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ORIGINAL ARTICLE

Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH)

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

**Department of Hematology, S. Bortolo Hospital, Vicenza, Italy; †Departments of Clinical Epidemiology and Biostatistics and Medicine, McMaster University, Hamilton, Canada; ‡Department of Medicine, University of Perugia, Perugia, Italy; §Department of Hematology, Addenbrookes Hospital, Cambridge, UK; ¶Department of Medicine, University of Vermont, Burlington, US; **Department of Medicine I, Medical University of Vienna, Vienna, Austria; ††Department of Angiology and Blood Coagulation, University Hospital S. Orsola-Malpighi, Bologna; ‡‡Thrombosis Center, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; §§Department of Haematology, Royal Infirmary, Glasgow, UK; and ¶¶Department of Medicine, McMaster University, Hamilton, Canada*

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Summary. *Background:* In patients with unprovoked venous thromboembolism (VTE), the optimal duration of anticoagulation is anchored on estimating the risk of disease recurrence. *Objectives:* We aimed to develop a score that could predict the recurrence risk following a first episode of unprovoked VTE, pooling individual patient data from seven prospective studies. *Methods:* One thousand eight hundred and eighteen cases with unprovoked VTE treated for at least 3 months with a vitamin K antagonist were available for analysis. Optimism-corrected Cox regression coefficients were used to develop a recurrence score that was subsequently internally validated by bootstrap analysis. *Results:* 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 and were used to derive a prognostic recurrence score (DASH, D-dimer, Age, Sex, Hormonal therapy) showing a satisfactory predictive capability (ROC area = 0.71). The annualized recurrence risk was 3.1% (95% confidence interval [CI], 2.3–3.9) for a score ≤ 1, 6.4% (95% CI, 4.8–7.9) for a score = 2 and 12.3% (95% CI, 9.9–14.7) for a score ≥ 3. By considering at low recurrence risk those patients with a score ≤ 1, life-long anticoagulation might be avoided in about half of patients with unprovoked VTE. *Conclusions:* The DASH prediction rule appears to predict recurrence risk in patients with a first unprovoked VTE and may be useful to decide whether anticoagulant therapy should be continued indefinitely or stopped after an initial treatment period of at least 3 months.

Keywords: D-dimer, recurrence, risk, venous thrombosis

Correspondence: Alberto Tosetto, Hematology Department, S. Bortolo Hospital, Via Rodolfi, 36100 Vicenza, Italy
Tel.: +39 0444 753679; fax: +39 0444 753922.
E-mail: tosetto@hemato.ven.it

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Introduction

The optimal duration of anticoagulant therapy in patients with a first episode of venous thromboembolism (VTE), occurring in the absence of antecedent major risk factors, is controversial. Based on a 5-year cumulative risk of disease recurrence of 25–30% in these patients [1], current guidelines recommend at least 3 months of treatment with a vitamin K antagonist (VKA), and an option for life-long anticoagulation in patients at low risk of bleeding [2]. While preventing most recurrences, this approach has several drawbacks. First, whereas the risk of recurrence appears to diminish with time [1], the risk of anticoagulant-related hemorrhage increases with ongoing anticoagulation and advancing age. Hence, the net clinical benefit of indefinite anticoagulation may vary considerably over the long term. Second, the risk of recurrent VTE may be lower in certain patients. For example, it appears that women have 45% lower risk of recurrent VTE than men (12% vs. 22% 3-year cumulative risk) [3] and that patients with a negative (or normal) D-dimer have 60% lower risk than those with abnormal D-dimer (3.5% vs. 8.9% annual risk) when D-dimer is measured after stopping anticoagulation [4]. Therefore, at least in some patient subgroups, the risk of recurrence approximates the annual risk of anticoagulant-related major hemorrhage, which is estimated at 1–3% overall [5], and up to 5% in the elderly [6].

Developing a clinical prediction guide for recurrent VTE is problematic, because the limited statistical power of available prospective studies precludes an adequate assessment of

interactions between individual patient characteristics, an issue that cannot be addressed by study-level meta-analyses. One way to overcome this problem is by pooling data from available studies in a patient-level meta-analysis. We therefore undertook a meta-analysis of individual patient data derived from prospective studies that included patients with a first VTE who received conventional anticoagulant therapy and were followed for up to 5 years after treatment was stopped. We aimed to develop a prediction guide that could help stratify patients with a first unprovoked VTE according to their risk of disease recurrence and, thereby, identify patients who may benefit from long-term (or stopping of) anticoagulant therapy.

Methods

The study design was developed by a core group of investigators (A.T., J.D. and A.I.), who prespecified the study selection criteria and data analysis plan, and was approved by all study co-authors before the beginning of the data collection phase. Criteria for selection of the source studies that were included in this patient-level meta-analysis [7–13] have been previously published [14].

Definition of eligible VTE cases and other clinical variables

A priori, we defined eligible VTE cases (and applied this definition to all source studies) as those that occurred in the absence of an antecedent major clinical VTE risk factor comprising surgery, trauma, active cancer, immobility, or pregnancy and the puerperium. VTE that occurred in association with hormonal therapy (oral contraceptive [OC] or hormone replacement therapy [HRT]) or a thrombophilic blood abnormality and no other VTE risks were also included. This was justified because hormonal therapy is considered a weak risk factor for VTE and because thrombophilic abnormalities, although increasing risk of initial VTE, do not appear to increase risk of recurrent VTE [15]. OC and HRT were combined because both types of oral hormonal therapy confer a similar 2- to 4-fold increased risk of VTE [16]. In our study, all hormonal therapy users had received an oral OC or oral HRT and our findings do not pertain to users of non-oral forms of hormonal therapy. Only cases of proximal vein deep vein thrombosis (DVT) or pulmonary embolism (PE), isolated or associated with DVT, were considered as eligible index events.

Patients with known antiphospholipid antibodies or antithrombin deficiency were excluded because these patients were excluded from the source studies. D-dimer was considered positive if abnormal in a qualitative test or ≥ 500 ng/mL in a quantitative test based on a measurement taken after stopping anticoagulant therapy, which was typically done 3–5 weeks after stopping such treatment.

Patient follow-up and outcomes

Follow-up started when anticoagulant therapy was stopped and ended when one of the following occurred: symptomatic recurrent VTE; death from another cause; resumption of anticoagulant therapy for another reason; or the study ended.

Statistics and clinical prediction model development

We first modeled the recurrence risk in all eligible patients using Cox regression, stratified by study, to identify variables associated with increased risk of recurrence, and starting with a full model that included the following variables: D-dimer; age; patient sex; hormone use at time of VTE (in women); mode of initial presentation (DVT alone or DVT and PE); and previous history of cancer, not active at the time of initial event. This limited set of variables was chosen to reduce over-fitting and because in a previous analysis on the same dataset the timing of post-anticoagulation D-dimer testing, the duration of anticoagulation, body-mass index and thrombophilia were not associated with an increased risk of recurrent VTE [14]. Variables were entered in the model as dichotomized dummy variables, and age as quartiles to control for potential non-linear effect of age, using linear splines with knots fixed at each quartile. Stratification according to source study was carried out in all Cox regression models to allow for potential across-study differences in patient characteristics and VTE recurrence rates. Model reduction was initially achieved using a backward approach, excluding from the model those variables with a $P > 0.10$. Because backward elimination on the whole dataset may lead to excessive optimism (i.e. result in a degree of classification that will not be confirmed in another, independent dataset), we evaluated the degree of over-optimism both by a heuristic formula [17] and by linear shrinkage with bootstrapping [18]. In practise, these methods calculate the degree of correction that should be applied to regression estimates: for example, for a calculated optimism of 0.02 and a regression coefficient of 0.90, optimism-corrected coefficient is 0.90*(1–0.02) = 0.88.

We therefore developed a prognostic score based on the Cox regression coefficients, adjusted for over-optimism, by multiplying all regression coefficients for a common factor and rounding the results to the nearest integer. In each individual, the final recurrence score was the linear combination (sum) of all scores for each predictor; the overall predictive ability of the score was assessed using time-dependent receiver-operator curves (ROC) analysis [19]. Incidence rates of recurrent VTE were calculated for each recurrence score in the whole cohort, aiming to identify a score threshold for low-risk patients. For this purpose, based on a consensus that an annual VTE recurrence rate below 5% was an acceptable risk [20], we graphically sought the score that could result in a recurrence risk below 5%. Further to this, we carried out an internal validation to verify the recurrence rate and its upper confidence interval (in subjects having a recurrence score below the previously identified cut-off), using a bootstrap procedure. In this procedure, a new sample of 1818 subjects was created by randomly drawing (with replacement) a subject from those of the original cohort and the recurrence rate is estimated in the new dataset (thus,

although statistically very unlikely, it is theoretically possible that a new sample formed by 1818 replication of the same subject could be created). This process was repeated 500 times.

All analyses were carried out using Stata (Stata, College Station, TX, USA) and R software packages (libraries Design, rms and survivalROC) [21].

Results

Patient characteristics

From the pooled database of 2554 patients, we excluded patients with calf or provoked DVT or PE (727 patients) and those whose follow-up ended before D-dimer was measured (nine patients). The median follow-up duration in the studied cohort, totaling 1818 patients, was 22.4 months; 826/1818 patients (45.4%) had an abnormal D-dimer measured a median of 30 days after anticoagulant therapy was stopped.

The patient characteristics at the time of the initial VTE are shown in Table 1.

Table 1 Clinical characteristics of the investigated cohort

	Recurrent VTE (n = 239)	No recurrence (n = 1579)	P
Age, median	63	61	0.184
Males, %	69.4	48.6	< 0.0001
Body-mass index, median*	27.2	27.2	0.923
Use of hormones at time of index VTE, % of females	19.2	36.2	0.003
Thrombophilia, %†	23.4	20.9	0.396
Abnormal D-dimer, %	67.7	42.0	< 0.0001
Duration of anticoagulation (months), median	6.7	6.8	0.570

*Available in 802 subjects, †Thrombophilia data unavailable for 33 subjects (2.3%)

Clinical prediction guide

With univariate analysis, significant differences in age, sex, hormonal therapy use at the time of initial VTE and post-anticoagulation D-dimer status were observed between patients with and without recurrent VTE. These variables – together with the mode of presentation (DVT alone or DVT and PE) and previous history of cancer, not active at the time of initial event – were included in a backward multivariable Cox regression analysis, stratified by source study; there were no missing data in this analysis. Table 2 reports the results for both the full and reduced (i.e. after backward elimination) model. Patients in the first quartile of age, comprising subjects aged 14–48 years, had a significantly higher risk of recurrent VTE than subjects aged ≥ 48 years (≥ 2nd quartile); in subsequent analyses, we therefore included age as a dichotomous variable coding subjects as younger or as older than 50 years. After backward elimination, D-dimer, age < 50 years, patient sex and hormone use at time of initial VTE were retained in the model. Age < 50 years, sex and hormone use were retained by the backward elimination even in the absence of D-dimer in the model; no significant interaction was observed between age and sex or age and hormone use.

Using both the heuristic formula and linear shrinkage with bootstrapping, the degree of optimism of the final Cox model was 0.026; moreover, all variables identified by Cox regression were retained after bootstrapped shrinkage. All regression coefficients were recalibrated by multiplying for the optimism correction factor (0.974) and based on the corrected coefficients, we derived a prognostic recurrence score. In this analysis, patients received the following scores: +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 ($D_2A_1S_1H_{-2}$ score, hereafter referred to as DASH score). Time-dependent ROC analysis showed that the DASH score had a predictive capability

Table 2 Multivariate Cox regression analysis and derivation of prediction score

	Full model		After backward elimination		Optimism corrected	Derived score†
	β coefficient	P	β coefficient	P		
D-dimer (abnormal vs. normal)	1.01	< 0.0001	0.99	< 0.0001	0.96	2
Age						
1st quartile (14–47 years) vs. 4th	0.57	0.005	0.45*	0.002	0.43	1
2nd quartile (47–61 years) vs. 4th	−0.12	0.565	–	–	–	
3rd quartile (61–72 years) vs. 4th	0.23	0.179	–	–	–	
Men (vs. women with no previous hormone-associated VTE)	0.62	< 0.0001	0.60	< 0.0001	0.58	1
Women with hormone-associated VTE (vs. women with no previous hormone-associated VTE)	−0.82	0.004	−1.08	0.002	−1.05	−2
Prior history of cancer	−0.09	0.257	–	–	–	
PE or VTE + PE (vs. VTE without PE)	0.11	0.686	–	–	–	–

*Computed as age < 50 years vs. ≥ 50 years after quartile analysis. †Scores were computed by doubling and next-integer rounding of optimism-corrected β coefficients.

significantly higher than that based on D-dimer alone (AUC = 0.71 vs. 0.61, $P < 0.0001$). Use of the regression beta coefficients instead of scores resulted in a marginally higher AUC (0.72).

Risk of recurrent VTE according to clinical prediction guide

Table 3 and Fig. 1 show the distribution of DASH scores in the studied patients and the associated annual risk of recurrent VTE; Fig. 2 reports the stratified Cox regression-derived cumulative rates of recurrence-free survival according to the DASH score. For example, in a patient with a DASH score of 1, it may be considered acceptable to stop anticoagulation after 3–6 months of treatment because the score predicts an annual recurrence risk of 3.9% and a 1-year cumulative recurrence of 5.1%. In the entire study sample, the annual incidence of recurrent VTE was 3.1% (95% confidence interval [CI], 2.4–3.9) in patients with a DASH score ≤ 1 and 9.3% (95% CI, 8.1–10.8) in patients with a DASH score > 1. Considering patients with a DASH score ≤ 1as having an acceptably low risk of recurrence, life-long anticoagulation might have been avoided in 51.6% of patients in our cohort.

We used a bootstrap algorithm to internally validate our results, focusing on the recurrence rate in subjects having a DASH score ≤ 1. Based on 500 resamplings (with replacement) of the dataset, the annual rate of recurrence in those having a DASH score ≤ 1 was confirmed at 2.9% (95% bootstrapped CI, 2.2–3.8). As further support to the consistency of our findings, Fig. 3 shows the annual rate of recurrence for patients having a DASH score ≤ 1 or > 1 across all included studies.

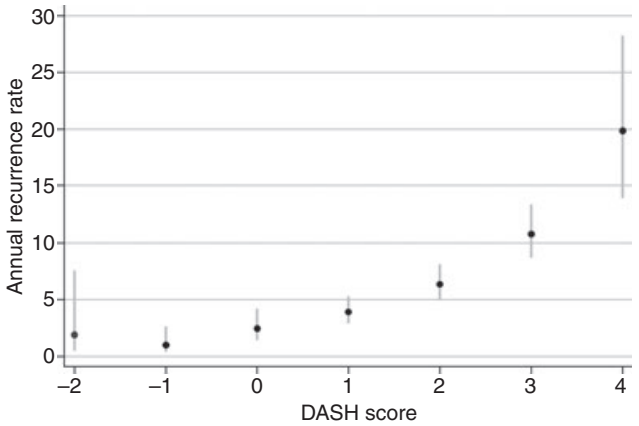

Fig. 1. Annual recurrence rates according to DASH score. Bars represent the 95% confidence interval. The horizontal line indicates the consensus acceptable annual VTE recurrence rate (5%).

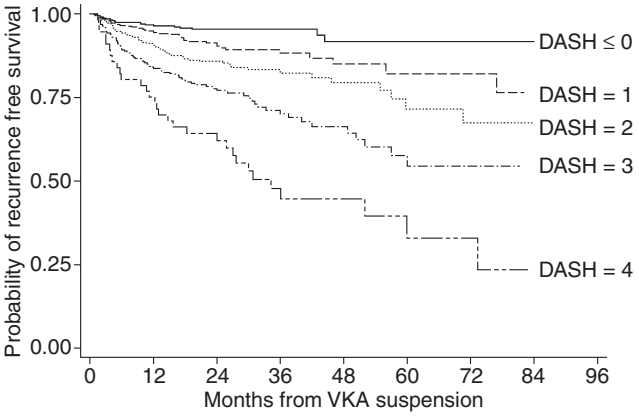

Fig. 2. Stratified Cox regression-derived cumulative rates of recurrence-free survival according to level of DASH score. Scores ≤ 0 were grouped together because of tight overlapping of these three scores.

Discussion

We aimed to determine if a simple clinical prediction guide could help clinicians decide whether anticoagulant therapy should be continued indefinitely or stopped in patients with a first unprovoked VTE who had completed at least 3 months of treatment. To this, we pooled individual patient data from seven prospective studies that evaluated VTE recurrence when D-dimer was measured after stopping VKA [7–13], and developed the DASH score, which comprises four easy-to-identify variables: post-anticoagulation D-dimer, age < 50 years, patient sex, and hormone-associated initial VTE. The strengths of our model, which support the validity of our findings, include the large patient sample studied with individual patient data, the parsimony of the statistical model using few clinically relevant predictors, the extensive internal validation by bootstrap and the consistency of the main study result in all considered studies.

Table 3 Patients distribution in the study cohort and annual recurrence rates and cumulative recurrence, according to DASH score

DASH score	Recurrence/ No recurrence (% of studied sample)	Annualized recurrence rate (95% CI)	Cumulative recurrence, % (95% CI)		
			1 year	2 years	5 years
−2	2/41 (2.3)	1.8 (0.5–7.6)	2.4 (0.3–15.8)	5.2 (1.3–19.2)	5.2 (1.3–19.2)
−1	4/152 (8.6)	1.0 (0.4–2.6)	1.9 (0.3–5.9)	1.9 (0.6–5.9)	5.7 (1.5–20.5)
0	13/236 (13.7)	2.4 (1.4–4.2)	4.2 (2.3–7.7)	5.4 (3.1–9.3)	9.5 (3.8–22.3)
1	43/448 (27.0)	3.9 (2.9–5.3)	5.1 (3.4–7.5)	8.7 (6.3–12.0)	15.9 (10.1–24.3)
2	64/390 (25.0)	6.3 (5.0–8.1)	8.4 (6.2–11.5)	12.8 (9.9–16.4)	25.3 (17.6–35.7)
3	82/279 (19.9)	10.8 (8.7–13.4)	14.6 (11.3–18.8)	20.5 (16.4–25.5)	40.9 (31.2–52.4)
4	31/33 (3.5)	19.9 (13.9–28.2)	21.9 (13.6–34.1)	33.6 (23.3–46.8)	61.3 (44.3–78.5)

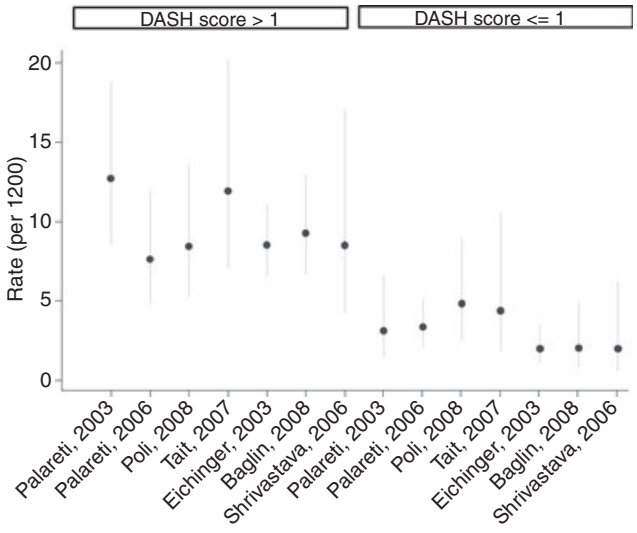

Fig. 3. Annual recurrence rates in patients having a DASH score ≤ 1 or > 1, across all considered studies. Bars represent the 95% confidence interval. The horizontal line indicates the consensus acceptable annual VTE recurrence rate (5%).

In general terms, a clinical prediction guide to predict recurrence after a first unprovoked VTE should identify patients who are at high risk of recurrent VTE (who might continue anticoagulation) or those at low risk (who might stop anticoagulation). For the first goal, the guide should have a high positive predictive value to predict recurrent VTE whereas for the second goal a high negative predictive value is required to predict recurrence-free survival. In either instance, a sensible clinical prediction guide should balance patient safety (avoiding the highest number of recurrences) while minimizing the number of patients who receive indefinite (or life-long) anticoagulation. Any prediction guide is anchored, therefore, on what is considered an acceptable annual risk of recurrent VTE that would justify stopping anticoagulant therapy. As the annual risk of major bleeding in patients who are receiving long-term anticoagulation is 1–3% overall and 4–5% in the elderly [5,22–24], an annual risk of recurrence below 5% is considered acceptable by expert consensus [20]. This recurrence rate is also similar to the annual risk for recurrent VTE in patients with provoked (or 'secondary') VTE [25], in whom indefinite anticoagulation is deemed unnecessary [2]. A systematic review addressing case-fatality rates of bleeding and recurrent VTE if patients with a first VTE continued or stopped anticoagulation has also suggested that an annual rate of recurrent VTE of 3% or lower would be required to justify stopping anticoagulation [26].

In our clinical prediction guide, a DASH score ≤ 1 fulfills the above requirements, and the associated annual risk of recurrence (3.1%) may be sufficiently low to justify stopping anticoagulation in an average patient after 3–6 months of anticoagulation. On the other hand, a DASH score ≥ 2 appears to confer a risk of recurrent VTE that warrants prolonged anticoagulation, unless a significant bleeding risk is present. One potential advantage of the DASH score is that it offers to clinicians and patients the flexibility to choose the score (and its associated risk of recurrent VTE) that could be acceptable. Hence, our suggested threshold (DASH ≤ 1) for stopping anticoagulation may be acceptable to some people but others may prefer a lower DASH score as the cut-point to stop anticoagulant therapy. It is also noteworthy that 939 of 1818 (51.6%) patients studied had a DASH ≤ 1, suggesting that anticoagulation may be potentially stopped in about one-half of patients with unprovoked VTE. Finally, we were able to demonstrate that the DASH score significantly improves the discriminating ability of a prediction rule based on D-dimer alone.

Few studies have assessed other prediction guides to help decide the duration of anticoagulation after unprovoked VTE. The REVERSE study proposed that women with fewer than two risk factors (comprising leg hyperpigmentation, edema or redness, abnormal D-dimer during anticoagulant therapy, increased body-mass index and age ≥ 65 years), could stop anticoagulant therapy but all men should continue [27]. In our study, body-mass index was not significantly associated with VTE recurrence and for most studies in our analysis information on leg symptoms after VTE was not available. Furthermore, post-anticoagulation D-dimer was the variable most strongly associated with recurrent VTE. These discrepant findings may be explained by the fact that the REVERSE study evaluated the predictive role of D-dimer during VKA, which is likely to substantially limit the power of D-dimer as a predictive variable for recurrent VTE. Another study by Eichinger et al [28] estimated the risk of recurrent VTE at 12 and 60 months, based on the combination of patient sex, post-anticoagulation D-dimer and the location of DVT (proximal or distal). The present study, which included 327 patients with proximal DVT enrolled in that study (23% of our sample size), further extends and confirms their findings, while resulting in a clinically simpler prediction rule.

Our study has potential limitations. First, several different D-dimer assays were used in the included studies, possibly introducing between-study heterogeneity and reducing discriminatory power. However, a separate analysis on the same patient database found no significant differences in the ability of different D-dimer assays to distinguish risk of recurrent VTE [14], thereby supporting the use of the DASH score with a range of commercially available D-dimer assays.

Second, despite the large patient sample, the number of recurrent VTEs was low (239, 13.1% of studied patients), possibly also because of the relatively short mean observation period. Given the absolute low number of recurrences, we preferred bootstrapping instead of splitting the sample into learning and validation subsets as an internal validation. Although an external validation of the DASH score in other patient populations is needed, a DASH score ≤ 1 resulted in an annual risk of recurrence below 5% across all included individual studies, further supporting the consistency of our findings.

Third, as meta-analysis is retrospective research, analyses are limited to the available data and we were unable to address the

question of whether other potential predictors of VTE recurrence, such as residual DVT detected by venous ultrasound or ongoing symptoms of post-thrombotic syndrome, could further improve the prognostic model [29]. Fourth, including hormone-associated VTE as unprovoked VTE may be questioned. This decision was made *a priori* and was justified because we considered hormonal therapy unlikely to have a major pathogenic role because it is a weak risk factor for VTE [15]. Other studies involving patients with unprovoked VTE have also included women with hormone-associated initial VTE [22,30,31]. We also acknowledge that our analysis could not account for all available hormonal therapy regimens and for the intervals from initiation of hormonal therapy and the subsequent index VTE.

To summarize, we developed a prediction score that could be potentially useful to decide whether to continue or stop anticoagulant therapy in patients with a first unprovoked VTE who have received at least 3 months of anticoagulation. The score appears to reliably predict recurrence risk and might identify patients with an annual risk of recurrence sufficiently low (3.1% per year) to justify stopping anticoagulation in more than half of patients with unprovoked VTE. If our statistical model is confirmed by further prospective studies in independent cohorts, it will be of major importance because of the substantial proportion of VTE occurring in the absence of major risk factors and the inconvenience and costs of long-term anticoagulant therapy. In fact, although based on studies involving patients receiving VKA, our findings might also pertain to patients who will be using new oral anticoagulants.

Addendum

A. Tosetto had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: A. Tosetto, J. Douketis and A. Iorio. Acquisition of data: T. Baglin, M. Cushman, S. Eichinger, G. Palareti, D. Poli, R.C. Tait and M. Marcucci. Analysis and interpretation of data: A. Tosetto, J. Douketis and A. Iorio. Drafting of the manuscript: A. Tosetto and J. Douketis. Critical revision of the manuscript for important intellectual content: T. Baglin, M. Cushman, S. Eichinger, G. Palareti, D. Poli and R.C. Tait. Statistical analysis: A. Tosetto and M. Marcucci.

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Disclosure of Conflicts of Interests

The authors state that they have no conflict of interest.

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