas women with two or more of these findings had a much higher recurrence risk [14.1% (95% CI 10.9%–17.3%)]. The authors of this study came to the conclusion that women but not men with less than two of the aforementioned risk factors may safely discontinue oral anticoagulant therapy after six months of therapy following a first unprovoked VTE.

Within the frame of the Austrian Study on Recurrent Venous Thromboembolism (AUREC), we developed a simple model...
(Vienna Prediction Model) that allows prediction of the recurrence risk in patients with unprovoked DVT and/or PE. We prospectively followed 929 patients for a median of 43 months after discontinuation of anticoagulation (25). A total of 176 patients had recurrent VTE. Age, sex, thrombus location, BMI, factor V Leiden, the prothrombin mutation, and D-dimer were preselected as relevant risk factors because their impact on the recurrence risk has been evaluated and independently confirmed and they can be determined by simple methods available in many laboratories. These variables were analysed in a Cox proportional hazards model, and those associated with recurrence were used to compute risk scores. Only the patient’s sex, thrombus location and D-dimer were relevant predictors of the recurrence risk. Based on these variables we developed a nomogram that can be used to calculate risk scores and to estimate the cumulative probability of recurrence in an individual patient. Our model has undergone an extensive internal cross-validation process. We divided our cohort into test and validation samples thereby mimicking independent validation. This process was repeated 1,000 times and the results were averaged to avoid dependence of the validation results on a particular partition of our cohort. Patients were assigned to different risk categories according to their risk score. When we calculated cumulative recurrence rates for patients within quartiles of the risk score, these risk categories corresponded well with the recurrence rate as patients with lower scores had lower recurrence rates. A web-based risk calculator is available for ease of calculation (www.meduni-wien.ac.at/user/georg.heinze/zipfile/). We believe that this prediction model is suitable to identify patients with a recurrence risk that is low enough that discontinuation of anticoagulation after three months is justified. Application of this model in routine care should await the results of a validation study that is currently ongoing in a separate patient population.

Recently, Douketis et al. published the results of an individual patient data meta-analysis of seven prospective studies enrolling patients with a first objectively diagnosed VTE (26). Predictors of recurrent VTE were identified using stratified Cox regression, and the weight of predictors was obtained after model shrinkage to correct for over-optimism. The discriminative ability of the prediction rule was estimated using time-dependent c-statistics, and was internally validated by bootstrap analysis. The patient population consisted of 1,818 cases with unprovoked VTE treated for at least three months with a VKA. Abnormal D-dimer after stopping anticoagulation, age < 50 years, male sex and VTE not associated with hormonal therapy (in women) were the main predictors of recurrence. Optimism-corrected regression coefficients were used to derive a prognostic recurrence score that showed a good predicting capability (receiver-operating characteristics [ROC] area = 0.71). The score attributes the following points: +2 for positive (abnormal) post-anticoagulation D-dimer, +1 for age ≤ 50 years, +1 for male sex, –2 for hormone use at time of initial VTE (in women only). The annualised recurrence risk was 3.1% (95% CI 2.3–3.9) in patients with a score ≤ 1, 6.4% (95% CI 4.8–7.9) in patients with a score 2, and 12.3% (95% CI 9.9–14.7) in patients with a DASH score ≥ 3. The authors concluded that by considering at low recurrence risk those patients with a score ≥ 1, life-long anticoagulation might be avoided in 51.6% of patients with unprovoked VTE.

**Conclusion**

Identification of thrombosis patients with a low risk of recurrence is important as these patients most likely will not benefit from long-term anticoagulation. Evidence is lacking that this goal can be achieved by searching for single thrombophilic defects (i.e. thrombophilia screening). Measurement of global markers of coagulation activation, above all D-dimer, allows much better distinction between patients with high or low recurrence risk. A novel approach for assessing risk of recurrent VTE consists of linking clinical patient characteristics with laboratory testing. Several scoring models that allow assessing the risk of recurrent VTE have been developed over the last years and several studies to improve the pre-

**Table 1: Models to predict recurrence risk of venous thromboembolism.**

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Number of patients</th>
<th>Design</th>
<th>Predictive variables</th>
<th>Recurrence risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodger et al. (24)</td>
<td>646</td>
<td>Prospective cohort</td>
<td>Men: none, Women: Age ≥ 60 years, Signs of PTS, BMI ≥ 30 kg/m², D-dimer ≥ 250 μg/l during anticoagulation</td>
<td>≤ 1 point</td>
<td>1.6% (95% CI 0.3%–4.6%)</td>
</tr>
<tr>
<td>Eichinger et al. (25)</td>
<td>929</td>
<td>Prospective cohort</td>
<td>Sex, Location of first VTE, D-dimer after anticoagulation</td>
<td>≤ 180 points (according to nomogram)</td>
<td>4.4% (95% CI 2.7%–6.2%)</td>
</tr>
<tr>
<td>Tosetto et al. (26)</td>
<td>1,818</td>
<td>Patient level meta-analysis</td>
<td>Abnormal D-Dimer after anticoagulation, Age &lt; 50 years, Male sex, Hormonal therapy</td>
<td>≤ 1 point</td>
<td>3.1% (95% CI 2.3 – 3.9)</td>
</tr>
</tbody>
</table>
dictive accuracy of these models are ongoing. Before the results of these studies are available, however, implementation of scoring models into routine clinical practice is too premature.

Conflicts of interest
None declared.

References