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ORIGINAL ARTICLE

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Evaluation of the predictive value of the bleeding prediction score VTE-BLEED for recurrent venous thromboembolism

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Abstract

Introduction: VTE-BLEED is a validated score for identification of patients at increased risk of major bleeding during extended anticoagulation for venous thromboembolism (VTE). It is unknown whether VTE-BLEED high-risk patients also have an increased risk for recurrent VTE, which would limit the potential usefulness of the score.

Methods: This was a post hoc analysis of the randomized, double-blind, placebo-controlled PADIS-PE trial that randomized patients with a first unprovoked pulmonary

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embolism (PE) initially treated during 6 months to receive an additional 18-month of warfarin vs. placebo. The primary outcome of this analysis was recurrent VTE during 2-year follow-up after anticoagulant discontinuation, that is, after the initial 6-month treatment in the placebo arm and after 24 months of anticoagulation in the active treatment arm. This rate, adjusted for study treatment allocation, was compared between patients in the high- vs. low-risk VTE-BLEED group.

Results: In complete case analysis (n = 308; 82.4% of total population), 89 (28.9%) patients were classified as high risk; 44 VTE events occurred after anticoagulant discontinuation during 668 patient-years. The cumulative incidence of recurrent VTE was 16.4% (95% confidence interval [CI], 10.0%-26.1%; 14 events) and 14.6% (95% CI, 10.4%-20.3%; 30 events) in the high-risk and low-risk VTE-BLEED groups, respectively, for an adjusted hazard ratio of 1.16 (95% CI, 0.62-2.19).

Conclusion: In this study, patients with unprovoked PE classified at high risk of major bleeding by VTE-BLEED did not have a higher incidence of recurrent VTE after cessation of anticoagulant therapy, supporting the potential yield of the score for making management decisions on the optimal duration of anticoagulant therapy.

KEYWORDS

anticoagulation therapy, bleeding, prediction score, recurrence, venous thromboembolism

Essentials

- VTE-BLEED is a validated score for identification of patients at higher risk of major bleeding.
- This was a post hoc analysis of the PADIS-PE trial to assess the association of VTE-BLEED and recurrent venous thromboembolism (VTE).
- Patients classified at high risk by VTE-BLEED did not have a higher incidence of recurrent VTE.
- VTE-BLEED may be useful for determination of the optimal duration of anticoagulant therapy.

1 | INTRODUCTION

One of the most debated challenges of management of patients with venous thromboembolism (VTE) is the determination of the optimal duration of anticoagulation. As the risk of recurrent VTE is low after VTE associated with a major transient risk factor (eg, major surgery), current international guidelines recommend cessation of anticoagulant treatment after a minimum of 3 months.[1–5] On the other hand, patients with active cancer-associated VTE are candidates for extended anticoagulation in light of the substantial risk for recurrence. However, the benefit of long-term anticoagulation is not fully established because of their concomitant high risk of bleeding.[1,2,6–8]

The risk of recurrent VTE after anticoagulant discontinuation in patients with unprovoked VTE is reported to be high as well, with a 20-year rate of 30% to 50%.[3,9,10] Therefore, indefinite anticoagulant therapy after unprovoked VTE events is usually recommended, with the important exception of patients at high risk of bleeding.[1,2] Although several risk prediction scores have been developed over the years for the identification of VTE patients at a high risk of bleeding, these tools present major limitations for use in routine practice, including the fact that they were derived from observational data of moderate quality, lack proper validation in adequately powered studies with adjudication of the events, and mostly focus on the acute phase of treatment with vitamin K antagonist (VKA) anticoagulation, rather than long-term treatment with DOACs. Furthermore, many of these scores were originally derived using data of patients outside of VTE populations (eg, atrial fibrillation, cardiac surgery) and may thereby not be completely relevant in the context of the VTE patients.[11] Most importantly, these score variables largely overlap with predictors of VTE recurrence demonstrating that these scores are not useful for decision making regarding optimal duration of anticoagulation in unprovoked VTE patients.

In a previous study, we derived VTE-BLEED, a simple 6-variable risk score designed to predict major bleeding in patients with VTE on stable, long-term anticoagulation (Table 1).[12] This score was found to identify VTE patients at a 3- to 5-fold increased risk of bleeding during therapy with either VKA, direct thrombin inhibitors, or direct factor Xa inhibitors, both in a clinical trial setting and in a large practice-based cohort.[12–15] The score demonstrated good predictive ability, with the C-statistic reaching 0.78. That being said, it is currently unknown whether implementation of the VTE-BLEED into clinical practice will present physicians with a confounding effect between risk of bleeding and risk of recurrence similar to that described above. In light of this question, we performed a post hoc analysis of the PADIS-PE trial[16] to assess and compare the incidence

TABLE 1 The VTE-BLEED score with original definition of variables[12]

Factor	Score
Active cancer[a]	2
Male with uncontrolled arterial hypertension[b]	1
Anemia[c]	1.5
History of bleeding[d]	1.5
Age ≥60 y old	1.5
Renal dysfunction[e]	1.5
Classification of patients with the VTE-BLEED score	
Low bleeding risk	Total score <2
High bleeding risk	Total score ≥2

[a]Cancer diagnosed within 6 mo before diagnosis of VTE (excluding basal-cell or squamous-cell carcinoma of the skin), recently recurrent or progressive cancer, or any cancer that required anticancer treatment within 6 mo before the VTE was diagnosed.
[b]Males with uncontrolled arterial hypertension were defined by values of systolic blood pressure ≥140 mm Hg at baseline.
[c]Hemoglobin <13 g/dL in men or <12 g/dL in women.
[d]Including prior major or nonmajor clinically relevant bleeding event, rectal bleeding, frequent nose bleeding, or hematuria.
[e]The estimated glomerular filtration rate (eGRF) <60 mL/min defined the presence of renal dysfunction: eGRF was calculated at baseline with the Cockcroft-Gault formula, which includes serum creatinine, age, and body weight.

of recurrent VTE after discontinuation of anticoagulant treatment in patients in the high- vs. low-risk VTE-BLEED category in order to determine whether there was an association between risk classification according to the VTE-BLEED and VTE recurrence in these patients.

2 | METHODS

2.1 | Study setting and patients

The design of the PADIS-PE study and patients' selection criteria are detailed in the original publication.[16] In short, PADIS-PE was a randomized, double-blind, placebo-controlled trial in patients with a first unprovoked pulmonary embolism (PE). The trial aimed at determining the benefits and harms of 6 vs. 24 months of anticoagulation with VKA. Patients were randomized after an initial 6-month course of anticoagulants to either continuation of anticoagulant treatment or placebo. The primary outcome was the composite of recurrent VTE or major bleeding at 18 months after randomization. One of the secondary outcomes was the incidence of the primary outcome after a follow-up period of 42 months. Symptomatic recurrent VTE was diagnosed upon clinical suspicion and objective confirmation by ultrasonography, ventilation-perfusion lung scanning, spiral computed tomographic angiography, pulmonary angiography, or autopsy, and in the event of a sudden death for which no other cause could be identified.[17] Definition of major bleeding was based on the ISTH recommendations.[18] All outcomes were adjudicated by an independent central adjudication committee.[16]

For the current analysis, we considered all patients with complete baseline data (complete case analysis) in whom VTE-BLEED could be calculated.

2.2 | VTE-BLEED

The 6-variable VTE-BLEED score (Table 1) was calculated from the baseline variables. Renal insufficiency was defined as an estimated creatinine clearance (Cockcroft-Gault) <60 mL/min, and uncontrolled arterial hypertension as a systolic blood pressure ≥140 mm Hg. A score of ≥2 points served to identify those patients at a predicted high risk of bleeding.[12]

2.3 | Study aim

The aim of the current analysis was to assess and compare the incidence of recurrent VTE after discontinuation of anticoagulant treatment in patients stratified according to the VTE-BLEED score (high risk [≥2 points] vs. low risk [<2 points]). For each included patient, incidence of recurrence was measured during the 24 months following the individual's personal date of treatment discontinuation. For the patients in the placebo group of the PADIS-PE study, all events occurred during the 24 months following randomization (ie, the initial 18-month study period plus the 6-month follow-up period after discontinuation of the study drug) were considered. For the patients randomized to active treatment, only the events that occurred during the 24 months after study treatment discontinuation were included. Therefore, in patients having discontinued active treatment prematurely for any reason (eg, patient's decision, bleeding), the 24-month period was counted starting from the date of premature treatment discontinuation.

2.4 | Statistical analysis

For the presentation of the baseline characteristics, continuous variables are described with means and standard deviation, and categorical variables are presented as proportions (n/N) and percentage (%). The absolute number and cumulative incidence of the primary and secondary outcomes are presented with corresponding 95% confidence intervals (CIs). A Cox regression model using VTE-BLEED and treatment group as covariates was applied to compare the incidence of recurrent VTE in the 2 VTE-BLEED risk categories, adjusted for study treatment allocation. Statistical analyses were performed using SAS V9.4 software (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Patients

From all 374 patients included in the original study, 3 withdrew informed consent, and data for calculation of the VTE-BLEED score were missing in 63 (16%; see characteristics in Table S1): data on the presence of anemia in 44 patients, on hypertension in 8 patients,

TABLE 2 Characteristics of analyzed patients

	All (n = 308)
Age, mean (SD), y	58.7 (18.0)
Women, n (%)	164 (53.2)
Body mass index, mean (SD)	27.3 (5.6)
≥30, n (%)	71 (23.1)
Estimated creatinine clearance (Cockroft-Gault) category, n (%)	
<30 mL/min	0
≥30-<50 mL/min	21 (6.8)
≥50 mL/min	287 (93.2)
Comorbidities, n (%)	
Previous cancer	13 (4.2)
Previous distal deep vein thrombosis or superficial vein thrombosis	25 (8.1)
Chronic heart failure	11 (3.6)
Chronic respiratory failure	70 (22.7)
Thrombophilia, n (%)	
Minor	44 (14.7)
Major	62 (20.7)
Treatment of pulmonary embolism prior to randomization	
Warfarin, n (%)	220 (71.4)
Fluindione, n (%)	90 (29.2)
Acenocoumarol, n (%)	5 (1.6)
Duration of initial anticoagulation, mean (SD), mo	6.3 (0.5)
Percentage of time in therapeutic INR range, mean (SD)	68.0 (23.0)
Use of compression stockings, n (%)	189 (61.4)
Main concomitant treatments, n (%)	
Antiplatelet agent	24 (7.8)
Statins	56 (18.2)

Note: Previous cancer was defined as cancer resolved more than 2 y before patient inclusion; thrombophilia was defined as minor if patients had heterozygous factor V Leiden or heterozygous G20210A prothrombin gene variant or elevated factor VIII (90th percentile); thrombophilia was defined as major if patients had antithrombin or protein C or protein S deficiency or anticardiolipin antibodies (99th percentile) or lupus anticoagulant or homozygous factor V Leiden or combined thrombophilia.
INR, international normalized ratio; SD, standard deviation.

on renal dysfunction in 2, and on anemia plus renal dysfunction in 9 patients. Those patients were excluded. The mean age of the 308 (82.4%) patients left for analysis was 58.7 years (±18.0), 164 (53.2%) patients were women, 21 (6.8%) patients had an estimated creatinine clearance (Cockcroft) <50 mL/min and 13 (4.2%) patients had a history of cancer (Table 2).

3.2 | VTE-BLEED

Of the 308 patients included in the current analysis, 89 (28.9%) were classified as VTE-BLEED high risk and 219 (71.1%) as VTE-BLEED low risk. Most prevalent VTE-BLEED variable was age ≥60 years (163, 52.9%); 59 patients had uncontrolled hypertension at randomization (19.2%), 44 anemia (14.3%), 38 renal dysfunction (12.3%) and 14 history of bleeding (4.5%; Table 3). Being an exclusion criterion of the original PADIS-PE trial, none of the patients had active cancer.

3.3 | Recurrent VTE

A total of 44 adjudicated VTE events occurred after anticoagulant discontinuation during 668 patient-years, that is, from the date of randomization in the placebo group and from the date of study treatment discontinuation in the active treatment group. Median individual follow-up time was 753 days. Of 44 patients with recurrent VTE events, 7 had symptomatic DVT, and 37 had symptomatic PE (28 without associated DVT and 9 in association with DVT). Recurrent PE was fatal in 4 (1%; 95% CI, 0.52-3.7) patients: 1 fatal PE event occurred in the VTE-BLEED low-risk group and 3 in the VTE-BLEED high-risk group. The cumulative incidence of recurrent VTE was 16% (95% CI, 10.0%-26.1%; 14 events) in the high-risk VTE-BLEED group and 15% (95% CI, 10.4%-20.3%; 30 events) in the low-risk VTE-BLEED group (adjusted hazard ratio [HR], 1.16; 95% CI, 0.62-2.19; Figure 1). All episodes were unexplained sudden deaths considered to be fatal PE by the adjudication committee.

4 | DISCUSSION

Our main finding is that, after anticoagulant discontinuation, patients with unprovoked VTE in the VTE-BLEED high-risk category (29% of all patients) did not have a higher risk of developing recurrent VTE than patients in the low-risk VTE-BLEED category (adjusted HR, 1.16; 95% CI, 0.62-2.19). This observation supports the use of the VTE-BLEED score in future management studies of patients with unprovoked VTE for whom the duration of anticoagulant treatment is driven by risk stratification according to the individual bleeding risk.

To ensure usefulness in clinical practice, prediction scores aiming at determining the optimal duration of anticoagulant therapy for VTE should demonstrate consistency and straightforwardness in their application. In the case of the present clinical question, this may be complicated by the time-varying nature of numerous bleeding risk predictors included in scores such as the HAS-BLED and the American College of Chest Physicians score.[2,19–23] In contrast, the VTE-BLEED includes only 1 potentially inconstant variable, namely, "male with uncontrolled arterial hypertension," while all other variables are clearly defined and largely objective and tend to be fairly constant over time in most patients. This suggests more consistent and thereby likely reliable estimates of bleeding risks and broader functionality of the VTE-BLEED than other available scores. Furthermore, in contrast with other currently available bleeding risk scores, the VTE-BLEED was evaluated and validated both in nonselected VTE patients and in patients with unprovoked VTE, as well as for all currently available classes of oral anticoagulants.[12–14,19–27] Additionally, the binary categorization used in the VTE-BLEED limits the commonly encountered ambiguity surrounding clinical

TABLE 3 Prevalence of the VTE-BLEED score items among the study population

	VTE-BLEED Low risk (n = 219)	VTE-BLEED High risk (n = 89)	All (n = 308)
Male with uncontrolled arterial hypertension, n (%)	21 (9.6)	38 (42.7)	59 (19.2)
Anemia, n (%)	12 (5.5)	32 (36.0)	44 (14.3)
History of bleeding, n (%)	5 (2.3)	9 (10.1)	14 (4.5)
Age ≥60 y, n (%)	75 (34.2)	88 (98.9)	163 (52.9)
Renal dysfunction (Cockcroft), n (%)	0	38 (42.7)	38 (12.3)
Active cancer	0	0	0

management of patients classified at "intermediate risk" according to other bleeding prediction scores. Results of the present analysis strengthen the currently available arguments in favor of the use of the VTE-BLEED in clinical practice by demonstrating the absence of the previously discussed common and problematic confounding effect of predictions of anticoagulant-related bleeding and VTE recurrence.

It remains challenging for clinicians to determine whether the risk of bleeding in patients on long-term anticoagulant therapy exceeds risk of recurrence after prompt discontinuation of treatment. One meta-analysis of recent studies (>4500 patients with unprovoked VTE who discontinued treatment) reported a pooled rate of fatal recurrent VTE at 0.17 (95% CI, 0.047-0.33) per 100 patient-years with an associated case fatality rate of 2.6% (95% CI, 0.86-5.0), while another found a pooled rate of fatal VKA-associated bleeding at 1.31 (95% CI, 1.30-1.32) per 100 patient-years with a case fatality of 13.4% (95% CI, 9.4-17.4).[10,28] While observation of a higher case-fatality rate of major bleeding than that of recurrent VTE has been proven for VKA treatment, reliable practice-based numbers are unavailable for long-term direct oral anticoagulant (DOAC) treatment, although a lower rate may be anticipated than for VKA.[29] Moreover, because recurrent VTE occurs mostly in the first years after anticoagulant cessation and diminishes over time, while in contrast the risk of bleeding during stable anticoagulation increases with advancing age, only an adequately powered randomized controlled trial with long-term follow-up can answer the question of optimal duration of anticoagulation for unprovoked VTE.

Strengths of this analysis include the randomized design of the study as well as the blinded adjudication of primary and secondary end points. The main limitation of our study rests in its post hoc nature, resulting in a relatively high proportion of patients with missing data for the calculation of the VTE-BLEED score, potentially introducing selection bias and resulting in a relatively small sample size that did not allow us to evaluate bleeding events and/or a net clinical benefit outcome. However, the VTE-BLEED has previously been validated in 3 independent high-quality cohorts totaling over 17 000 patients[12,13,15] in which results were deemed to be sufficiently conclusive and validation of the score was therefore not part of the aims of the present analysis. Further, our results cannot be generalized

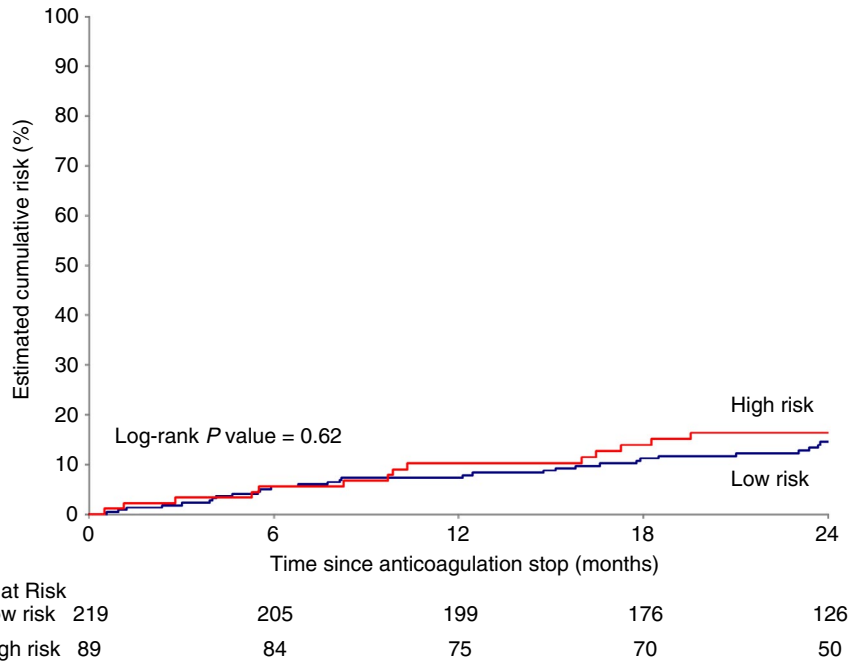

FIGURE 1 Kaplan Meier curve showing estimated cumulative incidence of recurrent deep vein thrombosis and/or pulmonary embolism in the first 2 years after treatment cessation according to the VTE-BLEED score (high: red curve; low: blue curve). Number of patients left in analysis are indicated in the table

to patients with provoked PE or those with DVT or treated with DOACs, although we do not anticipate relevant differences in the 2 latter patient categories.

In conclusion, the current analysis shows that, after stopping anticoagulant therapy, patients with a first unprovoked PE and a high risk of major bleeding by VTE-BLEED did not have a higher incidence of recurrent VTE than did patients in the VTE-BLEED low-risk category. These results support the appropriateness of the score for making management decisions on the optimal duration of anticoagulant therapy. Whereas long-term anticoagulant treatment has been suggested to be safe and appropriate in patients with unprovoked VTE in the VTE-BLEED low-risk category, further outcome studies should explore the optimal duration of anticoagulant therapy of VTE-BLEED high-risk patients.

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AUTHOR CONTRIBUTIONS

All authors have contributed significantly to this manuscript and take responsibility for the analyses.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX

PADIS-PE STUDY GROUP

Members of the PADIS-PE Study Group (all in France) were as follows: Steering Committee – F. Couturaud (Chair), P. Mismetti, C. Leroyer, G. Meyer, O. Sanchez, P. Jego, G. Pernod, E. Duhamel, K. Provost, F. Parent, L. Bertoletti, C. Tromeur, D. Mottier; Coordinating Committee – F. Couturaud (Chair), M. Guégan, S. Mélac, A. Le Hir; Independent Central Adjudication Committee (Critical Events) – P. Girard (Chair), S. Lenoir, C. Lamer; Data Safety Monitoring Board – J.F. Bergmann (Chair), D. Wahl, L. Drouet; Statistical Analysis: E. Presles, S. Laporte; Data Management (ClinInfo, Lyon) – P. Chevarier, N. Monte; Operation team (Brest University Hospital) – F. Morvan, V. Kouassi,

N. Ibrir, G. El Asri; Lung Scintigraphy Panel – P.Y. Salaun, P. Robin, P.Y. Le Roux; Ultrasound Panel – L. Bressollette, P. Quéhé, S. Gestin; Computerised Tomography Scan Panel – M. Nonent, J. Bahuon, L. Deloire, C. Tromeur, B. Planquette; Echocardiography Panel – Y. Jobic, Y. Etienne, R. Didier, F. Leven; Central Laboratory – L. Leroux, H. Galinat, C. Le Maréchal, L. Gourhant, F. Mingant; Investigators (by city and in order of the number of patients enrolled) – Brest (198 patients): F. Couturaud, C. Leroyer, C. Tromeur, F. Leven, K. Lacut, E. Lemoigne, L. De Saint Martin, A. Delluc, G. Le Gal, N. Paleiron, R. Le Mao, D. Mottier; Paris (53 patients): O. Sanchez, G. Meyer, B. Planquette; Grenoble (33 patients) G. Pernod, C. Pison; Rennes (33 patients): P. Jego, P. Guéret; Saint-Etienne (21 patients): P. Mismetti, H. Décousus, C. Lassagne, L. Bertoletti; Saint-Brieux (9 patients): E. Duhamel; Lannion (8 patients): K. Provost; Le Kremlin-Bicêtre (5 patients): F. Parent; Quimper (3 patients): B. Pan-Petesh; Toulouse (2 patients): A. Bura-Riviere; Tours (2 patients): B. Delahousse, Y. Gruel; Paris (2 patients): C. Lorut; Clermont-Ferrand (1 patient): J. Schmidt; Nantes (1 patient): J. Connault.