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ORIGINAL ARTICLE

Management of patients with venous thromboembolism and a high recurrence risk estimated by the Vienna Prediction Model: a prospective cohort study

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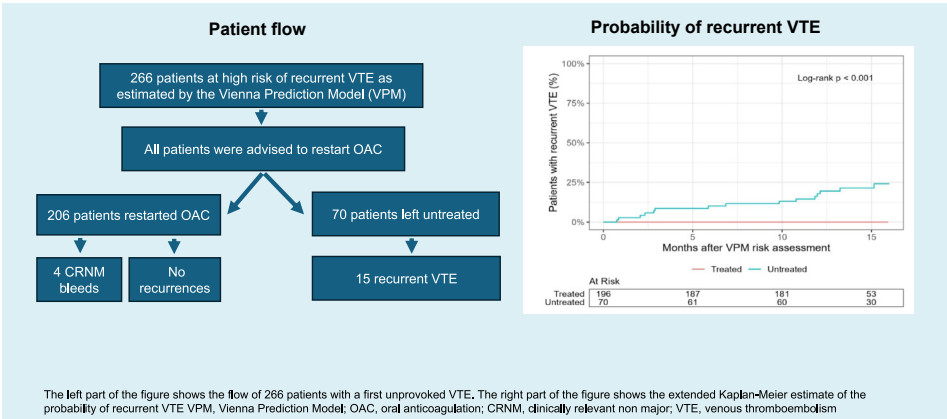
Abstract

Background: The Vienna Prediction Model (VPM) identifies patients with a first unprovoked deep vein thrombosis of the leg and/or pulmonary embolism who have a low recurrence risk and may, therefore, not benefit from extended-phase anticoagulation.

Objectives: The aim of this study was to evaluate patients with a predicted high risk of recurrent venous thromboembolism (VTE).

Methods and Results: We prospectively followed 266 patients in whom the VPM had predicted a recurrence risk of more than 5.5% at 1 year for a median of 13.5 months. Their median age was 56 years, and 96% were men. After the VPM risk assessment, 196 patients restarted anticoagulation. While on anticoagulation, none of the patients experienced recurrent VTE, whereas 4 patients had nonmajor clinically relevant bleeding (absolute bleeding rate, 1.8 [95% CI, 0.5-4.5] events per 100 patient-years). Seventy patients were left untreated after VPM risk assessment for various reasons. Among patients not using anticoagulation, 15 had recurrence (absolute recurrence rate, 18.1 [95% CI, 10.1, 29.9] events per 100 person-years). According to the extended Kaplan–Meier analysis, the probability of VTE recurrence in patients not on anticoagulation was 10.1% and 17.9% at 6 and 12 months after VPM risk assessment, respectively.

Conclusion: Anticoagulant therapy is effective and safe in patients with an unprovoked VTE, in whom the VPM had predicted a high risk of recurrent VTE. If these patients are left untreated, the risk of recurrence is high.



The left part of the figure shows the flow of 266 patients with a first unprovoked VTE. The right part of the figure shows the extended Kaplan-Meier estimate of the probability of recurrent VTE VPM, Vienna Prediction Model; OAC, oral anticoagulation; CRNM, clinically relevant non major; VTE, venous thromboembolism

KEYWORDS
deep vein thrombosis, pulmonary embolism, venous thromboembolism, Vienna Prediction Model recurrence

Essentials

- The VPM estimates recurrence risks after unprovoked VTE.
- We followed 266 patients with a predicted recurrence risk by the VPM of >5.5% at 1 year.
- In 196 patients who restarted anticoagulation, treatment was effective and safe.
- Seventy-seven patients stopping anticoagulation had a high recurrence risk (18.1 [95% CI, 10.1, 29.9]/100 person-years).

1 | INTRODUCTION

Venous thromboembolism (VTE) is a chronic disease with a tendency to recur [1]. Recurrence as deep vein thrombosis (DVT) of the leg can be associated with the development or worsening of a postthrombotic syndrome; recurrence as pulmonary embolism (PE) can result in pulmonary hypertension or even death. Recurrent VTE can be prevented by secondary thromboprophylaxis with oral anticoagulants, albeit at the price of bleeding [2]. Clearly distinguishing between patients with a high recurrence risk (who may benefit from extended-phase anticoagulation) and those with a lower risk (in whom the bleeding risk may outweigh the risk of recurrent VTE) is an important goal of thrombosis research.

In 2010, we presented the Vienna Prediction Model (VPM), a risk assessment model (RAM) developed to optimize the decision on the duration of anticoagulation of patients with a first unprovoked DVT of the leg or PE [3]. The VPM estimates the individual recurrence risk using easily accessible determinates, including patient sex, location of index VTE, and D-dimer. The VPM was successfully validated in a pooled individual patient dataset and a prospective management study [4,5].

In 2013, we initiated a prospective cohort study to find out if the VPM allows the identification of patients with a recurrence risk low enough to consider stopping oral anticoagulation after 3 to 7 months. We included only patients with a VPM risk assessment score of 180 or less, which corresponds to a predicted recurrence risk at 1 year equal to or less than 5.5%. The results of this study were recently published [6].

Patients with a VPM risk assessment score exceeding 180 (equivalent to a 1-year predicted recurrence risk greater than 5.5%) were excluded from the aforementioned study, as we considered them candidates for extended-phase anticoagulation. Here, we report (i) how many of these high-risk patients followed our advice to restart anticoagulation, (ii) the reasons for not restarting anticoagulation, (iii) the incidence of VTE recurrence in patients who did not restart anticoagulation, and (iv) the incidence of anticoagulation-related bleeding in patients who restarted anticoagulation.

2 | METHODS

2.1 | Patients and study design

We performed a prospective cohort study, which was carried out at the Department of Medicine I of the Medical University of Vienna, Austria, and at the Division of Angiology, Department of Medicine, Medical University of Graz, Austria. The study was approved by the ethics committees of both institutions, and all patients gave written informed consent. The study design has recently been published [6].

Noncancer patients older than 18 years who had been treated with an oral anticoagulant over 3 to 7 months for a first objectively verified symptomatic unprovoked DVT of the leg and/or PE who did not have an indication for long-term anticoagulation for reasons other than VTE, were eligible. Three weeks after withdrawal of anticoagulation, VPM risk assessment (based on patient sex, location of incident VTE, and D-dimer plasma concentration) was performed using a web-based calculator [3]. D-dimer was measured by a quantitative immunoassay. Patients at low risk of recurrence, as reflected by a VPM risk assessment score of 180 points or less (which corresponds to a predicted recurrence risk at 1 year of equal to or less than 5.5%), were excluded.

Patients were seen in person for VPM risk assessment. After obtaining the result of D-dimer, which took an average of 2 hours, the recurrence risk was calculated, and the results and consequences were extensively discussed. In particular, those patients with a high recurrence risk were informed that they were excluded from the study. They were candidates for resuming anticoagulation because of their high recurrence risk. Consequently, we also provided written information to their referring practitioner/family doctor, who eventually decided on further management of the patient.

After a median of 13.5 months, patients were contacted via a standardized questionnaire and were asked about measures and duration of anticoagulant treatment, recurrent VTE, and bleeding, in which case the clinical circumstances were verified and documented by contacting the patient in person and/or by retrieving their medical files. Recurrent VTE had to be objectively diagnosed by imaging. Bleeding was categorized according to the International Society on Thrombosis and Haemostasis criteria [7].

2.2 | Statistical analysis

Patients were followed up from the day of VPM risk assessment until recurrence of VTE, which was considered as an event, or were censored when they returned the questionnaire. Regarding patient characteristics, continuous variables were described using median (25th and 75th percentiles) and categorical variables by absolute frequencies (percentages). We considered that patients could switch from the use of anticoagulation to nonuse or *vice versa* during follow-up. We, therefore, used extended Kaplan–Meier analysis to graphically compare the probability of recurrent VTE of patients stratified for the use of anticoagulation [8]. The extended Kaplan–Meier curves of both groups were compared by the log-rank test. The absolute rate of recurrent VTE among patients not using anticoagulation was calculated as the number of recurrences per 100 patient-years. Similarly, the absolute rate of bleeding was obtained for patients using anticoagulation. The corresponding 95% CIs were calculated based on the Poisson distribution. R software (version 4.3.2, 2023, R Core Team, R Foundation for Statistical Computing) was used for statistical analysis.

3 | RESULTS

3.1 | Patients

Between January 2013 and May 2019, 282 patients with a first unprovoked DVT of the leg and/or PE in whom we found a predicted recurrence risk greater than 5.5% at 1 year were included. Sixteen patients (5.7%) did not respond to the questionnaire and were excluded from the analysis. The characteristics of the remaining 266 patients are shown in the Table. Their median age was 56 years, and 96% were males. Most patients (70%) had a history of PE, and none of them had an incident distal DVT. They had received anticoagulation for a median of 4.4 months (IQR, 3.4-5.8) before VPM risk assessment and were followed up for a median of 13.5 months (IQR, 11.9-16.3).

After VPM risk assessment, oral anticoagulation was restarted in 196 (74%) patients, and 70 (26%) patients were left untreated. Seven patients discontinued anticoagulation later during the follow-up period, while 8 patients who initially remained untreated restarted anticoagulation during follow-up. Of those patients who restarted anticoagulation after VPM risk assessment, 189 (96%) patients received a direct oral anticoagulant at full dose, and 7 (4%) patients were treated with a vitamin K antagonist. The main reasons for not restarting anticoagulation after VPM risk assessment were patient preference (55 patients, 79%) followed by the presence of a contraindication against oral anticoagulants (9 patients, 13%), physician preference (4 patients, 6%), and side effects of anticoagulation other than bleeding (2 patients, 3%). Among the 7 patients who discontinued anticoagulation during follow-up, the reasons were patient preference in 2 patients, physician preference in 2 patients, side effects of anticoagulation other than bleeding in 2 patients, and anticoagulation-related bleeding during follow-up in 1 patient.

3.2 | Recurrent VTE

Fifteen patients who were left untreated during follow-up had recurrent VTE: 6 patients had nonfatal PE, 6 patients had proximal DVT, and 3 patients had distal DVT. Two patients with recurrence were women who had an incident PE and very high D-dimer (3460 ng/mL and 12.080 ng/mL, respectively) at the time of VPM risk assessment. The absolute recurrence rate for patients who were left untreated was 18.1 (95% CI, 10.1, 29.9) events per 100 person-years. According to the extended Kaplan–Meier analysis, among patients who did not restart anticoagulation, 10.1% experienced a recurrent VTE at 6 months and 17.9% at 1 year, while no recurrences occurred among patients who had restarted anticoagulation ($P < .001$; Figure).

3.3 | Bleeding

None of the patients who had restarted anticoagulation had major or fatal bleeding. Four patients experienced clinically relevant nonmajor

TABLE Characteristics of 266 patients with a Vienna Prediction Model risk assessment score of more than 180 points and classified based on whether they restarted anticoagulation after Vienna Prediction Model risk assessment or not.

Characteristic	All patients (*N* = 266)	Patients restarting anticoagulation (*n* = 196)	Patients not restarting anticoagulation (*n* = 70)
Age (y)	56 (45, 68)	55 (45, 67)	60 (48, 71)
Sex, *n* (%)			
Male	255 (96)	189 (96)	67 (96)
Female	11 (4)	8 (4)	3 (4)
Location of index event, *n* (%)			
Proximal DVT	79 (30)	55 (28)	24 (34)
Distal DVT	0	0	0
PE	187 (70)	141 (72)	46 (66)
Anticoagulation before VPM risk assessment (mo)	4.4 (3.4, 5.8)	4.6 (3.5, 5.8)	4.1 (3.3, 5.6)
Follow-up (mo)	13.5 (11.9, 16.3)	12.8 (11.9, 15)	16 (13.4, 17.4)
D-dimer (ng/mL)	500 (330, 765)	490 (318, 755)	510 (415, 762)
VPM-RAS (points)	195 (188, 209)	195 (187, 209)	199 (189, 206)

Values are medians (25th and 75th percentiles) or absolute frequencies (%).

DVT, deep vein thrombosis; PE, pulmonary embolism; VPM, Vienna Prediction Model; VPM-RAS, Vienna Prediction Model risk assessment score.

bleeding. All 4 patients had rectal bleeding during treatment with a direct oral anticoagulant. The absolute rate of bleeding among patients on oral anticoagulation was 1.8 (95% CI, 0.5, 4.5) events per 100 patient-years of follow-up.

4 | DISCUSSION

The VPM identifies patients at low risk of VTE recurrence who might not benefit from extended anticoagulation [6]. In contrast, the analysis

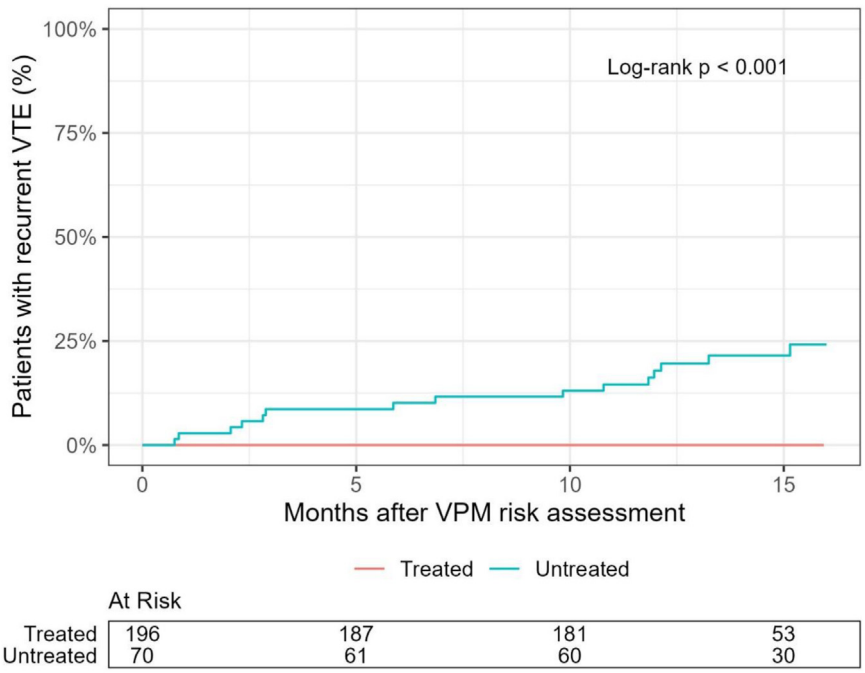


FIGURE Extended Kaplan–Meier plot of recurrent venous thromboembolism (VTE). One year after the Vienna Prediction Model (VPM) risk assessment, the extended Kaplan–Meier estimate of the probability of recurrent VTE of patients not using anticoagulation was 17.9%, while no recurrence occurred among patients using anticoagulation ($P < .001$).

presented in this article focuses on patients with a predicted high recurrence risk, ie, a recurrence risk greater than 5.5% at 1 year. More than 70% of these patients restarted oral anticoagulation immediately after VPM risk assessment (structured graphical abstract). Only 4 patients who did not restart oral anticoagulation did so because they were advised against anticoagulant treatment by their local physician. This finding is reassuring as it indicates awareness among primary care providers of the high recurrence risk of patients with unprovoked VTE, the need to prescribe extended-phase anticoagulation, and to adhere to guidelines [9–11]. Ten of 55 patients who had refused to restart anticoagulation against medical advice had recurrent VTE. This observation emphasizes the urgent need for intense counseling of these patients regarding their high recurrence risk.

None of the patients who had restarted anticoagulation had a recurrent VTE. This reflects the efficacy of oral anticoagulation – in our study, mainly with direct oral anticoagulants – in patients at high risk of recurrence. This observation aligns with findings from Elsebaie et al. [12], who did not find a significant increase in the recurrence risk during anticoagulation with a direct oral anticoagulant among patients with a high risk of VTE due to the presence of thrombophilia compared with those without a thrombophilic state.

Bleeding related to anticoagulation was rare: 1.8 clinically relevant nonmajor bleeding events per 100 person-years among patients who were receiving an oral anticoagulant, none of whom had fatal or major bleeding. There are several explanations for the low incidence of bleeding: (i) the bleeding risk of anticoagulant therapy is highest during the initial phase, ie, during the first 3 months of treatment, and then declines. In a meta-analysis from Canada, the rate of major bleeding during extended-phase anticoagulation with a direct oral anticoagulant was only 0.48 per 100 patient-years [13]. All our patients had already received oral anticoagulants over a period of at least 3 months, and none of the patients who restarted anticoagulation had a history of bleeding. (ii) The prevalence of strong risk factors of bleeding, such as advanced age, comorbidities like renal insufficiency, heart disease, or diabetes mellitus, and concomitant antiplatelet or nonsteroidal anti-inflammatory therapy in our patient cohort, was low. Only 9 patients were left untreated because of a supposed contraindication against anticoagulants. (iii) Most patients were treated with a direct oral anticoagulant. There is evidence that the risk of bleeding with a direct oral anticoagulant is lower than that with a vitamin K antagonist, also in the extended-phase anticoagulation setting [14]. (iv) Our patient population was almost exclusively male. Consequently, uterine bleeds could not meaningfully contribute to the overall bleeding frequency.

The optimal duration of anticoagulation after VTE entails balancing the risk of recurrence against the risk of bleeding caused by anticoagulation. Clearly, only patients in whom the recurrence risk outweighs the risk of bleeding are candidates for extended-phase anticoagulation. Seventy patients categorized by the VPM as having a high risk of recurrence did not restart anticoagulation after VPM risk assessment. The absolute rate of recurrent VTE among patients who did not restart anticoagulation was 18.1 events (95% CI, 10.1, 29.9) per 100 person-years, and the extended Kaplan–Meier analysis suggested the recurrence probability for those patients to be as high as 10.1% after 6 months and 17.9% after 1 year (structured graphical abstract). Although the VPM is intended to identify low-risk patients, these findings indicate that the model is also useful for patients with a high recurrence risk.

Many clinical and laboratory risk factors of recurrent VTE have been identified [1]. Male sex and location of incident VTE are the most important clinical components of several RAMs, including the VPM [6,15,16]. It was, therefore, not unexpected that more than 95% of the high-risk population was male, and none of the patients had an incident distal DVT. This observation is in line with the findings of Rodger et al. [15], who found that their RAM, the HERDOO2 rule (Hyperpigmentation, Edema, or Redness in either leg; D-dimer level ≥250 μg/L during treatment with anticoagulants; Obesity with body mass index ≥30; and Older age, ≥65 years), was predictive for women only as all men were categorized as being at high risk of recurrence.

Two of the 4 women who did not restart anticoagulation experienced recurrence. Both had PE as the initial VTE event. They also had excessively high D-dimer at VPM risk assessment, highlighting the presence of a hypercoagulable state as an important prerequisite for VTE recurrence.

Our study has strengths. The patient cohort was large and homogenous. We prospectively studied 266 patients with an unprovoked DVT of the leg and/or PE. Almost all patients received a direct oral anticoagulant rather than a vitamin K antagonist. Patients were managed by primary healthcare physicians in a real-world setting, allowing for the generalizability of data. The response rate to our standardized questionnaire was as high as 94%, permitting almost complete acquisition and validation of follow-up data. Our study also has limitations. Patients were not seen at prescheduled intervals at our institution but were contacted via a standardized questionnaire. We decided to refrain from thrombophilia screening and thus cannot comment on the impact of acquired or genetic laboratory abnormalities on the risk of recurrent VTE. The number of untreated patients was limited, which precludes a more accurate evaluation of their recurrence risk. We included a few patients with other ethnicities than Caucasian. Diagnosis of bleeding and recurrence was performed according to standard routine clinical practice rather than by endpoint verification criteria prespecified in a study protocol.

In conclusion, we prospectively followed a large number of patients with a history of unprovoked DVT of the leg and/or PE who were categorized by the VPM as being at high risk of recurrence. We made the following observations: (i) anticoagulant therapy was effective as none of the high-risk patients had a recurrence, (ii) the incidence of bleeding of extended-phase anticoagulation was low, and (iii) the recurrence risk was high among untreated patients. Our data indicate that the VPM, intended to identify low-risk patients, can be used to detect patients with a high risk of recurrent VTE who could benefit from extended-phase anticoagulation.

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AUTHOR CONTRIBUTIONS

H.S., P.A.K., L.E., G.H., and S.E. contributed significantly to the design, analysis, and interpretation of data and study conduct; L.E., P.G., T.G., and M.B. contributed significantly to patient recruitment and study conduct; and all authors had access to data outputs, had key roles in the writing/editing of the manuscript, and have primary responsibility for the final approved manuscript.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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