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Validation of a score for predicting fatal bleeding in patients receiving anticoagulation for venous thromboembolism ☆

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SUMMARY

Background: The only available score to assess the risk for fatal bleeding in patients with venous thromboembolism (VTE) has not been validated yet.
Methods: We used the RIETE database to validate the risk-score for fatal bleeding within the first 3 months of anticoagulation in a new cohort of patients recruited after the end of the former study. Accuracy was measured using the ROC curve analysis.
Results: As of December 2011, 39,284 patients were recruited in RIETE. Of these, 15,206 had not been included in the former study, and were considered to validate the score. Within the first 3 months of anticoagulation, 52 patients (0.34%; 95% CI: 0.27-0.45) died of bleeding. Patients with a risk score of <1.5 points (64.1% of the cohort) had a 0.10% rate of fatal bleeding, those with a score of 1.5-4.0 (33.6%) a rate of 0.72%, and those with a score of >4 points had a rate of 1.44%. The c-statistic for fatal bleeding was 0.775 (95% CI 0.720-0.830). The score performed better for predicting gastrointestinal (c-statistic, 0.869; 95% CI: 0.810-0.928) than intracranial (c-statistic, 0.687; 95% CI: 0.568-0.806) fatal bleeding. The score value with highest combined sensitivity and specificity was 1.75. The risk for fatal bleeding was significantly increased (odds ratio: 7.6; 95% CI 3.7-16.2) above this cut-off value.
Conclusions: The accuracy of the score in this validation cohort was similar to the accuracy found in the index study. Interestingly, it performed better for predicting gastrointestinal than intracranial fatal bleeding.

Introduction

Venous thromboembolism (VTE) is a commonly diagnosed condition with significant morbidity and mortality [1]. Current guidelines recommend patients with VTE to be initially treated with low-molecular-weight heparin (LMWH), unfractionated heparin or fondaparinux, followed by long-term anticoagulation, which is usually accomplished with vitamin K antagonists (VKA) [2,3]. Recommendations for long-term therapy are based on randomized clinical trials [2–10] that assessed relevant outcomes like VTE recurrences and major bleeding rates, because most trials were underpowered to assess fatal VTE or fatal bleeding events. Furthermore, a number of patients are often excluded from randomized trials of anticoagulation because of co-morbid conditions, short life expectancy, pregnancy or contraindications to therapy, which means that treatment regimens based on the results from randomized clinical trials might not be generalisable to all patients with VTE.

When weighing the risks and benefits of anticoagulation in an individual patient, in addition to considering the absolute risk of VTE recurrences and major bleeding, the mortality associated with each of these outcomes should be considered. While a number of prognostic models have the potential to predict the risk for major bleeding [11–13], little has been done to identify patients at increased risk to die of bleeding during the course of anticoagulation. In a previous study using data from the RIETE registry [14], we identified 9 clinical

Abbreviations: VTE, VenousTthromboembolism; RIETE, Registro Informatizado de Enfermedad tromboEmbolica; LMWH, Low Molecular Weight Heparin; DVT, Deep Vein Thrombosis; PE, Pulmonary Embolism; VKA, Vitamin K Antagonists; ROC, Receiver Operating Characteristics.

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and laboratory variables at baseline that were independently associated with an increased risk for fatal bleeding within the first 3 months of anticoagulation, and built a prognostic score to identify patients at low-, moderate- or high risk. In the current study, we tried to validate this score using a new sample of patients recruited in RIETE after the end of the former study.

Patients and Methods

The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) Registry is an ongoing, multicenter, international (Spain, Italy, France, Israel, Portugal, Germany, Switzerland, Czech Republic, Macedonia, United States, Brazil and Ecuador), observational registry of consecutive patients with symptomatic, objectively confirmed, acute VTE [15–17].

Consecutive patients with symptomatic, acute deep vein thrombosis (DVT) or pulmonary embolism (PE), confirmed by objective tests (contrast venography or ultrasonography for suspected DVT; pulmonary angiography, lung scintigraphy, or helical computed tomography scan for suspected PE), were enrolled in RIETE. Patients were excluded if they did not receive any anticoagulant therapy or were currently participating in a therapeutic clinical trial with a blinded therapy. All patients provided consent to their participation in the registry, in accordance with local Ethics Committee requirements.

In the RIETE registry, participating physicians ensured that eligible patients were consecutively enrolled. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The study coordinating center assigned patients with a unique identification number to maintain patient confidentiality and was responsible for all data management. Data quality was regularly monitored electronically, including checks to detect inconsistencies or errors, which were resolved by the local coordinators. Data quality was also monitored by periodic visits to participating hospitals by contract research organizations that compared medical records with the submitted data, and made sure that consecutive patients had been recruited into RIETE.

Study Outcomes

Fatal bleeding was defined as any death occurring within 7 days of a major bleeding episode, in the absence of an alternative cause of death. Major bleeding was defined as an overt bleed that required a transfusion of 2 or more units of blood, was retroperitoneal, spinal or intracranial, or was fatal. The causes of death were assigned by their attending physicians.

Baseline Variables and Score

The baseline variables registered in RIETE have been described elsewhere [15–17]. Data were recorded when the qualifying episode of VTE was diagnosed. The 9 independent variables associated with an increased risk for fatal bleeding and the points assigned to each variable are presented in Table 1. The patient's score is the sum of the points assigned to each variable.

Treatment and Follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). The type and dose of anticoagulant therapy, as was the insertion of an inferior vena cava filter, were recorded. After discharge, all patients were followed-up for up to 3 months in the outpatient clinic. During each visit, any signs or symptoms suggesting either DVT or PE recurrences or bleeding complications were noted. Most outcomes were classified as reported by the clinical centers. However, if the staff at the coordinating center was in disagreement on how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events). Patients who had major bleeding or recurrent VTE within 3 months of enrollment remained under surveillance until 3 months of follow-up was completed.

Table 1
RIETE score for fatal bleeding in patients receiving anticoagulation for acute venous thromboembolism [14].

	Points
Age >75 years	1
Metastatic cancer	2
Immobility ≥4 days*	1
Recent major bleeding#	1.5
Abnormal prothrombin time	1
CrCl < 30 ml/min	1
Platelet Count $<100 \times 10^9$/L	1
Anemia†	1
Distal DVT	-1

* defined as non-surgical patients who were confined to bed with bathroom privileges for ≥4 days in the 2-months prior to VTE diagnosis.
\# major bleeding less than 30 days before VTE diagnosis.
† defined as hemoglobin <13 g/dL in men or <12 g/dL in women.

Statistical Analysis

Student's t test and the Mann-Whitney test were used to compare continuous variables. Qualitative variables were compared by the Fisher exact test, and the odds ratio and 95% confidence intervals were calculated. Survival curves were constructed according to the Kaplan-Meyer method. The cut-off points for risk categories of fatal bleeding have been previously reported [14]. Receiver Operating Characteristics (ROC) curve analysis and the c-statistic was used to assess the accuracy of the score and to identify the score values

Table 2
Clinical characteristics of patients with and without subsequent fatal bleeding.

	Fatal bleeding	No fatal bleeding	p value
Patients, N	52	15,154	
Clinical characteristics,			
Gender (males)	26 (50%)	7,367 (49%)	0.89
Age >75 years	24 (46%)	5,260 (35%)	0.11
Body weight <70 kg	30 (58%)	5,544 (37%)	0.002
Underlying diseases,			
Chronic lung disease	7 (14%)	1,759 (12%)	0.66
Chronic heart disease	5 (9.6%)	1,079 (7.1%)	0.42
Recent major bleeding	2 (3.8%)	316 (2.1%)	0.30
Risk factors for VTE,			
Recent immobility ≥ 4 days	15 (29%)	3,470 (23%)	0.32
Recent surgery	5 (9.6%)	1,680 (11%)	1.00
Cancer	29 (56%)	3,439 (23%)	<0.001
Metastatic cancer	20 (39%)	1,405 (9.3%)	<0.001
Prior VTE	3 (5.8%)	2,341 (15%)	0.054
Baseline blood tests,			
Anemia	32 (62%)	5,232 (55%)	<0.001
Platelet count $<100 \times 10^9$/L	6 (12%)	374 (2.5%)	0.002
Abnormal prothrombin time	9 (17%)	1,114 (7.4%)	0.013
CrCl levels <30 ml/min	10 (19%)	1,119 (7.4%)	0.004
VTE characteristics,			
Symptomatic PE	32 (62%)	7,782 (51%)	0.17
Bilateral DVT	6 (12%)	578 (3.8%)	0.01
Distal DVT	3 (5.8%)	1,728 (11%)	0.27
Initial therapy			
LMWH	45 (88%)	13,550 (89%)	0.50
Unfractionated heparin	3 (5.9%)	887 (5.9%)	1.00
Thrombolytics	3 (5.9%)	158 (1.0%)	0.02
Vena cava filter	1 (1.9%)	372 (2.5%)	1.00
Long-term therapy			
LMWH	17 (33%)	3,994 (26%)	0.34
Vitamin K antagonists	13 (25%)	10,358 (68%)	<0.001

Abbreviations: VTE, venous thromboembolism; CrCl, creatinine clearance; PE, pulmonary embolism; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin.

Table 3
Sites of major and fatal bleeding.

	Fatal bleeding (n = 52)	Non-fatal major bleeding (n = 198)	Major bleeding (n = 250)
Gastrointestinal	19 (36.5%)	62 (31.1%)	81 (32.4%)
Intracranial	14 (26.9%)	18 (9.1%)	32 (12.8%)
Genitourinary	2 (3.8%)	26 (13.1%)	28 (11.2%)
Hematoma	11 (21.2%)	65 (32.8%)	76 (30.4%)
Other	6 (11.5%)	27 (13.6%)	33 (13.2%)

with highest combined sensitivity and specificity. SPSS software (version 15, SPSS Inc., Chicago, Illinois) was used for the statistical management of the data, and a two-sided p <0.05 was considered to be statistically significant.

Results

As of December 2011, 39,284 patients were recruited into the RIETE registry. Of these, 15,206 had not been included in the former study, and were considered for validating the score. In all, 7,814 patients (51%) initially presented with PE (with or without concomitant DVT) and 7,392 with DVT alone. Their clinical characteristics are shown in Table 2. Most patients (89%) received initial therapy with LMWH, 5.9% received unfractionated heparin, 1.1% thrombolytic therapy, and 2.5% an inferior vena cava filter. For long-term therapy, 10,371 patients (68%) received VKA and 4,011 (26%) had LMWH.

Within the first 3 months of anticoagulation, 250 patients (1.64%; 95% CI: 1.45-1.86) had major bleeding complications and 52 (0.34%; 95% CI: 0.27-0.45) died of bleeding. Patients subsequently dying of bleeding more likely had cancer, and more likely presented with anemia, platelet count $<100 \times 10^9$/L, abnormal prothrombin time or renal insufficiency compared with those with no fatal bleeding (Table 2). The most frequent site of fatal bleeding (19 of 52 fatal bleeds, 36.5%) was gastrointestinal (GI), and the highest mortality occurred after intracranial bleeding (14 of 32 major bleeds, 43.7%), as shown in Table 3. One in every 5 fatal bleeding events occurred after a second episode of major bleeding in the same location.

The rate of fatal bleeding increased in parallel to the patient's risk score (Table 4). Patients with a risk score of <1.5 points (64.1% of the whole series) had a 0.10% rate of fatal bleeding (10 in 9,748 patients), those with a risk score of 1.5-4.0 (33.6% of patients) a rate of 0.72% (37 in 5,111 patients), and those with a score of >4 had a rate of 1.44% (5 in 347 patients). The c-statistic for fatal bleeding with the continuous score was 0.775 (95% CI: 0.720-0.830). Performance was highest for GI bleeding (0.869; 95% CI: 0.810-0.928) and lowest for intracranial bleeding (0.687; 95% CI: 0.568-0.806), as shown in Table 5. Accuracy of the high risk (>4 points) score for GI, extracranial or intracranial fatal bleeding appears in Table 6.

Table 5
C-statistic according to site of bleeding.

	c-statisic	95% CI	Standard error	n
Fatal bleeding,				
All sites	0.775	0.720–0.830	0.028	52
Extracranial	0.807	0.750–0.864	0.029	38
Intracranial	0.687	0.568–0.806	0.061	14
Gastrointestinal	0.869	0.810–0.928	0.030	19
Muscular/Hematoma	0.737	0.630–0.843	0.054	11
All-cause death	0.839	0.828–0.850	0.06	1181
Major bleeding	0.719	0.689–0.749	0.015	250

Abbreviations: CI, confidence intervals.

The score value with highest combined sensitivity and specificity was 1.75 (Fig. 1). Risk for fatal bleeding was significantly increased above this cut-off point (odds ratio [OR]: 7.6; 95% CI: 3.7-16.2), and most fatal bleeding events (42 of 52, 80.1%) occurred in patients exceeding it. The accuracy of the cut-off score (1.75 points) for GI, extracranial or intracranial fatal bleeding appears in Table 6. The negative predictive value for any fatal bleeding is 99.9% and the negative likelihood ratios for GI and extracranial fatal bleeds is 0.08 and 0.20, respectively (Table 6). The cumulative rate of fatal bleeding using the cut-off point appears in Fig. 2. The majority of patients (18 of 19, 94.7%) dying after GI bleeding (OR: 32.5; 95% CI: 4.6-115.8) and most patients (33 of 38, 86.8%) dying after extracranial bleeding (OR: 12.0; 95% CI 4.5-34.8) had score values above the cut-off point.

Discussion

Our findings, obtained from a large series of consecutive patients receiving anticoagulation for acute VTE, confirm the validity of the score. About two-thirds of patients were considered to be at low-risk according to the risk score with a 3-month rate of fatal bleeding of 0.10%, about one-third were considered to be at moderate-risk and had a rate of 0.72%, and about 2% were considered to be at high-risk with a rate of 1.44%. Interestingly, the best cut-off point (score, 1.75, only slightly over the upper limit of the low risk category) correctly identified the subgroup of patients with 7 to 30-fold higher risk for fatal bleeding (depending on sites of bleeding). In patients at high risk for fatal bleeding it may be wise to administer anticoagulants at a lower intensity (or even to withhold anticoagulation and insert a vena cava filter), alter other medications, or monitor therapy and signs of bleeding more closely, as early detection of major bleeding might reduce mortality. On the other hand, our score also identified two in every 3 patients (64.1%) with a very low (0.10%) rate of fatal bleeding, which is also reassuring. Only 10 of 52 patients with fatal bleeds scored less than

Table 4
Risk categories (low-, intermediate-, high-) of the patients according to score, and corresponding rates of fatal bleeding.

Points	All patients (N = 15,206)	Fatal bleeding (N = 52)	Fatal bleeding rate per risk category
-1	667 (4.4%)	0	0
0-0.99	4,646 (30.6%)	2 (3.8%)	0.04%
1-1.99	4,465 (29.4%)	8 (15.4%)	0.18%
2-2.99	2,774 (18.2%)	15 (28.9%)	0.54%
3-3.99	1,664 (10.9%)	13 (25%)	0.78%
4-4.99	704 (4.6%)	11 (21.2%)	1.56%
5-5.99	229 (1.5%)	3 (5.8%)	1.31%
6-6.99	49 (0.3%)	0	0
7-7.99	7 (0.05%)	0	0
8-8.5	1 (0.007%)	0	0
Risk category,			
Low (<1.5)	9,748 (64.1%)	10 (19.2%)	0.10%
Moderate (1.5-4)	5,111 (33.6%)	37 (71.2%)	0.72%
High risk (>4)	347 (2.28%)	5 (9.6%)	1.44%

Table 6
Accuracy of the high-risk (>4 points) and the cut-off (1.75 points) scores for predicting fatal bleeding.

	Any	Gastrointestinal	Extracranial	Intracranial
High-risk score (>4 points),				
Sensitivity	9.6%	15.8%	10.5%	7.1%
Specificity	97.8%	97.7%	97.7%	97.7%
Positive predictive value	1.4%	0.9%	1.2%	0.35%
Negative predictive value	99.7%	99.9%	99.8%	99.9%
Positive likelihood ratio	4.27	6.97	4.65	3.14
Negative likelihood ratio	0.92	0.86	0.92	0.95
Cut-off score (1.75 points),				
Sensitivity	80.8%	94.7%	86.8%	64.3%
Specificity	64.5%	64.4%	64.4%	64.3%
Positive predictive value	0.8%	0.3%	0.6%	0.2%
Negative predictive value	99.9%	100%	99.9%	99.9%
Positive likelihood ratio	2.27	2.66	2.44	1.80
Negative likelihood ratio	0.30	0.08	0.20	0.56

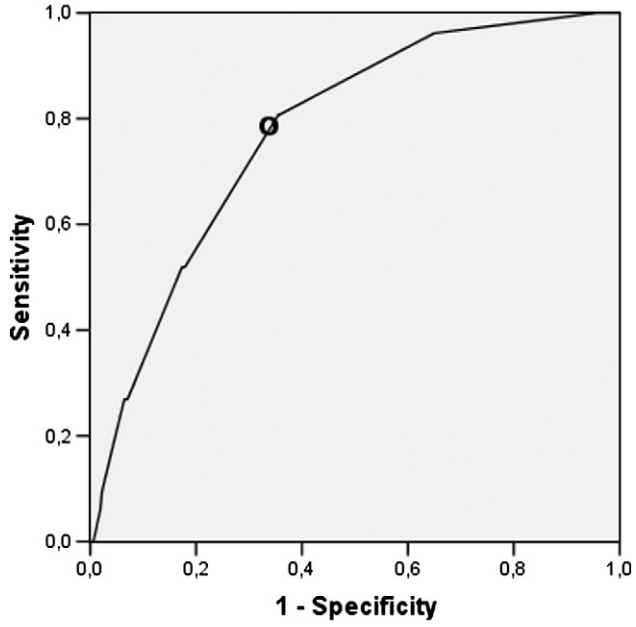

Fig. 1. Receiver operating characteristics curve for any fatal bleeding according to the continuous score (c-statistic 0.775). The black circle represents the position of the cut-off point (score, 1.75) with the highest combined sensitivity (81%) and specificity (64.5%).

1.75 (false negative), what explains the roughly 100% negative predictive value. According to the c-statistic, our score performance was comparable to (or even better than) other well known scores used in clinical practice [18,19] to predict major bleeding in different patient populations.

Our score had statistically significant value, but should be considered only a first step for better understanding the effect of combined risk factors. Its positive predictive value in patients at high-risk is low (1.4%), and its positive likelihood ratio (4.27) is close to the level for moderate performance [20]. The c-statistic reflects the ability of the prediction model to discriminate the outcome (a value of 1.0 reflects perfect discrimination; 0.5 is no better than chance alone). Thus, it seems to be of value for decision making in clinical practice. Moreover, our score performed better in predicting fatal GI bleeding according to the

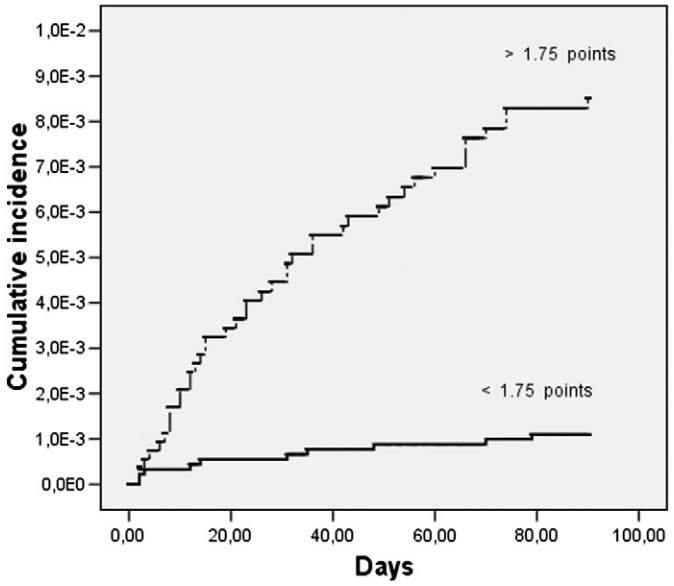

Fig. 2. Cumulative incidence of fatal bleeding according to a cut-off score of 1.75.

c-statistic (0.869) and the positive likelihood ratio (6.97), and worse in predicting fatal intracranial bleeding. Thus, our findings suggest that GI and intracranial bleeding may have different risk factors, and may deserve a different approach. Specific risk-factors for intracranial bleeding (i.e., arterial hypertension or previous intracranial bleeding) are not adequately weighed in our score to predict this outcome. Therefore, in order to more precisely assess the risk for fatal bleeding, it would be wise to use specific scores for different sites of bleeding.

The present study has some potential limitations that should be addressed. First, RIETE does not have a standardized protocol to treat their patients. Thus, physicians treat VTE and bleeding episodes according to local clinical practice. Second, we do not have enough data to assess the influence of elements that may change during the course of the disease, like the INR control, the use of concomitant medications or the presence of intercurrent diseases. Third, the score was validated in a further RIETE cohort, which is not a completely independent patient sample, and therefore, unrecognized flaws that could be present in the previous study may be reproduced in this. However, while only Spanish patients were included in the index study, in the current cohort sample one in every 3 patients was coming from other countries. Finally, the rate of fatal bleeding in the former study was 0.55% (95% CI: 0.47-0.65)[14] and in the current study 0.34% (95% CI: 0.27-0.45). A plausible explanation for the lower rate of fatal bleeding in the current study may be the lower proportion of patients with independent predictors for fatal bleeding, such as age over 75 years (46% vs. 63%), recent immobility (29% vs. 47%) or severe renal insufficiency (19% vs. 27%) compared to the former series [14]. In contrast, the use of thrombolytics was more frequent in patients with fatal bleeding in this study (3 cases, 5.9%) compared to the original (2 cases, 1.5%). This is a relevant difference between the derivation and the validation cohorts that may explain part of the variation in the score accuracy.

In summary, the current study validated the accuracy of the fatal bleeding score, and reveals the greatest performance for extracranial bleeds. This score still needs to be validated in an independent patient sample, but it might represent a valid tool for tailoring anticoagulation of VTE patients at high-risk for fatal bleeding.

Conflict of Interest Statement

No conflicts of interest that could influence this work were declared.

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Appendix A

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