Evaluation of VTE-BLEED for predicting intracranial or fatal bleeding in stable anticoagulated patients with venous thromboembolism

To the Editor:

Current international guidelines recommend discontinuing anticoagulant therapy for unprovoked acute pulmonary embolism or deep vein thrombosis after the first 3 months of treatment only in patients considered at high risk of bleeding [1, 2]. The rationale for this recommendation is that unprovoked venous thromboembolism (VTE) is associated with high rates of recurrence after anticoagulant therapy quantified as up to 50% in the first 10 years [3]. It remains, however, unknown how the assessment of the bleeding risk in the individual patient should be performed given the lack of sufficiently validated risk assessment models or scores, as well as outcome trials that successfully applied those tools [4, 5].

In an attempt to overcome this issue, we recently derived and externally validated VTE-BLEED, a risk score designed to predict the risk of major bleeding in VTE patients on stable, long-term anticoagulation (table 1) [6, 7]. VTE-BLEED was derived from patients included in the two RE-COVER trials that were randomised to treatment with dabigatran and was then validated in the warfarin arm of the same trial [8, 9]. With c-statistics >0.75 and odds ratios of 6.5 (95% CI 2.0–21) and 6.5 (95% CI 2.8–15) for the derivation and validation cohorts, respectively, the score seemed to have solid predictive accuracy [6]. In a subsequent study, we tested VTE-BLEED in the patients included in the HOKUSAI-VTE trial [10]. We concluded that VTE-BLEED adequately identified patients at high risk for major bleeding, which occurred in 2.0% of cases in the high-risk group (*versus* 0.5% in the low-risk group), with comparable accuracy for edoxaban-treated (OR 3.1, 95% CI 1.5–6.2) and warfarin-treated patients (OR 5.0, 95% CI 2.6–9.7) [7]. Based on these two studies, VTE-BLEED is the only available externally validated bleeding score for VTE patients that has been proven to be applicable to patients treated with vitamin K antagonists and direct thrombin inhibitors, as well as direct factor Xa inhibitors, across all relevant patient subcategories. Of note, VTE-BLEED includes the variable "active cancer", which is by definition not present in patients with unprovoked VTE. Although subgroup analyses demonstrated adequate predictive value of the score in selected patients with unprovoked VTE in both the RE-COVER trials as well as the HOKUSAI study, the presence of this variable is a limitation for the application of VTE-BLEED in clinical practice.

When deciding to continue or stop anticoagulants in the individual patient, it is relevant to consider the risk of fatal recurrent VTE once treatment is discontinued against the risk of intracranial haemorrhage (ICH) and/or fatal bleeding during ongoing treatment in addition to the overall risks of recurrent VTE and major bleeding, since these are the ultimate events that an optimal management decision aims to prevent. Since the accuracy of VTE-BLEED to predict these severe major bleeding events has not been reported, we set out to compare the event rates of ICH and fatal bleeding in patients with a high *versus* a low risk of bleeding according to VTE-BLEED.

We studied the identical study populations from the RE-COVER and HOKUSAI-VTE trials that were evaluated in the derivation and validation studies of VTE-BLEED [6–10]. The study design, inclusion and exclusion criteria, outcome measures and baseline population characteristics of both studies have been presented in the original reports of these trials [8–10]. As in the derivation and validation analyses of VTE-BLEED, we only considered all ICH and fatal bleeding events that occurred during chronic, "stable"

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TABLE 1 The six VTE-BLEED items with corresponding weights and the predictive value of VTE-BLEED for the end-points of intracranial haemorrhage (ICH), fatal bleeding and ICH or fatal bleeding during stable anticoagulant therapy in the combined RE-COVER trials, the HOKUSAI-VTE study and the pooled data from both studies

Item	Score	Study	OR (95%CI)	Chi^2	I^2
The six VTE-BLEED items					
Active cancer[#]	2				
Male with uncontrolled arterial hypertension[¶]	1				
Anaemia[+]	1.5				
History of bleeding[§]	1.5				
Age ⩾60 years	1.5				
Renal dysfunction[f]	1.5				
Classification of patients with VTE-BLEED					
Low bleeding risk	Total score <2				
High bleeding risk	Total score ⩾2				
End-point					
ICH		RE-COVER	4.4 (0.74–26)		
		HOKUSAI-VTE	3.8 (1.5–10)		
		Pooled data	4.0 (1.7–9.3)	0.02	0%
Fatal bleeding		RE-COVER	4.4 (0.74–26)		
		HOKUSAI-VTE	6.7 (1.3–35)		
		Pooled data	5.6 (1.7–19)	0.12	0%
ICH or fatal bleeding		RE-COVER	4.9 (1.2–21)		
		HOKUSAI-VTE	4.6 (1.8–12)		
		Pooled data	4.7 (2.2–10)	0	0%

[#]: cancer diagnosed within the 6 months before diagnosis of venous thromboembolism (VTE) (excluding basal-cell or squamous-cell carcinoma of the skin), recently recurrent or progressive cancer or any cancer that required anti-cancer treatment within 6 months before the VTE was diagnosed; [¶]: males with uncontrolled arterial hypertension were defined by values of systolic blood pressure ⩾140 mmHg at baseline; [+]: haemoglobin <13 $g \cdot dL^{-1}$ in men or <12 $g \cdot dL^{-1}$ in women; [§]: including prior major or non-major clinically relevant bleeding event, rectal bleeding, frequent nose bleeding, or haematuria; [f]: estimated glomerular filtration rate (eGFR) <60 $mL \cdot min^{-1}$ defined the presence of renal dysfunction, eGFR was calculated at baseline using the Cockcroft–Gault formulas, which include serum creatinine, age and body weight.

anticoagulation, defined as the active treatment period after the first 30 days from enrolment. In both the RE-COVER and HOKUSAI-VTE trial, the bleeding events were adjudicated by an independent adjudication committee.

The ability of the VTE-BLEED score to predict the risk of the three outcomes of ICH, fatal bleeding and ICH or fatal bleeding was estimated by calculating odds ratios and corresponding 95% confidence intervals. Because VTE-BLEED was found to predict major bleeding equally well for warfarin- and direct oral anticoagulant (DOAC)-treated patients, and the number of ICH and fatal bleeding events in both the RE-COVER and the HOKUSAI-VTE trial were very low, we decided to analyse each study cohort as one group without differentiating between the allocated treatments. Further, we pooled the data from both studies using Review Manager (version 5.3 for Windows; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for all three outcomes. Mantel–Haenszel methods for combining trials were used for weighting the studies. Cochran's Chi-squared test and the I^2 test for heterogeneity were used to assess inter-study heterogeneity. The Chi-squared test assesses whether observed differences in results are compatible with chance alone. I^2 describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. Statistically significant heterogeneity was considered present at Chi-squared $p<0.10$ and $I^2>50\%$.

The follow-up period in the RE-COVER trials (5107 VTE patients) was 6 months and ranged between three and 12 months in the HOKUSAI-VTE trial (8240 VTE patients) [8–10]. During stable anticoagulation, five (0.10%) ICH, five (0.10%) fatal bleeding events and eight (0.17%) ICH or fatal bleeding events occurred in the combined RE-COVER trials, and 17 (0.22%), seven (0.09%) and 19 (0.24%) occurred in the HOKUSAI-VTE trial, respectively. In the low-risk category, the incidence of the three outcome events were 0.06%, 0.06% and 0.08% in the RE-COVER trial and 0.12%, 0.04% and 0.12% in the HOKUSAI-VTE study, respectively. In the high-risk category, the incidence of the three outcome events were 0.24%, 0.24% and 0.41% in the RE-COVER trial and 0.24%, 0.47% and 0.57% in the HOKUSAI-VTE study, respectively. Table 1 shows the odds ratios of the two studies for all three outcomes, as well as the pooled odds ratios. In line with what was previously shown for the prediction of major bleeding, the odds ratio for all three outcomes ranged between 3.8 and 6.7 for the two individual studies. The pooled odds ratio for ICH was 4.0 (95% CI 1.7–9.3), for fatal bleeding it was 5.6 (95% CI 1.7–19) and for ICH or fatal bleeding it was

4.7 (95% CI 2.2–10), respectively. We found no relevant heterogeneity between the two studies, and the effect was consistent for all three anticoagulant drug classes (p=0.56 for interaction).

These data support the hypothesis that VTE-BLEED may be useful for making management decisions on the duration of anticoagulant therapy since we could demonstrate that VTE-BLEED not only predicts major bleeding in general, but especially ICH or fatal bleeding events. Importantly, the rate of ICH or fatal events was not zero among the patients in the low-risk category indicating that VTE-BLEED might not completely rule out the occurrence of the most severe major bleeding events in anticoagulated patients, since other genetic, pharmacological and clinical factors may play a role. Nonetheless, the estimated absolute risk of ICH in low-risk VTE-BLEED patients after ~6 months of anticoagulant treatment appears comparable to what was observed for first primary (not anticoagulant-related) ICH in adults aged 45–74 years, corresponding to 0.016–0.098 per 100 person-years [11]. Despite the favourable results of this analysis, VTE-BLEED still awaits prospective validation in practice-based conditions as well as final proof of efficacy in an outcome trial before it may be recommended for use in daily clinical practice.

Frederikus A. Klok, Stefano Barco and Stavros V. Konstantinides
Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg University, Mainz, Germany.

Correspondence: Frederikus A. Klok, Center for Thrombosis and Hemostasis, University Medical Center Mainz, Langenbeckstrasse 1, Building 403, 55131 Mainz, Germany. E-mail: f.a.klok@LUMC.nl

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