Risk Assessment of Recurrence in Patients With Unprovoked Deep Vein Thrombosis or Pulmonary Embolism

The Vienna Prediction Model

Sabine Eichinger, MD*; Georg Heinze, PhD*; Lisanne M. Jandeck, MSc; Paul A. Kyrle, MD

Background—Predicting the risk of recurrent venous thromboembolism (VTE) in an individual patient is often not feasible. We aimed to develop a simple risk assessment model that improves prediction of the recurrence risk.

Methods and Results—In a prospective cohort study, 929 patients with a first unprovoked VTE were followed up for a median of 43.3 months after discontinuation of anticoagulation. We excluded patients with a strong thrombophilic defect such as a natural inhibitor deficiency, the lupus anticoagulant, and homozygous or combined defects. A total of 176 patients (18.9%) had recurrent VTE. Preselected clinical and laboratory variables (age, sex, location of VTE, body mass index, factor V Leiden, prothrombin G20210A mutation, D-dimer, and in vitro thrombin generation) were analyzed in a Cox proportional hazards model, and those variables that were significantly associated with recurrence were used to compute risk scores. Male sex (hazard ratio versus female sex 1.90, 95% confidence interval 1.31 to 2.75), proximal deep vein thrombosis (hazard ratio versus distal 2.08, 95% confidence interval 1.16 to 3.74), pulmonary embolism (hazard ratio versus distal thrombosis 2.60, 95% confidence interval 1.49 to 4.53), and elevated levels of D-dimer (hazard ratio per doubling 1.27, 95% confidence interval 1.08 to 1.51) were related to a higher recurrence risk. Using 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. The model was cross validated, and patients were assigned to different risk categories based on their risk score. Recurrence rates corresponded well with the different risk categories.

Conclusions—By use of a simple scoring system, the assessment of the recurrence risk in patients with a first unprovoked VTE and without strong thrombophilic defects can be improved.

Key Words: venous thrombosis • recurrence • risk • D-dimer

Venous thrombosis is a chronic disease, and recurrent events are fatal in approximately 5% to 9% of patients.1 Predicting the likelihood of recurrence in an individual patient is of utmost importance, because most recurrences can be prevented by antithrombotic therapy. The presence or absence of certain clinical and laboratory patient characteristics determines a low or high recurrence risk. The risk is low among patients with venous thromboembolism (VTE) provoked by surgery, trauma, immobilization, pregnancy, or female hormone intake, whereas it is higher among those with unprovoked thrombosis.2 Stratification of patients with unprovoked VTE according to their recurrence risk can be achieved on the basis of clinical risk factors including patient’s sex, comorbidities, or overweight or by measuring laboratory markers of thrombophilia such as factor V Leiden, the prothrombin mutation, natural coagulation inhibitor deficiencies, elevated coagulation factors, and antiphospholipid antibodies.3 A novel approach to assess the recurrence risk is the use of global coagulation markers, including D-dimer,4 or in vitro thrombin generation.5–8

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Despite substantial progress in identifying the determinants of recurrence risk, its prediction in an individual patient is often not feasible in daily routine care. VTE is a disease with many causes, and the combined effect of clinical and laboratory characteristics on the risk of recurrence is unknown. The determination of some laboratory risk factors is costly, lacks standardization, or is too elaborate for routine purposes. To overcome these limitations, we aimed to develop a simple...
risk model that improves prediction of the recurrence risk in patients with unprovoked VTE.

Methods

Patients

Patients were recruited from 4 thrombosis centers in Vienna, Austria, between July 1992 and August 2008. Consecutive patients older than 18 years with a first VTE who had been treated with oral anticoagulants for at least 3 months were included. Patients were excluded if they had VTE provoked by surgery, trauma, pregnancy, or oral hormone intake; deficiency of antithrombin, protein C, or protein S; presence of the lupus anticoagulant; or cancer. All patients initially received unfractionated or low-molecular-weight heparin at therapeutic doses. During high-risk situations, including surgery, trauma, or immobilization, patients received thromboprophylaxis with a low-molecular-weight heparin according to local standard practice based on national or international guidelines.

Diagnosis of deep vein thrombosis was established by a positive finding on venography or color duplex sonography (in case of proximal thrombosis). The diagnosis of pulmonary embolism was confirmed either by ventilation-perfusion scanning or by spiral computed tomography. Patients with symptomatic pulmonary embolism and deep vein thrombosis were classified as having a pulmonary embolism.

Patients entered the study at the time of discontinuation of oral anticoagulation. The end point of the study was recurrent symptomatic deep vein thrombosis confirmed by venography or color duplex sonography (in case of proximal thrombosis of the contralateral leg) or recurrent symptomatic pulmonary embolism confirmed by ventilation-perfusion scanning and/or spiral computed tomography.

An adjudication committee that consisted of independent radiologists established the diagnosis. The ethics committee of the Vienna University Hospital approved the study, and all patients provided written informed consent to participate.

Selection of Risk Factors for Development of the Model

Clinical variables (age at venous thrombosis, sex, location of VTE, and body mass index [determined by dividing weight in kilograms by the square of height in meters]) and laboratory variables (factor V Leiden mutation, prothrombin G20210A mutation, D-dimer, and, in vitro thrombin generation) were preselected by the principal investigators (SE, PAK) as relevant risk factors on the basis of the following criteria: Independent confirmation of the impact on the recurrence risk, availability of assay methods, and ability to change management. Only variables for which the 95% CIs excluded a regression coefficient of zero were further considered. Next, we developed a model based on the clinical variables and peak thrombin, because only this laboratory variable was significant in the first step. We eliminated clinical variables if they were not significant in this model and if their exclusion from the model did not alter the results on the remaining variables. The model that included sex, location of VTE, and peak thrombin could still be overoptimistic in the sense that in future samples, the effect of these variables on recurrence could be less than expected from the model (regression to the mean effect). The amount of overoptimism can be expressed by a shrinkage factor, which was again computed by use of bootstrap resampling and used to multiply the coefficients of the final model to obtain a model free of optimism and suitable for predictive purposes. We repeated the computation of the risk model replacing peak thrombin with D-dimer and compared results. Because it showed a very skewed distribution, D-dimer entered these computations using its logarithm. For both models, we computed goodness-of-fit tests. By multiplying the estimated regression coefficients of the final risk model by the shrinkage factor, a risk score from a patient’s particular value of sex, location of VTE, and D-dimer can be obtained, which directly translates into estimates of cumulative recurrence rates at various time points during follow-up. This translation is depicted in a nomogram that includes D-dimer that can be used for routine purposes. We expressed the predictive ability of the model using a 0.632 bootstrap estimate of the discrimination index. Time-dependent receiver operating characteristic curves at 12 and 60 months were computed by the method of Heagerty and colleagues. To assess the predictive ability of the models, we computed bootstrap cross-validated risk scores for each patient; in each bootstrap resample, we estimated model coefficients, and using these numbers, we computed shrunken risk scores for those patients not included in that particular resample. Finally, each patient’s risk score was the overall average of such cross-validated risk scores for that patient. This process resembles validation in an independent sample. The risk scores were stratified into quartiles and compared with the observed time to recurrence by Kaplan-Meier analysis, accompanied by a log-rank trend test. All models were estimated with all available complete cases with regard to covariate information. Statistical analysis was performed with the SAS system version 9.2 (2008; SAS Institute Inc., Cary, NC). For graphs and nomograms, the statistical software R was used (www.r-project.org, mainly using F. Harrell’s “Design” package).

Results

Study Population

The study population comprised 929 patients (Table 1). The median follow-up was 43.3 months (25th percentile 14.7 months, 75th percentile 78.5 months). Symptomatic recurrent VTE was seen in 176 (18.9%) of 929 patients (deep-vein thrombosis in 100 patients and pulmonary embolism in 76 patients; 3 embolisms were fatal). In 160 patients, VTE recurred spontaneously; in 16 patients, recurrence was pro-
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Subjects</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>929</td>
<td>54 (43, 63)</td>
</tr>
<tr>
<td>Female sex</td>
<td>929</td>
<td>367 (40.0)</td>
</tr>
<tr>
<td>Location of first VTE</td>
<td>929</td>
<td></td>
</tr>
<tr>
<td>Distal deep vein thrombosis</td>
<td>929</td>
<td>164 (17.7)</td>
</tr>
<tr>
<td>Proximal deep vein thrombosis</td>
<td>929</td>
<td>327 (35.2)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>929</td>
<td>438 (47.1)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>909</td>
<td>27.1 (24.4, 30.1)</td>
</tr>
<tr>
<td>Body mass index &gt;30 kg/m²</td>
<td>909</td>
<td>236 (26.0)</td>
</tr>
<tr>
<td>D-Dimer, μg/L</td>
<td>832</td>
<td>355 (236, 558)</td>
</tr>
<tr>
<td>Peak thrombin, nmol/L</td>
<td>629</td>
<td>358 (283, 439)</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>916</td>
<td>224 (24.4)</td>
</tr>
<tr>
<td>Factor II G20210A mutation</td>
<td>915</td>
<td>49 (5.4)</td>
</tr>
<tr>
<td>Duration of anticoagulation, mo</td>
<td>929</td>
<td>6.6 (6.1, 8.0)</td>
</tr>
<tr>
<td>Observation time, mo</td>
<td>929</td>
<td>43.3 (14.7, 78.5)</td>
</tr>
</tbody>
</table>

Values are median (25th, 75th percentiles) or frequency (%).

Validation of the Risk Model

To validate the risk model, we used an internal validation procedure based on bootstrap cross-validation in the following way: A bootstrap sample of 929 patients was drawn with replacement from the original sample. Owing to drawing with replacement, some patients appeared several times in this resample, whereas others were missing. The resample constituted a training sample in our validation process, and the risk model was reestimated from the training sample data, which yielded slightly different coefficients associated with sex, location of VTE, and D-dimer than seen in the original total sample. The patients not included in the training sample were used as an independent validation set, for which shrunken risk scores were computed on the basis of the estimates from the training sample multiplied by the overall shrinkage factor, which was estimated as 0.88. This process was repeated 1000 times. Finally, each patient was used in validation samples several times, and his or her risk scores obtained in each of those validation samples were averaged to obtain 1 risk score for each patient of the original sample. These risk scores were divided into quartiles that defined patients with expected low risk, intermediate low risk, intermediate high risk, and high risk. The cumulative probabilities (95% CI) of recurrence within 5 years of patients within risk quartiles (lowest to highest risk, respectively) were 9.2% (5.4% to 15.5%), 21.0% (14.9% to 29.2%), 29.7% (21.5% to 40.0%), and 33.1% (25.5% to 42.1%) in the D-dimer–based model (P<0.001 for trend). Figure 2 shows the receiver operating characteristic curves with the cross-validated and shrunken risk scores, assessing the ability to predict recurrence up to 12 months and up to 60 months.

Nomogram for Risk of Recurrent VTE

We developed a nomogram that can be used to calculate risk scores and expected cumulative recurrence rates from a patient’s sex, location of initial VTE, and D-dimer levels (Figure 3 and the online-only Data Supplement) in individual patients. The precision of the estimated cumulative recurrence rates is expressed in 95% CIs. A straight line must be

![Figure 1. Overall cumulative recurrence rate in 929 patients with a first unprovoked VTE estimated by Kaplan-Meier analysis, with 95% CIs (dotted lines).](image-url)
drawn upward to the points to determine how many points a patient will receive for sex, location of VTE, and level of D-dimer. The sum of the points for each predictor must be located on the total point axis. By drawing a straight line downward, the patient’s cumulative recurrence rate after 1 and 5 years can be found.

Discussion

In the present analysis of patients with a first unprovoked VTE, the overall recurrence risk was high. VTE recurred in approximately one fourth of the patients within 5 years after discontinuation of anticoagulation, and these data are in good agreement with findings from other cohorts.21–26 Although recurrence rates were slightly higher when patients with isolated calf vein thrombosis were excluded,27 the recurrence risk of patients with unprovoked calf vein thrombosis has been reported to be as high as 25% 6 years after discontinuation of anticoagulation.28 According to current guidelines, long-term anticoagulant treatment is recommended for all patients with unprovoked VTE except those with isolated calf vein thrombosis, in whom treatment for 3 months is suggested to be sufficient.2 The level of evidence for the recommendation relative to the latter group, however, is low. Because at least some of these patients could have a higher risk of recurrence and might therefore benefit from extended anticoagulation, we decided not to restrict the present analysis to patients with proximal deep vein thrombosis or pulmonary embolism only; however, we did not include patients with VTE related to a transient, reversible risk factor such as surgery, trauma, or female hormone intake, because these patients have a well-established low risk of recurrence and should receive anticoagulation for only 3 months.2

One must keep in mind that despite an overall high recurrence risk, the majority of patients with a first unprovoked VTE will stay recurrence free for many years and will be exposed to a considerable risk of bleeding when the aforementioned guidelines are applied. Therefore, identifica-

Table 2. Univariate and Bootstrap Zero-Corrected Multivariable Cox Regression Models With All Risk Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude HR</th>
<th>95% CI</th>
<th>( P )</th>
<th>Bootstrap Zero-Corrected Multivariable HR*</th>
<th>95% CI</th>
<th>( P )†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male vs female)</td>
<td>1.91</td>
<td>1.37–2.67</td>
<td>&lt;0.001</td>
<td>2.01</td>
<td>1.30–3.22</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (per 10 y)</td>
<td>0.95</td>
<td>0.86–1.06</td>
<td>0.395</td>
<td>0.96</td>
<td>0.80–1.16</td>
<td>0.730</td>
</tr>
<tr>
<td>BMI (per 5 kg/m²)</td>
<td>1.19</td>
<td>1.02–1.38</td>
<td>0.026</td>
<td>1.03</td>
<td>0.78–1.36</td>
<td>0.806</td>
</tr>
<tr>
<td>BMI ≥30 vs BMI &lt;30 kg/m²</td>
<td>1.18</td>
<td>0.85–1.64</td>
<td>0.338</td>
<td>1.05</td>
<td>0.65–1.70</td>
<td>0.806</td>
</tr>
<tr>
<td>Location: proximal vs distal thrombosis</td>
<td>2.76</td>
<td>1.57–4.84</td>
<td>&lt;0.001</td>
<td>1.69</td>
<td>0.85–3.79</td>
<td>0.138</td>
</tr>
<tr>
<td>Pulmonary embolism vs distal thrombosis</td>
<td>3.15</td>
<td>1.83–5.44</td>
<td>&lt;0.001</td>
<td>2.77</td>
<td>1.44–6.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak thrombin (per 100 nmol/L)</td>
<td>1.31</td>
<td>1.11–1.54</td>
<td>0.001</td>
<td>1.36</td>
<td>1.15–1.65</td>
<td>0.002</td>
</tr>
<tr>
<td>D-dimer (per doubling)</td>
<td>1.24</td>
<td>1.05–1.45</td>
<td>0.010</td>
<td>1.34‡</td>
<td>1.06–1.70‡</td>
<td>0.016‡</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td>1.54</td>
<td>1.12–2.11</td>
<td>0.007</td>
<td>1.68</td>
<td>1.00–2.71</td>
<td>0.106</td>
</tr>
<tr>
<td>Factor II G20210A mutation</td>
<td>1.24</td>
<td>0.70–2.18</td>
<td>0.458</td>
<td>1.00</td>
<td>0.38–2.19</td>
<td>1.000</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio.
*Median from 1000 resamples.
†Computed by \( P = 2 \min \{ f(\text{HR} \leq 1), f(\text{HR} > 1) \} \), where \( f(\text{HR} > 1) \) denotes the relative frequency of an HR > 1 among the 1000 resamples.
‡From the bootstrap zero-corrected multivariable model excluding peak thrombin.

Table 3. Multivariable Cox Regression Models Including D-Dimer (A) and Peak Thrombin Levels (B)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs female sex</td>
<td>1.90</td>
<td>1.31–2.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary embolism vs distal thrombosis</td>
<td>2.60</td>
<td>1.49–4.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proximal vs distal thrombosis</td>
<td>2.08</td>
<td>1.16–3.74</td>
<td>0.01</td>
</tr>
<tr>
<td>D-dimer (per doubling)</td>
<td>1.27</td>
<td>1.08–1.51</td>
<td>0.005</td>
</tr>
<tr>
<td>Model B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs female sex</td>
<td>2.05</td>
<td>1.36–3.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary embolism vs distal thrombosis</td>
<td>2.32</td>
<td>1.32–4.09</td>
<td>0.004</td>
</tr>
<tr>
<td>Proximal vs distal thrombosis</td>
<td>1.88</td>
<td>1.03–3.44</td>
<td>0.04</td>
</tr>
<tr>
<td>Peak thrombin (per 100 nmol/L)</td>
<td>1.38</td>
<td>1.17–1.63</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figure 2. Receiver operating characteristic curves based on cross-validated risk scores from the model that included sex, localization, and D-dimer for recurrence up to 12 months (solid line) and 60 months (dashed line). AUC indicates area under the curve.
tion of patients with unprovoked VTE in whom the risk of recurrence is low enough to consider short-term anticoagulation is a major goal in the management of these patients.

It was therefore our aim to develop a simple risk assessment model in patients with unprovoked deep vein thrombosis or pulmonary embolism. In our model, the combination of location of the initial VTE event and the patient’s sex together with D-dimer or peak thrombin levels was well suited to discriminate between low- and high-risk patients. The predictive ability of the model was comparable whether D-dimer or peak thrombin levels were used. Because D-dimer is a well-standardized, widely established parameter that can be easily applied in daily practice, we further developed our risk model on the basis of this parameter.

We computed a nomogram to calculate risk scores and to estimate the cumulative recurrence rate in an individual patient. Examples of how to apply the nomogram are given in the legend to Figure 3. D-dimer was used as a continuous variable, which, in contrast with the use of a dichotomized variable, allows for more variability with regard to different levels. Points for the risk model were based on the regression coefficients obtained from our final model and reflect the impact of the respective variable on the recurrence risk.

Our model has undergone an extensive cross-validation process. We divided the present study cohort into test and validation samples, thereby mimicking independent validation. This process was repeated 1000 times, and the results were averaged to avoid dependence of the validation results on a particular partition of the study 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, because patients with lower scores had lower recurrence rates. Our risk model could now be applied to independent cohorts to evaluate its validity in patients with different thrombophilic risk profiles.

The model was particularly well suited to identify patients at low risk of recurrence. Women, patients with isolated calf deep vein thrombosis, and patients with low levels of D-dimer all gained lower scores, which indicates a lower probability of recurrence. In patients within the lowest quartile of the risk score, for instance, the annual recurrence rate was as low as 1.9%. The model does not predict, however, whether a single patient will have recurrence or not, because this is influenced by a large variety of genetic and acquired factors, some of which are still unknown.

Predicting the risk of recurrence by a combination of risk factors has thus far been attempted in only 1 other study. Compared with the present study, the number of patients and recurrences were lower in that study, and the mean observation time was only 18 months. No combination among the 69 potential predictors of recurrence satisfied the authors’ criteria of a low-risk group (<3% per year) in male patients with unprovoked VTE. In women, however, a low-risk group with an annual recurrence risk of 1.6% (95% CI 0.3 to 4.6) could be identified when none or only 1 feature (signs of postthrombotic syndrome, D-dimer level ≥250 µg/L, body mass index ≥30 kg/m², or age ≥65 years) was present.

Some limitations of the present study need to be addressed. Patients with strong thrombophilic factors, including a natural inhibitor deficiency, a lupus anticoagulant, or double heterozygous or homozygous carriers of factor V Leiden or the prothrombin mutation, were not included because they received long-term anticoagulation after the first venous thrombosis. Our model, therefore, cannot be applied to these patients. Clinical and laboratory variables that were used to develop the risk model have been preselected on the basis of their established relevance for recurrence risk and solid methodology for assessment. It would stand to reason that if other determinants of the risk of recurrence, such as high clotting factor levels or residual vein thrombosis, were included in the model, risk prediction could improve. It was our aim, however, to develop a simple model that could be easily applied in routine care. Although we developed the model within one of the largest data sets of patients with venous thrombosis, the prediction of recurrence could be improved by increasing the number of patients. As pointed out above, variables to estimate recurrence rates in the present study were selected on the basis of practical considerations with regard to methodology and general availability of a specific risk factor, as well as statistical considerations, ie, only variables were selected for which we could statistically prove an association with recurrence rates. With a larger data set, the set of variables could be selected with less uncertainty, thus providing more precise estimates of recurrence probabilities for individuals. D-dimer was measured only once shortly after discontinuation of anticoagulation. It remains to be investigated whether prediction of recurrence can be improved by serial D-dimer measurements during follow-up. D-dimer values were missing in 97 of 929 patients; however, clinical and laboratory characteristics did not differ between patients with and without D-dimer values (data not shown).

Prediction of the risk of recurrence is important to determine the optimal duration of anticoagulation. By use of a simple, easy to apply scoring system, the assessment of the recurrence risk in patients with a first unprovoked VTE without strong thrombophilic defects can be improved. Anticoagulants are very effective in preventing recurrent VTE, but their duration is limited by the risk of bleeding. By use of our risk assessment model, identification of those patients with unprovoked VTE in whom the recurrence risk is low enough to consider a limited duration of anticoagulation can be achieved. The model should undergo external validation before it is applied in routine clinical practice. Our prediction model could be used to stratify patients according to their recurrence risk in randomized clinical trials that investigate the optimal duration of anticoagulation in patients with unprovoked deep vein thrombosis or pulmonary embolism.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Venous thromboembolism (VTE) is a common disease with a high recurrence risk that is particularly high among patients in whom VTE occurred in the absence of a triggering factor. These patients are candidates for indefinite anticoagulation. Despite the high recurrence risk, the majority of patients will remain recurrence free for many years and will unnecessarily be exposed to a bleeding risk with treatment. Therefore, identification of patients in whom the risk of recurrence is low enough to consider short-term anticoagulation is a major goal in patient management. It was our aim to develop a simple risk assessment model in patients with unprovoked VTE. In a prospective cohort study, 929 patients were followed up for a median of 43.3 months after discontinuation of anticoagulation. A total of 176 patients (18.9%) had recurrent VTE. Preselected clinical and laboratory variables (age, sex, location of VTE, body mass index, factor V Leiden, prothrombin G20210A mutation, D-dimer, and in vitro thrombin generation) were analyzed, and those that were significantly associated with recurrence were used to compute risk scores. The combination of location of the initial VTE event and the patient’s sex together with D-dimer levels was well suited to discriminate between low- and high-risk patients. With 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. In conclusion, by use of a simple scoring system, the assessment of the recurrence risk in patients with a first unprovoked VTE can be improved.

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