EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

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

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Twitter feed: VTE-BLEED predicts fatal and/or intracranial bleedings in patients with VTE treated with long-term anticoagulants.

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Dear Editor,

Current international guidelines recommend discontinuing anticoagulant therapy for unprovoked acute pulmonary embolism (PE) or deep vein thrombosis (DVT) after the first three 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 in 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 considering the lack of sufficiently validated risk assessment models or scores, as well as outcome trials that successfully applied those.[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 who were randomized to treatment with dabigatran and 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 indeed 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 (Odds Ratio 3.1, 95%CI 1.5-6.2) and warfarin-treated patients (Odds Ratio 5.0, 95%CI 2.6-9.7).[7] Based on those 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, 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 hemorrhage (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 are aimed to be prevented with an optimal management decision. Since the accuracy of VTE-BLEED to predict these severe major bleeding events has not been reported yet, we set out to compare the event rates of ICH and fatal bleeding of patients with a high versus those with 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 with the derivation and validation analyses of VTE-BLEED, we only considered all ICH and fatal bleeding events that occurred during chronic, 'stable' 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 ICH, fatal bleeding and ICH or fatal bleeding was estimated by calculating Odds Ratios and corresponding 95% Confidence Intervals (95%CI). 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 as well as the HOKUSAI-VTE trial were very low, we decided to analyze each study cohort as one group without differentiating between allocated treatment. 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-square test and the I^2 test for heterogeneity were used to assess inter study heterogeneity. The Chi-square 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-square p<0.10 and I^2 >50%.

The follow-up period in the RE-COVER trials (5107 VTE patients) was six months and ranged between three and 12 months in the HOKUSAI-VTE trial (8240 VTE patients).[8-10] During stable anticoagulation, 5 ICH (0.10%), 5 fatal bleeding events (0.10%) and 8 ICH or fatal bleeding events (0.17%) occurred in the combined RE-COVER trials, and 17 (0.22%), 7 (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 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 study, respectively. **Table 2** shows the Odds Ratios of the two studies for all three outcomes, as well as the pooled Odds Ratios. In line with 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 5.6 (95%CI 1.7-19) and for ICH or fatal bleeding 4.7 (95% 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 does not only predict 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 approximately six months of anticoagulant treatment appears comparable to what 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 favorable 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 to be used in daily clinical practice.

Acknowledgements

Authorship statement

All authors have contributed significantly to this manuscript and take responsibility for the analyses. FK and SB designed the study, interpreted the data and drafted the manuscript. SK designed the study, interpreted the data and critically revised the manuscript for important intellectual content.

Disclosures

Frederikus Klok reports research grants from Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi-Sankyo, MSD and Actelion. Stefano Barco S. Barco has received congress and travel payments from Daiichi-Sankyo and financial support for the printing costs of his PhD thesis from Pfizer BV, CSL Behring bv, Sanquin Plasma Products, Boehringer Ingelheim bv, Aspen Netherlands and Bayer bv. Stavros Konstantinides reports having received consultancy and lecture honoraria from Bayer HealthCare, Boehringer Ingelheim, Daiichi-Sankyo, and Pfizer – Bristol-Myers Squibb; payment for

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Tables

Table 1: The six VTE-BLEED items with corresponding weights.

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

[a]Cancer diagnosed within 6 months before diagnosis of 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. [b]Males with uncontrolled arterial hypertension were defined by values of systolic blood pressure ≥140 mmHg at baseline. [c]Haemoglobin <13 g/dL in men or <12 g/dL in women. [d]Including prior major or non-major clinically relevant bleeding event, rectal bleeding, frequent nose bleeding, or haematuria. [e]The estimated glomerular filtration rate (eGFR) <60 mL/min defined the presence of renal dysfunction: eGRF was calculated at baseline with the Cockcroft-Gault formulas, which include serum creatinine, age, and body weight.

Table 2: Predictive value of VTE-BLEED for 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.

Endpoint	Study	OR	95%CI	Chi^2	I^2
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%

Note: ICH=intracranial hemorrhage; CI=confidence interval; OR=Odds Ratio