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Regular Article

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.