ORIGINAL ARTICLE

Risk of recurrence after a first unprovoked venous thromboembolism: external validation of the Vienna Prediction Model with pooled individual patient data

M. MARCUCCI,*† A. IORIO,† J. D. DOUKETIS,‡ S. EICHINGER,§ A. TOSETTO,¶ T. BAGLIN,**
M. CUSHMAN,†† G. PALARETI,‡‡ D. POLI,§§ R. C. TAIT¶¶ and P. A. KYRLE§

*Geriatrics, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico & Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; †Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON; ‡Department of Medicine, St Joseph's Hospital, McMaster University, Hamilton, ON, Canada; §Department of Medicine I, Medical University of Vienna, Vienna, Austria; ¶Department of Hematology, S. Bortolo Hospital, Vicenza, Italy; **Department of Haematology, Addenbrookes Hospital, Cambridge, UK; ††Department of Medicine, University of Vermont, Colchester, VT, USA; ‡‡Department of Medicine, University of Bologna, Bologna; §§Centro di Riferimento Regionale per la Trombosi, Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy; and ¶¶Department of Haematology, Royal Infirmary, Glasgow, UK

Summary. *Background:* In order to stratify patients with a first unprovoked venous thromboembolism (VTE) according to their recurrence risk and to identify those who would actually benefit from indefinite anticoagulation, three prediction models have been developed so far; none of them has been yet externally validated. *Objective:* To externally validate the Vienna Prediction Model (VPM), a prediction guide for estimating the recurrence risk after a first unprovoked VTE developed through Cox modeling and including sex, D-dimer and index VTE site as predictors. *Patients/Methods:* Nine hundred and four patients pooled from five prospective studies evaluating the prognostic value of D-dimer for VTE recurrence served as the validation cohort. The validity of the VPM in stratifying patients according to their relative recurrence risk (discrimination) and in predicting the absolute recurrence risk (calibration) was tested with survival analysis methods. *Results:* The ability of the VPM to distinguish patients' risk for recurrent VTE in the validation cohort was at least as good as in the original cohort, with a calibration slope of 1.17 (95% confidence interval 0.71–1.64; $P = 0.456$ for the hypothesis of a significant difference from 1), and a c-statistic of 0.626 (vs. 0.651 in the original derivation cohort). The VPM absolute predictions in terms of cumulative rates tended to underestimate the observed recurrence rates at 12 months. *Conclusions:* By using a pooled individual patient database as a validation cohort, we confirmed the ability of the VPM to stratify patients with a first unprovoked VTE according to their risk of recurrence.

Keywords: decision support technique; pulmonary embolism; recurrence; venous thromboembolism; venous thrombosis.

Correspondence: Paul Kyrle, Department of Medicine I, Medical University of Vienna, Wahringer Guertel 18-20, 1090 Vienna, Austria.
Tel.: +43 664 5080608; fax: +43 1 40400 40300.
E-mail: paul.kyrle@meduniwien.ac.at

Introduction

Patients with unprovoked venous thromboembolism (VTE) who have received 3–6 months of anticoagulant therapy have a recurrence risk of 5–10% per year after anticoagulation is stopped [1–3]. The challenge for the clinician is to stratify such patients according to their risk of recurrent VTE, so as to distinguish patients who would derive a net clinical benefit from indefinite anticoagulant therapy from those in whom long-term anticoagulation would not be justified. Several clinical and laboratory risk factors have been identified as determinants of recurrence risk in patients with unprovoked VTE [4,5]. Three clinical prediction models, which have embedded some of these risk factors, have been developed but are not yet validated [6–8]. Among these prediction models, the Vienna Prediction Model (VPM) [7] provides an easy-to-use web-based risk

calculator (http://cemsiis.meduniwien.ac.at/en/kb/science-research/software/clinical-software/recurrent-vte/) that incorporates patient sex, VTE site and D-dimer to estimate VTE recurrence risk in individual patients after anticoagulation is stopped. Validating a clinical prediction model such as the VPM in an independent population is a pivotal step towards confirming its validity and generalizability [9,10]. This step should comprise both the quantification of the model's ability to distinguish between patients with and those without the event of interest (discrimination), and a comparison between observed and predicted event rates for groups of patients (calibration) [9,10].

We aimed to externally validate the VPM by using an independent individual patient dataset that was pooled from prospective cohort studies that assessed, in part, the clinical utility of D-dimer in predicting recurrent VTE. We used methods proposed in the literature to validate predictive models that were developed, as with the VPM, by the use of Cox (time-to-event) analyses [9,11,12].

Methods

VPM

The VPM was derived from 929 patients with unprovoked VTE (derivation cohort) recruited from four thrombosis centers in Vienna, Austria, between 1992 and 2008 [7]. In this cohort, the following patients were excluded: women with estrogen-associated VTE; patients with a deficiency of antithrombin, protein C, or protein S, or with a lupus anticoagulant; double heterozygous or homozygous carriers of the factor V Leiden and prothrombin mutations; and patients with cancer-associated VTE. The VPM was based on a multivariable Cox regression of seven candidate risk factors, comprising age, sex, VTE site (pulmonary embolism, proximal deep vein thrombosis, or distal deep vein thrombosis), body mass index, factor V Leiden, prothrombin mutation, and D-dimer measured after anticoagulant therapy had been stopped. Only sex, VTE site and D-dimer were significant predictors of the recurrence risk and were included in the final model [7].

Validation cohort

We validated the VPM in a multicohort dataset comprising individual patient data originally obtained from seven prospective studies that included the Vienna study [13–19]. We found no significant heterogeneity between the seven studies in a previous meta-analysis evaluating the predictive value of D-dimer for recurrent VTE [1,20]. To obtain an independent validation cohort for this analysis, we excluded the Vienna study from this multicohort database. To ensure consistency of patient characteristics in the derivation and validation cohorts, we excluded

women with estrogen-associated VTE (not included in the Vienna study), patients with missing D-dimer data, and patients with incomplete data for classification of the index VTE site. Patients excluded because of missing or incomplete data ($n = 266$) differed slightly from those included in the validation cohort ($n = 904$), as the proportion of males (51.5% vs. 60.5%) and median age (median 64 years vs. 68 years) were lower. No differences were found regarding the frequency of and time to VTE recurrence ($P = 0.59$ for by-study stratified analysis). Figure 1 summarizes the generation of the validation cohort from the original multistudy database. To meet the above-mentioned criteria, the final validation cohort was composed of patients derived from five of the seven original studies. All patients in the derivation and validation cohorts received at least 3 months of anticoagulant therapy and had follow-up for symptomatic recurrent VTE, which comprised deep vein thrombosis and/or pulmonary embolism. All outcome events were objectively confirmed by compression ultrasound, lung scanning, or computed tomography.

Statistical analysis

For the VPM, not only the relative risk (in terms of hazard ratios [HRs]) associated with each risk factor (sex, index VTE site, and D-dimer) [7] but also the Cox-derived cumulative hazards (or cumulative rates) of recurrent VTE at 12 months were provided in the form of a risk calculator. From the latter, we could approximate the predicted baseline risks and calculate the cumulative rates of recurrence at that time point for each patient of the validation cohort. In this way, we could test both the discrimination and calibration of the VPM in the validation cohort.

Validation of the predicted relative risk of recurrence (discrimination)

First, we assessed the validity of the predicted relative risk of recurrence associated with the predictors in the VPM (sex, index VTE site, and D-dimer), also called the prognostic index [12]. The Vienna prognostic index ($X\beta_{Vienna}$) corresponded to the linear predictor from the Vienna Cox model, which was calculated for each patient as the sum of the predictors weighted for the corresponding Cox regression coefficients (back-calculated from the published HR). $X\beta_{Vienna}$ expresses the risk of an individual as compared with an individual with a prognostic index of 0, so that patients or groups with higher values for $X\beta_{Vienna}$ have a worse prognosis [12]. Thus, we calculated $X\beta_{Vienna}$ for each patient of the validation set, and then we performed a Cox regression in the validation cohort with time-to-recurrence as outcome and $X\beta_{Vienna}$ as predictor. The regression coefficient (α) thus obtained for $X\beta_{Vienna}$, also called the calibration slope, provided
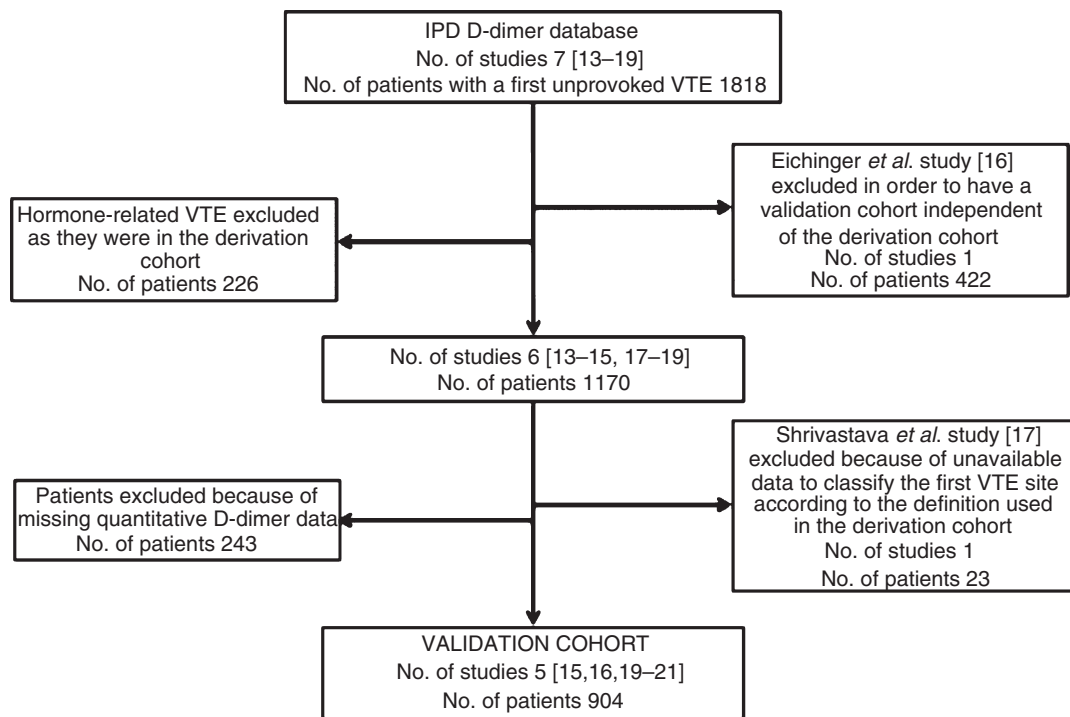
Fig. 1. Flow chart: generation of the validation cohort from the multistudy D-dimer database. IPD, individual patient data; VTE, venous thromboembolism.

information for both the discrimination and the calibration/accuracy of the VPM in the validation cohort (taking into account that the same coefficient would be, by definition, equal to 1 in the derivation cohort) [11,12]. Discrimination of the VPM in the validation cohort was also measured by the use of Harrell's *c*-statistic. Further details of these statistical methods are provided in Data S1.

Validation of the predicted absolute risk of recurrence (calibration)

We next evaluated the performance of the VPM by testing the accuracy of the predictions of the absolute risk (cumulative rates) made by the VPM in the validation cohort at 12 months. We first used the common graphical calibration approach (calibration plot), in which absolute predicted and observed risks (taking into account the time-to-event) were plotted. In particular, we plotted the VPM-predicted and the observed cumulative rates in the validation cohort for five groups (quintiles) at increasing predicted risk [9,12]. We repeated the analysis with a higher number of groups (20). The observed cumulative rates for each group were calculated with the Nelson–Aalen estimator at 12 months. A random effect model was used to test the statistical significance of the difference between observed and predicted cumulative rates.

We adopted an additional approach to further test calibration, i.e. the use of a parametric survival model, which, unlike a Cox model, allows the function for the

baseline risk of recurrence to be parameterized. Details of the method are shown in Data S2.

Sensitivity analyses

As the Vienna derivation cohort was, on average, younger than the validation cohort (Table 1), the validation processes were repeated with a subset of the validation cohort comprising only patients aged ≤ 65 years (Data S3).

To account for the multistudy nature of the individual patient database, all survival semiparametric and parametric models were performed with and without stratification by study. The proportional hazard assumption of the Cox calibrating models was checked by the use of Schoenfeld's residuals. All analyses were performed with STATA statistical software , version 12.0 (StataCorp 800-STATAPC, College Station, TX, USA).

Results

Patient characteristics

Table 1 compares the patient characteristics of the derivation and validation cohorts. Patients included in the validation cohort tended to be older with less frequent presentation of the index event as distal vein thrombosis, and with higher postanticoagulation D-dimer levels, than those included in the derivation cohort. The overall median postanticoagulation follow-up was 22 months (25th, 75th percentiles: 14 months, 29 months) in the validation

Table 1 Validation cohort: baseline characteristics in comparison with the derivation cohort*

Variables	Derivation cohort (n = 929)*	Validation cohort (n = 904)
Age (years), median (25th, 75th percentiles)	54 (43, 63)	68 (58, 76)
Men, n (%)	562 (60.5)	547 (60.5)
Venous thromboembolism site, n (%)		
PE	438 (47.1)	291 (32.2)
Proximal DVT	327 (35.2)	601 (66.5)
Distal DVT	164 (17.7)	12 (1.3)
D-dimer (µg L^{-1}), median (25th, 75th percentiles; range)	355 (236, 558; NA)†	520 (310, 906; 80–6740)
Follow-up time (months), median (25th, 75th percentiles)	43.3 (14.7, 78.5)	21.6 (14.0, 29.1)
Recurrent VTE, n (%)	176 (18.9)	123 (13.6)

DVT, deep vein thrombosis; NA, not available; PE, pulmonary embolism; VTE, venous thromboembolism. *From the derivation paper [7].
†Quantitative D-dimer values available for 832 of 929 patients [7].

cohort, and 43 months (25th, 75th percentiles: 15 months, 78 months) in the derivation cohort [7].

There were 123 (13.6%) recurrent VTEs in the validation cohort, of which 84 (68.3%) occurred during the first year after anticoagulation had been stopped. The cumulative rates of recurrent VTE after 1 year and 5 years were 10.0% (95% confidence interval [CI] 8.1–12.4%) and 30.7% (95% CI 21.3–44.2%), respectively (Fig. 2). As few studies in the validation cohort had data after 2 years of patient follow-up (Fig. 2), we restricted our analysis to 12 months. Table 2 compares the observed frequency of recurrence (as raw frequencies and cumulative rates) with the cumulative rates at 12 months predicted by the VPM for five risk groups in the validation cohort.

VPM validation

The Cox calibration slope α had a point estimate of 1.2, which was not statistically significantly different from 1, indicating that $X\beta_{Vienna}$ had equal-to-better discrimination in the validation cohort than in the derivation cohort, as confirmed by the *c*-statistic being slightly lower than in the derivation cohort (0.626 vs. 0.651; Data S1).

The calibration plot (Fig. 3) showed that the predicted cumulative rates tended to underestimate the observed cumulative rates at 12 months (P = 0.02 for a statistically significant difference between predicted and observed).

The results for the calibration coefficient obtained with the parametric models overlapped with those obtained
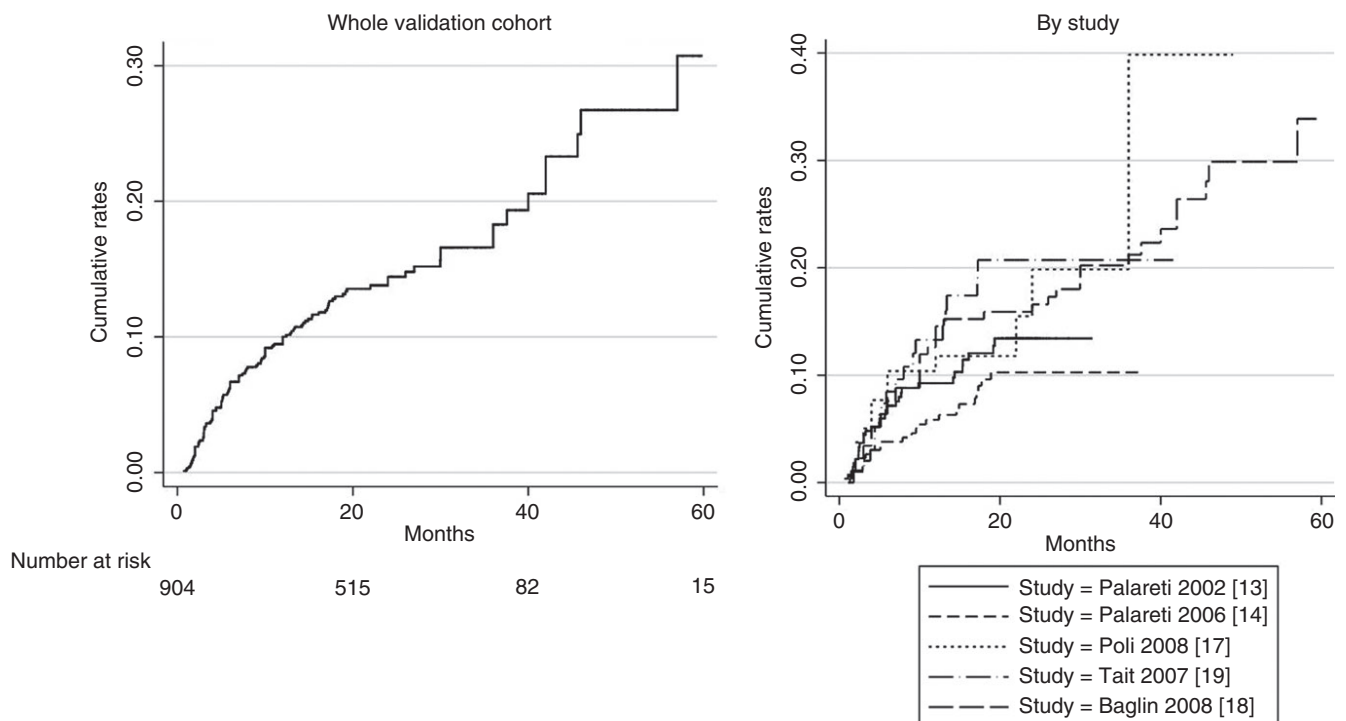

Fig. 2. Observed cumulative rates of recurrence in the validation cohort and by study included in the validation cohort. Few studies provided substantial data for a follow-up longer than 24 months.

Table 2 Predicted risk of recurrence and observed events/rates by risk groups

VPM quintiles* (number of patients)	Observed VTE recurrences, no. (raw percentage)	Observed cumulative rate at 12 months† (95% CI)	Predicted cumulative rate at 12 months, mean (range)
1 (181)	13 (7.2)	5.1 (2.7–9.9)	3.0 (1.3–3.7)
2 (184)	19 (10.3)	7.1 (4.0–12.5)	4.3 (3.7–4.9)
3 (180)	23 (12.8)	9.0 (5.4–14.9)	5.4 (4.9–6.0)
4 (179)	28 (15.6)	13.3 (8.8–20.3)	6.6 (6.0–7.5)
5 (180)	40 (22.2)	15.9 (10.9–23.4)	9.5 (7.5–18.5)

CI, confidence interval; VPM, Vienna Prediction Model; VTE, venous thromboembolism. *1, 2, 3, 4 and 5 correspond to groups (quintiles) at increasing predicted risk in the validation cohort. †Calculated with the Nelson–Aalen estimator.
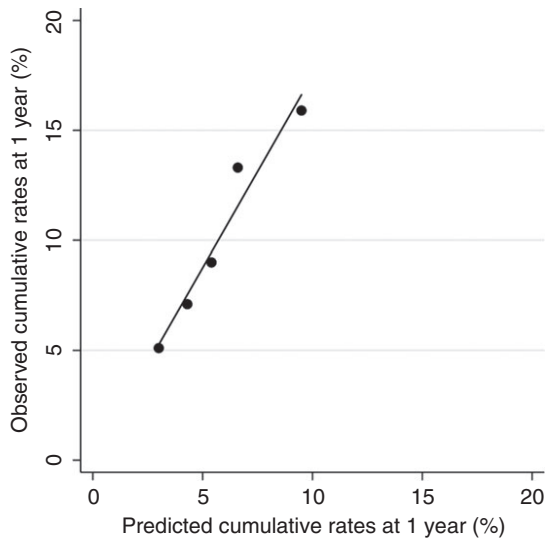

Fig. 3. Calibration plot comparing the observed cumulative rates of recurrence (as calculated with the Nelson–Aalen estimator) and the cumulative rates predicted by the Vienna Prediction Model, at 12 months after anticoagulation withdrawal, for five risk groups (quantiles) into which the validation cohort was divided. Each point represents the observed–predicted comparison within each group. The line depicts the results of linear regression used to approximate the average relationship between the observed and the predicted cumulative rates. Similar results were obtained when the observed and the predicted rates were plotted for a higher number of groups [20].

with the Cox models. The estimated parameters for the baseline risk function were similar to those obtained from the derivation cohort (Data S2).

Sensitivity analyses

In the validation cohort, there was a higher risk of recurrence in younger than in older patients. There were 370 (41%) patients in the validation cohort who were aged ≤ 65 years. During a median follow-up of 22 months (range: 15.3–30.0 months), 52 (14.0%) of these patients developed recurrent VTE. In this patient subset, the calibration slope was comparable to those obtained in the main analyses with a wider confidence interval due to the smaller sample size. Details of the results for patients aged ≤ 65 years are shown in Data S3.

Discussion

We externally validated the VPM, a clinical prediction guide developed to estimate the risk of disease recurrence in patients with a first unprovoked VTE by using sex, index VTE site and D-dimer levels as predictors. We used a pooled individual patient database from five studies as a validation cohort. The ability of the VPM to distinguish patients' risk for recurrent VTE in the validation cohort was at least as good as in the original cohort. The robustness of the VPM in distinguishing between patients at high or low risk of recurrence in the validation cohort is evident, despite differences in patient characteristics in the two cohorts. Hence, patients in the validation cohort were older, had higher D-dimer levels, less often had distal DVT, and experienced recurrences over a slightly shorter time-to-event. Thus, although the derivation cohort showed a higher cumulative raw frequency of recurrences than the validation cohort (19% vs. 14%), owing to the longer average follow-up, a 25% cumulative rate was reached at 5 years in the derivation cohort [7], whereas it was reached within 4 years in the validation cohort.

This study, to our knowledge, is the first external validation of a clinical prediction guide for recurrent VTE risk. We used rigorous methodology for a time-to-event model to validate the VPM [9,11,12], and appraised the model's performance in the new population to predict both the relative effect of the risk factors and the absolute risk of recurrence. In terms of relative increase in risk across groups, the performance of the VPM in distinguishing recurrence risk that was observed in the original study was confirmed in the validation cohort. In terms of predicting the absolute recurrence risk, the VPM tended to slightly underestimate the absolute recurrence rates found in the validation cohort. Absolute observations and predictions could only be performed over 12 months of follow-up, because of limited outcome data after 12 months in the validation cohort studies. The comparison might have been affected by the estimation methods, as the need to account for censoring meant that the 'observed' recurrence rates had to be estimated (i.e. with the Nelson–Aalen estimator), and not simply reported. In addition, the way in which the observed recurrence rates were estimated was necessarily different from the way in

which the predicted recurrence rates were estimated (i.e. derived from a Cox model). Notwithstanding the possible role of the methods used, it is plausible that the different case mixes in the validation cohort and in the derivation cohort led to different absolute rates of recurrences.

The clinical implications of this study should be considered within the context of current clinical practice guidelines. On the basis of clinical study data [6,21], one guideline suggests that patients with unprovoked VTE who are at high risk of recurrence should be considered for indefinite anticoagulant therapy if they are at low risk for bleeding [22]. However, even in patients with a low bleeding risk, costs (for patients and healthcare systems), inconvenience, insurability and other potential drawbacks of indefinite anticoagulation should also be considered. Thus, distinguishing patients at high or low risk of recurrent VTE may have far-reaching ramifications. Easy-to-use prediction models that integrate clinical and laboratory risk factors are therefore attractive for guiding clinical decisions. In distinguishing recurrent VTE risk, three prediction rules are currently available: the VPM, the HERDOO-2, and the DASH score. Of these, the VPM is now the first to have been externally validated. It is important for caution to be exercised when such models are used to predict absolute risks for recurrent VTE in individual patients, as a model's performance in discrimination and calibration is tested in patient groups and not in individuals [12,23,24].

There are potential limitations of our study. First the optimal approach to validate a clinical prediction guide by using survival analyses with the aims of accounting for censoring and being consistent with the derivation methods, and to use a pooled population as a validation cohort, is not yet established. Second, as is often the case in clinical prognostic studies, in our comparisons we did not account for the uncertainty around predictions, but focused on the point estimates. Uncertainty around point predictions may affect the reliability and usability of a prediction model, especially when we are looking for instruments to use at an individual level, for which the stochastic uncertainty found around the average estimates should be even further inflated. Third, our findings are not applicable to patients with multiple VTE events, with severe thrombophilia, or with VTE occurring in the presence of temporary risk factors (e.g. recent surgery, or estrogen-containing oral contraceptives), or in cancer patients. Fourth, quantitative D-dimer levels were obtained with different D-dimer assays in the derivation cohort and in the studies comprising the validation cohort [1]. This might, in part, have contributed to the different D-dimer level distributions observed in the two cohorts. The use of different D-dimer levels is inevitable when the VPM is applied in general routine practice. We therefore believe that, in fact, this can also be seen as a strength of our analysis, as we could show good discrimination of the model despite the use of different D-dimer assay systems.

In conclusion, our study is an important step towards incorporating a clinical prediction guide for VTE recurrence into routine practice. Additional external validation studies and, most importantly, clinical impact or management studies [25] are now needed to formally assess the impact of the VPM on clinically relevant outcomes when it is used to decide on the duration of anticoagulation in patients with a first unprovoked VTE.

Disclosure of Conflict of Interests

M. Cushman reports receiving personal fees from Daiichi Sankyo, during the conduct of the study. A. Tosetto reports receiving non-financial support from Instrumentation Laboratories, outside the submitted work. The other authors state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. VPM validation: calibration by the use of Cox regression models.
Data S2. VPM validation: calibration by the use of Weibull regression models.
Data S3. Validation analyses on patients aged ≤ 65 years in the validation cohort.

References

1 Douketis J, Tosetto A, Marcucci M, Baglin T, Cushman M, Eichinger S, Palareti G, Poli D, Tait RC, Iorio A. Patient-level meta-analysis: effect of measurement timing, threshold, and patient age on ability of D-dimer testing to assess recurrence risk after unprovoked venous thromboembolism. *Ann Intern Med* 2010; **153**: 523–31.

2 Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, Moia M, Guazzaloca G, Bertoldi A, Tomasi C, Scannapieco G, Ageno W. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. *N Engl J Med* 2001; **345**: 165–9.

3 Boutitie F, Pinede L, Schulman S, Agnelli G, Raskob G, Julian J, Hirsh J, Kearon C. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. *BMJ* 2011; **342**: d3036.

4 Kyrle PA, Rosendaal FR, Eichinger S. Risk assessment for recurrent venous thrombosis. *Lancet* 2010; **376**: 2032–9.

5 Marcucci M, Iorio A, Douketis J. Management of patients with unprovoked venous thromboembolism: an evidence-based and practical approach. *Curr Treat Options Cardiovasc Med* 2013; **15**: 224–39.

6 Rodger MA, Kahn SR, Wells PS, Anderson DA, Chagnon I, Le Gal G, Solymoss S, Crowther M, Perrier A, White R, Vickars L, Ramsay T, Betancourt MT, Kovacs MJ. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. *CMAJ* 2008; **179**: 417–26.

7 Eichinger S, Heinze G, Jandeck LM, Kyrle PA. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model. *Circulation* 2010; **121**: 1630–6.

8 Tosetto A, Iorio A, Marcucci M, Baglin T, Cushman M, Eichinger S, Palareti G, Poli D, Tait RC, Douketis J. Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). *J Thromb Haemost* 2012; **10**: 1019–25.

9 Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; **15**: 361–87.

10 Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. *BMJ* 2009; **338**: b605.

11 van Houwelingen HC. Validation, calibration, revision and combination of prognostic survival models. *Stat Med* 2000; **19**: 3401–15.

12 Royston P, Altman DG. External validation of a Cox prognostic model: principles and methods. *BMC Med Res Methodol* 2013; **13**: 33.

13 Palareti G, Legnani C, Cosmi B, Valdré L, Lunghi B, Bernardi F, Coccheri S. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. *Circulation* 2003; **108**: 313–18.

14 Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A, Pengo V, Ghirarduzzi A, Pattacini C, Testa S, Lensing AW, Tripodi A. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med* 2006; **355**: 1780–9.

15 Shrivastava S, Ridker PM, Glynn RJ, Goldhaber SZ, Moll S, Bounameaux H, Bauer KA, Kessler CM, Cushman M. D-dimer, factor VIII coagulant activity, low-intensity warfarin and the risk of recurrent venous thromboembolism. *J Thromb Haemost* 2006; **4**: 1208–14.

16 Eichinger S, Minar E, Bialonczyk C, Hirschl M, Quehenberger P, Schneider B, Weltermann A, Wagner O, Kyrle PA. D-dimer levels and risk of recurrent venous thromboembolism. *JAMA* 2003; **290**: 1071–4.

17 Poli D, Antonucci E, Ciuti G, Abbate R, Prisco D. Combination of D-dimer, F_{1+2} and residual vein obstruction as predictors of VTE recurrence in patients with first VTE episode after OAT withdrawal. *J Thromb Haemost* 2008; **6**: 708–10.

18 Baglin T, Palmer CR, Luddington R, Baglin C. Unprovoked recurrent venous thrombosis: prediction by D-dimer and clinical risk factors. *J Thromb Haemost* 2008; **6**: 577–82.

19 Tait RC, Lowe GD, McColl MD, MacMahon AD, Robertson L, King L. Predicting risk of recurrent venous thrombosis using a 5-point scoring system including fibrin D-dimer. *J Thromb Haemost* 2007; **5**(Suppl. 2): OM 260.

20 Marcucci M, Smith CT, Douketis JD, Tosetto A, Baglin T, Cushman M, Eichinger S, Palareti G, Poli D, Tait RC, Iorio A. Patient-level compared with study-level meta-analyses demonstrate consistency of D-dimer as predictor of venous thromboembolic recurrences. *J Clin Epidemiol* 2013; **66**: 415–25.

21 Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, Iotti M, Tormene D, Simioni P, Pagnan A. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1626 patients. *Haematologica* 2007; **92**: 199–205.

22 Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR; American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**(Suppl. 2):e419S–94S.

23 Altman DG, Royston P. What do we mean by validating a prognostic model? *Stat Med* 2000; **19**: 453–73.

24 Henderson R, Keiding N. Individual survival time prediction using statistical models. *J Med Ethics* 2005; **31**: 703–6.

25 Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. *BMJ* 2009; **338**: b606.