



Early View

Original article

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Derivation and validation of a clinical prediction rule for thrombolysis-associated major bleeding in patients with acute pulmonary embolism: the BACS score

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Running head: Bleeding with lytics in PE

ABSTRACT

Background: Improved prediction of the risk of major bleeding in patients with acute pulmonary embolism (**PE**) receiving systemic thrombolysis is crucial to guide the choice of therapy.

Methods: The study included consecutive patients with acute PE who received systemic thrombolysis in the RIETE registry. We used multivariable logistic regression analysis to create a risk score to predict 30-day major bleeding episodes. We externally validated the risk score in patients from the COMMAND VTE registry. We also compared the newly created risk score against the Kuijer and RIETE scores.

Results: Multivariable logistic regression identified four predictors for major bleeding: recent major **Bleeding** (3 points), **Age >75 years** (1 point), active **Cancer** (1 point), and **Syncope** (1 point) (**BACS**). Among 1,172 patients receiving thrombolytic therapy in RIETE, 446 (38%) were classified as having low-risk (none of the variables present, 0 points) of major bleeding according to the BACS score, and the overall 30-day major bleeding rate of this group was 2.9% (95% CI, 1.6 to 4.9%), compared with 44% (95% CI, 14 to 79%) in the high-risk group (>3 points). In the validation cohort, 51% (149/290) of patients were classified as having low-risk, and the overall 30-day major bleeding rate of this group was 1.3%. In RIETE, the 30-day major bleeding event rates in the Kuijer and RIETE low-risk stratum were 5.3% and 4.4%, respectively.

Conclusions: The BACS score is an easily applicable aid for prediction of the risk of major bleeding in the population of PE patients who receive systemic thrombolysis.

Abstract word count: 250

Key Words: Pulmonary embolism, thrombolysis, bleeding, survival.

INTRODUCTION

Pulmonary embolism (**PE**) remains a worldwide major health issue (1). PE is among the most common causes of vascular death after myocardial infarction and stroke, and is the leading preventable cause of death in hospitalized patients (2).

The cornerstone of PE management includes rapid, effective anticoagulation (3). In patients with acute symptomatic PE, systemic thrombolytic therapy has been shown to reduce short-term all-cause and PE-specific mortality but is associated with increased risk of major bleeding (including intracranial hemorrhage [**ICH**]) (4). Since the net clinical benefit in unselected patients remains uncertain, clinical practice guidelines recommended the use of thrombolytic therapy for 1) patients with acute symptomatic PE and haemodynamic instability who do not have major contraindications owing to bleeding risk, and 2) patients without hypotension who experience hemodynamic deterioration while receiving anticoagulant therapy (5). Therefore, improved prediction of the risk of major bleeding in patients with acute PE receiving systemic thrombolysis is crucial to guide the choice of therapy (6). Unfortunately, however, no risk scores have been derived to predict major bleeds in PE patients treated with thrombolytics, and only one risk score has been developed, based on administrative claims data, to predict ICH in this group (PE-CH score) (7).

The Registro Informatizado de la Enfermedad TromboEmbólica (**RIETE**) Registry is an ongoing, multicenter, international, prospective registry of consecutive patients with symptomatic, objectively confirmed, acute venous thromboembolism (**VTE**) (8, 9). We derived and externally validated a clinical prediction score for major bleeding in PE patients treated with thrombolysis, identifying patients with either high or low probability of having a major bleed.

METHODS

Study design

We performed a derivation and validation study of a clinical scoring system to identify major bleeding events in PE patients treated with thrombolysis.

Derivation cohort

We used the data from the RIETE registry, which prospectively collects information on patients with confirmed acute VTE (ClinicalTrials.gov identifier, NCT02832245). All patients, or their healthcare proxy, provided written or oral informed consent for participation in the registry in accordance with local ethics committee requirements. Previous publications have described the design and conduct of the RIETE registry (10).

Patient selection

Confirmatory testing for PE consisted of high probability ventilation-perfusion (**V/Q**) scintigraphy (11), positive contrast-enhanced, PE-protocol, helical chest computerized tomography (**CT**) [single or multi-detector CT] for PE (12), or lower limb venous compression ultrasonography positive for proximal deep vein thrombosis (**DVT**) in a patient presenting with chest symptoms (13). This study included patients who were enrolled in RIETE, and underwent systemic thrombolytic therapy (at least 50% of the recommended dose of the thrombolytic agent) for acute PE from January 1, 2001, through January 31, 2019.

Study endpoint

The primary outcome used for derivation and validation of the prediction rule was major bleeding 30 days after diagnosis of acute symptomatic PE. We defined major bleeding episodes as those that required a transfusion of at least 2 units of blood, were retroperitoneal, intrapericardial, intraocular, spinal or intracranial, or were fatal (14).

Risk factors for bleeding

The following variables were examined: age (>75 years vs. ≤75 years), sex (male/female), weight (>70 Kg vs. ≤70 Kg), previous use of non-steroidal anti-inflammatory or antiplatelet therapy (yes/no), chronic heart or lung disease (yes/no), recent (<30 days before PE) major bleeding (yes/no), active cancer

(defined as newly-diagnosed cancer or cancer being treated [i.e., surgery, chemotherapy, radiotherapy, hormonal or support therapy]) (yes/no), recent immobility (defined as nonsurgical patients assigned to bed rest with bathroom privileges for ≥ 4 days in the 2 months before VTE diagnosis) (yes/no), surgery (defined as those who had undergone major surgery in the 2 months before VTE) (yes/no), heart rate (≥ 110 /min vs. <110 /min), syncope (yes/no), hemoglobin (<13 g/dL vs. ≥ 13 g/dL in men; <12 g/dL vs. ≥ 12 g/dL in women), platelet count ($\geq 100 \times 10^9$ /L vs. $<100 \times 10^9$ /L), and serum creatinine (>2 mg/dL vs. ≤ 2 mg/dL).

The RIETE registry restricted all values of these variables to the nearest recorded to the time of PE diagnosis. We imputed missing values where necessary as described below.

Validation cohort

The validation cohort for this study consisted of the subset of 290 patients enrolled in the COntemporary ManageMent AND outcomes in patients with Venous ThromboEmbolic (COMMAND VTE) registry who had acute symptomatic PE, received thrombolytic therapy, and had complete baseline and follow-up data required for this study (15). The COMMAND VTE registry defined major bleeding episodes in a way very comparable to RIETE (those that were fatal, and/or occurred in a critical area or organ [intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome], and/or those associated with a reduction in the hemoglobin level by at least 2 g/dL or leading to transfusion of at least 2 units of blood) (16).

Statistical analysis

We used a stepwise logistic regression model with backward elimination to determine the contribution of all candidate covariates, with a threshold for candidate elimination of >0.05 . Variable selection was based on clinical (see *Risk factors for bleeding*) and statistical significance. Candidate variables that were associated with 30-day major bleeding complications on univariable analysis ($P < 0.20$) were included as potential covariates in the multivariable

logistic regression model. Our main analyses used multiple imputation to replace missing values for non-steroidal anti-inflammatory use (5.5%), antiplatelet use (5.0%), heart rate (1.3%), and creatinine levels (26.8%). Our final model was fitted based on ten multiply imputed datasets using Rubin's rules to combine effect estimates and standard errors to allow for the uncertainty due to imputing missing data (17). We assessed performance of the model by the area under the receiver operating characteristic (**ROC**) curve (18). The study used the Brier score to quantify the overall accuracy of predictions, and used bootstrapping to calculate 95% bias-corrected bootstrap confidence intervals (**CI**) for the c-index. Investigators evaluated model calibration with the modified Hosmer-Lemeshow chi-square statistic, where values < 20 indicate good calibration (19). Model for 30-day major bleeds was assessed for possible overfit using linear shrinkage estimators (20, 21).

A score-based prediction rule for the primary endpoint at 30 days was developed from the logistic regression model by using a regression coefficient-based scoring method (22, 23). Integer scores were assigned by dividing risk-factor coefficients by the lowest coefficient and rounding up to the nearest unit for categorical variables (24). The overall risk score was calculated by adding each component together. We validated the 30-day endpoint model internally using the bootstrap in the derivation dataset by sampling with replacement for 200 iterations (25-27). To assess the robustness of the findings, we estimated the test and performance characteristics of the new risk score in the subgroups of patients with and without hemodynamic instability, and in the subgroup of patients with complete data on renal function. In addition, we also examined rates of major bleeding events within 7 days following the diagnosis of PE.

We also compared the newly created risk score against the Kuijer and RIETE bleeding scores (**Table S1** in the Supplemental Appendix), which were developed and have been validated for predicting the bleeding risk in VTE patients on anticoagulant therapy (28, 29). We examined the proportion of patients who would be reclassified into higher- or lower-risk categories between the new rule and the Kuijer and RIETE scores, and calculated the values of the net reclassification improvement (**NRI**) comparing the prognostic models.

Statistical significance was defined as a two-tailed *P*-value of <0.05 for all analyses. Analyses were performed using Stata, version 12.1 (StataCorp, College Station, Texas) for Windows.

RESULTS

Study derivation sample

The study cohort consisted of 1,172 patients (570 men and 602 women) with confirmed PE who received thrombolytic therapy (**Figure 1**). Of 927 patients with complete information on the type and thrombolytic dose, 463 (50%) received tissue plasminogen activator (**tPA**), 282 (30%) reteplase, 121 (13%) urokinase, 36 (3.9%) streptokinase, and 25 (2.7%) tenecteplase. Forty-two (4.5%; 95% confidence interval [**CI**], 3.3-6.1%) patients received reduced doses of lytics (i.e., between 50 and 75% of the standard regimen).

Table 1 shows the clinical symptoms, predisposing conditions, and relevant findings at presentation among the included patients. Median age was 63 years (interquartile range [**IQR**], 47-74). Of the 1,172 patients, 265 (23%; 95% CI, 20-25%) were older than 75 years, 147 (13%; 95% CI, 11-15%) had cancer, and 14 (1.2%; 95% CI, 0.7-2.0%) had a history of recent major bleeding. At baseline, 69 (5.9%; 95% CI, 4.6-7.4%) patients were receiving nonsteroidal anti-inflammatory drugs, and 149 (13%; 95% CI, 11-15%) patients were receiving antiplatelet agents. Overall, 359 patients (31%; 95% CI, 28-33%) had anemia, 34 (2.9%; 95% CI, 2.0-4.0%) had thrombocytopenia, and 64 (5.5%; 95% CI, 4.2-6.9%) had creatinine levels >2 mg/dL. Patients from the validation cohort had older age, less comorbidity (e.g., immobilization, chronic pulmonary disease, chronic heart disease), fewer signs of hemodynamic severity (e.g., syncope, tachycardia, hypotension), and more risk factors for bleeding (e.g., recent major bleeding, thrombocytopenia) compared to those from the RIETE cohort (**Table 1**).

Outcomes

The study had complete primary outcome information for all (100%) patients at the end of the 30-day follow-up. Within the first 30-days of follow-up, 8.0% of patients died (94 out of 1,172, 8.0%; 95% CI, 6.5% to 9.7%). Sixty-two percent (58 of 94 deaths, 62%; 95% CI, 51% to 72%) of deaths were attributed to PE. Bleeding (8.5%; 8 of 94 deaths), other miscellaneous diseases (26%; 24 of 94 deaths), and unknown disorders (4.3%; 4 of 94 deaths) caused the other deaths. A major bleeding episode occurred in 69 of the 1,172 (5.9%; 95% CI, 4.6-7.4%) PE patients who received thrombolysis in RIETE. The most frequent sites of major bleeding were intracranial (26%; 18 of 69 patients), subcutaneous (22%; 15 of 69 patients), and gastrointestinal (14%; 10 of 69 patients), and the highest mortality occurred after intracranial bleeding (8 of 18 major bleeds, 44%).

Predictors for 30-day major bleeding

The study assessed predictors for 30-day major bleeding complications in 1,084 patients who had complete baseline data required for this study. Results of univariable analysis for all potential predictors are shown in **Table 2**. Significant predictors of major bleeding through 30-day after the diagnosis of PE in multivariable analysis included recent major bleeding (adjusted odds ratio [OR_a] 10.4; 95% CI, 3.2-33.6), age >75 years (OR_a 2.0; 95% CI, 1.2-3.4), active cancer (OR_a 2.1; 95% CI, 1.1-3.9), and syncope as presentation of PE (OR_a 1.7; 95% CI, 1.0-2.9). Thrombolytic dosing, body mass index and creatinine clearance were not predictors of major bleeding in the univariable analysis. Also, there was not a significant interaction between thrombolytic dosing and body weight. Notably, although weight, previous use of non-steroidal inflammatory or antiplatelet therapy, anemia and thrombocytopenia were associated with the primary endpoint in univariable analysis (**Table 2**), there was no significant effect after adjustment for other factors in the multivariable model.

Risk score derivation

Patients with higher risk scores were at higher risk for major bleeding events; the odds ratio for complications per one-point increase in the score was 1.99 (95% CI, 1.55 to 2.55; P <0.001). Points were assigned to variable categories to

create a point-score model (range, 0-6) for prediction of major bleeding, as shown in **Table 3**. The total point scores were used to classify patients as low- (0 points), intermediate- (1-3 points), or high-risk (>3 points). Cumulative incidence of 30-day bleeding events differed substantially among stages for the model (2.9%, 7.3%, and 44% for low-, intermediate- and high-risk, respectively) (**Figure 2**) (**Table 3** and **Table S2 in the Supplemental Appendix**). The study showed (1) an increase in the rate of stage 3 classification in patients who died, compared to the rate of stage 3 classification in patients who survived (positive likelihood ratio [LR] 12.8; 95% CI, 3.5 to 46.6), and (2) a slight decrease in the rate of stage 1 classification in patients that died, compared to the rate of stage 1 classification in patients that survived (negative LR 0.48; 95% CI, 0.29 to 0.79). Of note, only 4 (0.9%; 95% CI, 0.2-2.3%) of the 446 low-risk patients experienced an episode of intracranial bleeding, and none of the low-risk PE patients suffered a fatal bleeding event.

In the cohort of stable patients (n =911), 43% (390/911) of patients were classified as having low-risk, and the overall 30-day major bleeding rate of this group was 2.7% (95% CI, 1.3 to 4.9%), compared with 5.4% (95% CI, 1.1 to 15%) in the low-risk group (21%; 56/261) of unstable patients. **Table S3** in the Supplemental Appendix shows the test and performance characteristics of the BACS score in the subgroup of patients who had complete information on renal function. Consistently, cumulative incidence of 7-day bleeding events differed substantially among stages for the model (2.5%, 6.4%, and 33% for low-, intermediate- and high-risk, respectively).

Risk score validation

Analyses suggested that the final model had modest predictive performance (**Table 4**). In the derivation set (n =1,084), the area under the ROC curve was 0.67 (0.58 to 0.72) for 30-day major bleeding events. The internally validated area under the curve and Brier score were 0.66 (95% CI, 0.59 to 0.73) and 0.02, respectively. The final model was well calibrated (Hosmer-Lemeshow chi-square statistic, 0.48; P value for the lack of fit = 0.79).

Of the 290 patients included in the COMMAND VTE validation cohort, the BACS score classified 51% (149 of 290) of patients as low-risk, 46% (134 of 290) as intermediate-risk, and 2.4% (7 of 290) as high-risk. Cumulative incidence of 30-day major bleeding complications differed substantially among BACS risk classes (1.3% [2/149], 6.7% [9/134], and 29% [2/7] for low-, intermediate- and high-risk, respectively). None of the 149 low-risk patients experienced an episode of intracranial bleeding or a fatal bleeding event (**Table 3**). The predictive model had a c-index of 0.72 (95% CI, 0.60 to 0.84) in the external validation cohort.

Comparison with previous bleeding scores

When dichotomized as low- versus intermediate- and high-risk, the Kuijer and RIETE scores identified 19% and 35% of patients in the derivation cohort as low-risk, respectively. The 30-day major bleeding event rates in the low-risk subgroups were 5.3% and 4.4%, respectively. Two patients (2 of 227 patients; 0.9%) in the Kuijer low-risk subgroup, and 5 patients (5 of 411 patients; 1.2%) in the RIETE low-risk subgroup experienced an episode of intracranial bleeding; and 1 patient in the Kuijer low-risk subgroup, and 1 patient in the RIETE low-risk subgroup had a fatal bleed (0.5%, 0.4% and 0.2%, respectively) (**Figure 3**).

Compared with the Kuijer score, the NRI was estimated at 0.18 ($P < 0.01$) with the BACS score, resulting from a net 1.5% decrease in patients who bled correctly identified as being at high risk but a net 19.8% increase in patients who did not bleed correctly identified as at lower risk. Compared with the RIETE score, the NRI was estimated at 0.11 ($P = 0.04$) with the BACS score, resulting from a net 7.2% increase in bleeding patients correctly identified as being at high risk and a net 3.6% increase in non-bleeding patients correctly identified as at lower risk (**Table S4** in the Supplemental Appendix).

DISCUSSION

We have developed and externally validated a practical risk score (**BACS**) that predicts a PE patient's risk of major bleeding after systemic thrombolysis on the basis of a set of routinely assessed patient characteristics. We found that the

largest amount of prognostic information was contained in four predictors: history of recent major bleeding, older age, active cancer, and syncope. The BACS score showed significant improvement on current scores for identification of PE patients at low-risk of major bleeding when receiving systemic thrombolytic therapy.

Reliable identification of prognostic factors for major bleeding after thrombolysis for PE management has been difficult, because the number of major bleeding events during follow-up in most individual studies was not large enough for robust analyses (30). By using data from the large RIETE registry, we were able to include 1,172 patients with acute symptomatic PE who received systemic thrombolysis, of whom 69 had a major bleeding episode during the first 30-days of follow-up. This number of hemorrhages enabled us to undertake multivariable analyses. In addition, we were able to externally validate the new score in a separate population to ensure that the low-risk group has low-risk of major bleeding events. The results confirmed the robustness of the model, with no evidence of over-fitting.

In our study, recent major bleeding was the most important predictor of hemorrhage in PE patients receiving thrombolytic therapy. This finding was in agreement with previous investigations aiming to predict the risk of major bleeding while on anticoagulant therapy (29). Prior history of bleeding may reflect on a group of other covariates that collectively increase the risk of bleeding. Our analyses showed that major bleeding under thrombolytic therapy is also related to age (7, 31). This raises the issue of the net clinical benefit of thrombolytic therapy in elderly versus younger patients with acute symptomatic PE (4). Prior evidence suggests that the risk of major bleeding events is greatly increased among patients with active cancer (32). We confirmed that, compared with patients with non cancer-associated PE, those with cancer-associated PE who received thrombolysis had a 2-fold increased risk for major bleeding complications. Patients with syncope as the initial presentation of PE had an increased risk of major bleeding (7.6%), and intracranial bleeding (1.7%). The reason for this excess risk is unclear. Some patients with syncope might suffer from head injury, and might be more likely to bleed after thrombolytic therapy.

For patients with syncope as the initial presentation of their PE, it might be reasonable to consider a CT scan of the head prior to administration of systemic thrombolysis. However, this issue requires further investigation.

The findings from this study may have practical implications. Over the past years, the technological landscape for management of acute severe PE is rapidly evolving, and novel endovascular procedures are increasingly being used to treat these patients (33, 34). In the absence of randomized clinical trials to provide a direct comparison of reperfusion strategies, the recent scientific statement from the American Heart Association suggests consideration of catheter-directed therapies for PE patients who have a significant bleeding risk (6). The BACS score provides clinicians and patients with a framework for discussing therapeutic strategies and researchers with the ability to identify at-risk study populations that maximize the efficiency and power of clinical trials. It is also important to highlight that this score should supplement, rather than supplant, clinical decision-making. For example, active liver cirrhosis, severe thrombocytopenia, or recent intracranial surgery are known to be associated with increased risk of bleeding, and hence, thrombolysis is rarely used in these patients. This might, in part, explain why such factors were not identified as predictors of major bleeding in multivariable analysis in our study.

Our study has some limitations. First, this model proposed had a modest discrimination. However, the BACS score was developed to identify PE patients who might receive systemic thrombolysis with a very low-risk for major bleeding, intracranial bleeding, and fatal bleeding. In fact, the score was able to identify one third of PE patients receiving thrombolysis with a risk for intracranial bleeding less than 1%, and none of these patients experienced a fatal bleeding episode. Second, the RIETE registry did not systematically collect data some clinical characteristics that had been previously reported as risk factors for bleeding, such as peripheral vascular disease or stroke, and we could not compare the newly created risk score against the PE-CH score (9). In addition, the score is relevant only to patients with similar characteristics to those who received thrombolysis in the RIETE registry and its generalizability to other patient populations for whom thrombolysis is not selected due to inherently high

risk of bleeding (e.g., very recent surgery, cirrhosis, severe thrombocytopenia) may be limited. Third, the RIETE registry does use a specific definition for major bleeding episodes, and our study could not test other bleeding classification (**Table S5** in the Supplemental Appendix). Finally, we used dichotomized variables that simplified the creation of a risk score, but may provide less granular information than continuous variables.

In conclusion, our proposed risk prediction rule, based on easily available patient characteristics, could support physicians in their assessment of the risk of bleeding with systemic thrombolysis and serve as a good starting point for discussing the pros and cons of the available reperfusion options. Future studies should assess the clinical usefulness of this score for patient selection for the choice of reperfusion therapies, and the safety of ensuing outcomes.

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Figure 1. Study cohort flow diagram

Figure 2. Cumulative major bleeding complications stratified by stage for the risk index

Figure 3. Frequency of a) 30-day major bleeding, b) 30-day intracranial bleeding, and c) 30-day fatal bleeding events according to baseline prognostic tests

Table 1. Baseline characteristics of patients in derivation and validation cohorts

	<i>Derivation cohort</i> <i>N = 1,172</i>	<i>Validation cohort</i> <i>N = 290</i>	<i>P value</i>
Clinical characteristics, n (%)			
Age, years, median (25 th -75 th percentiles)	63 (47-74)	66 (57-75)	0.03
Age >75 years	265 (23%)	67 (23%)	0.93
Male gender	570 (49%)	117 (40%)	0.01
Risk factors for VTE, n (%)			
Cancer [†]	147 (13%)	32 (11%)	0.55
Recent surgery [‡]	108 (9.2%)	23 (7.9%)	0.57
Immobilization ^γ	254 (22%)	20 (6.9%)	<0.001
Concomitant medication, n (%)			
Nonsteroidal anti-inflammatory drugs	69 (5.9%)	12 (4.1%)	0.31
Antiplatelet agents	149 (13%)	23 (7.9%)	0.02
Comorbid diseases, n (%)			
Recent major bleeding [‡]	14 (1.2%)	13 (4.5%)	<0.001
COPD	115 (9.8%)	9 (3.1%)	<0.001
Congestive heart failure	58 (4.9%)	4 (1.4%)	<0.01
Clinical symptoms and signs at presentation, n (%)			
Syncope	527 (36%)	58 (20%)	<0.001
Heart rate \geq 110/minute	577 (49%)	79 (27%)	<0.001
Arterial oxyhemoglobin saturation (SaO ₂) <90%	365 (31%)	239 (82%)	<0.001
SBP <90 mm Hg	261 (22%)	46 (16%)	0.02
Simplified PESI			
Low-risk	244 (21%)	28 (10%)	<0.001
High-risk	928 (79%)	262 (90%)	<0.001
Laboratory findings, n (%)			
Anemia*	359 (31%)	94 (32%)	0.57
Platelet count <100 x 10 ⁹ /L	34 (2.9%)	25 (8.6%)	<0.001
Creatinine >2 mg/dL	64 (5.5%)	8 (2.8%)	0.07

Abbreviations: VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; PESI, Pulmonary Embolism Severity Index.

[†] Active or under treatment in the last year.

[‡] In the previous month.

^y Immobilized patients are defined in this analysis as non-surgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for ≥ 4 days in the month prior to PE diagnosis.

* < 13 g/dL in men; < 12 g/dL in women.

Table 2. Factors associated with 30-day major bleeding in 1,172 patients with acute symptomatic pulmonary embolism who received thrombolysis

<i>Risk factor</i>	<i>Unadjusted OR (95% CI)</i>	<i>P value</i>	<i>Adjusted OR (95% CI)</i>	<i>P value</i>
Age >75 years	2.04 (1.23-3.41)	<0.01	2.02 (1.19-3.43)	<0.01
Male gender	0.71 (0.43-1.16)	0.17	-	-
Weight >70 Kg	0.99 (0.97-1.00)	0.09	-	-
Non-steroidal anti-inflammatory therapy	2.30 (1.05-5.03)	0.04	-	-
Antiplatelet therapy	1.86 (1.00-3.45)	0.05	-	-
Chronic heart disease	0.87 (0.26-2.84)	0.81	-	-
Chronic lung disease	1.04 (0.46-2.33)	0.92	-	-
Recent major bleeding [†]	9.50 (3.09-29.16)	<0.001	10.36 (3.20-33.56)	<0.001
Cancer [‡]	2.04 (1.12-3.72)	0.02	2.09 (1.12-3.89)	0.02
Immobilization ^γ	0.75 (0.40-1.42)	0.38	-	-
Recent surgery [†]	1.32 (0.61-2.83)	0.48	-	-
Systolic blood pressure >160 mmHg	2.04 (0.60-6.96)	0.25	-	-
Heart rate ≥110/min	1.25 (0.76-2.03)	0.38	-	-
Syncope	1.71 (1.05-2.80)	0.03	1.72 (1.04-2.85)	0.03
Anemia*	1.49 (0.91-2.46)	0.12	-	-
Thrombocytopenia**	2.20 (0.75-6.44)	0.15	-	-
Creatinine >2 mg/dL	1.60 (0.66-3.90)	0.30	-	-
Previous use of oral anticoagulation	1.82 (0.17-14.66)	0.57	-	-
Thrombolytic dosing***	1.21 (0.36-4.04)	0.76	-	-

Abbreviations: OR, odds ratio; CI, confidence interval.

[†] In the previous month.

[‡] Active or under treatment in the last year.

^γ Immobilized patients are defined in this analysis as non-surgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for ≥4 days in the month prior to PE diagnosis.

* <13 g/dL in men; <12 g/dL in women.

** <100 × 10⁹/L.

*** 50-75% vs. >75% of the standard regimen.

Hosmer and Lemeshow Goodness-of-Fit Test statistic was used for the complete case analysis: chi-square (3 degrees of freedom) = 0.48; P value = 0.79.

Table 3. The staging system

Predictor	Points		
Previous major bleeding	3		
Age >75 years	1		
Cancer	1		
Syncope	1		

Risk classification	Low	Intermediate	High
Points	0	1-3	>3
RIETE derivation cohort			
Patients, %	38.1	61.2	0.8
30-day major bleeding, %	2.9	7.3	44.4
30-day intracranial bleeding, %	0.9	1.8	11.1
30-day fatal bleeding, %	0	1.1	22.2
COMMAND VTE validation cohort			
Patients, %	51.4	46.2	2.4
30-day major bleeding, %	1.3	6.7	28.6
30-day intracranial bleeding, %	0	2.2	14.3
30-day fatal bleeding, %	0	0	0

Points are assigned for each variable of the scoring system to obtain a total point score (range, 0–6). The total point score is used to classify patients as low-risk (0 points), intermediate-risk (1-3 points), or high-risk (>3 points). Model-predicted 30-day major bleeding events are shown by stage.

Table 4. Model performance

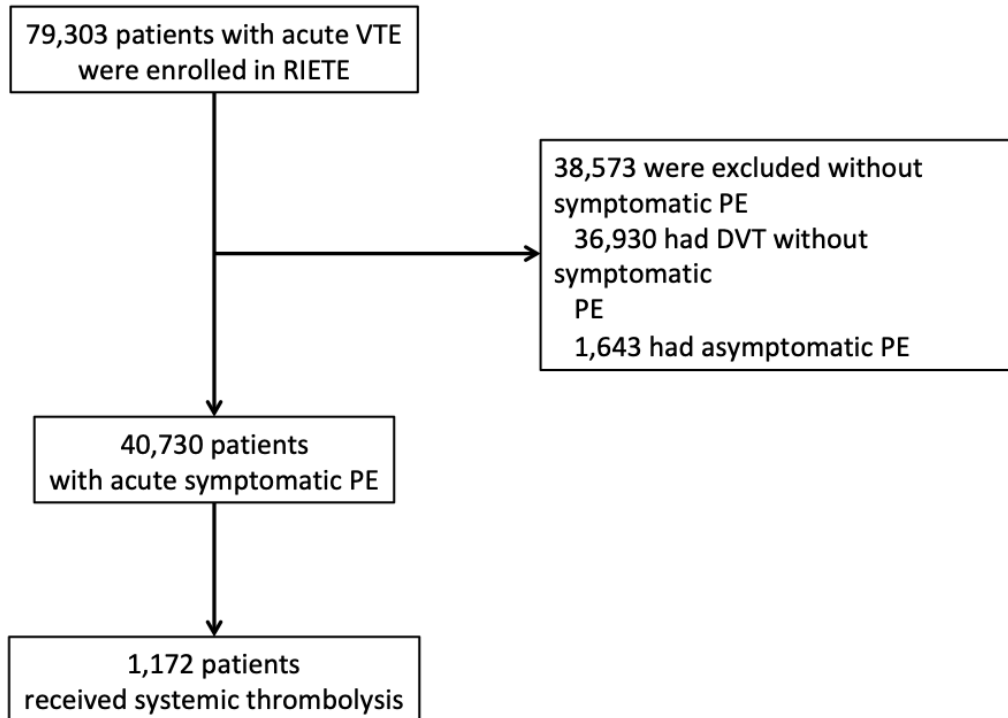
Variable	Study cohort	
	Predicted	Observed
C-index (95% CI)	0.67 (0.58-0.72)	
30-day major bleeding events, %		
Low-risk	3.4	2.9
Intermediate-risk	7.8	7.3
High-risk	43.7	44.4

Abbreviations: CI, confidence interval.

BACS score: recent major bleeding: 3 points; age >75 years: 1 point; active cancer: 1 point; syncope: 1 point. Points are assigned for the presence of each variable. The sum of the variable points produces the total point score (range, 0–6). BACS risk staging increased with point totals: low-risk (0 points), intermediate-risk (1–3 points), or high-risk (>3 points).

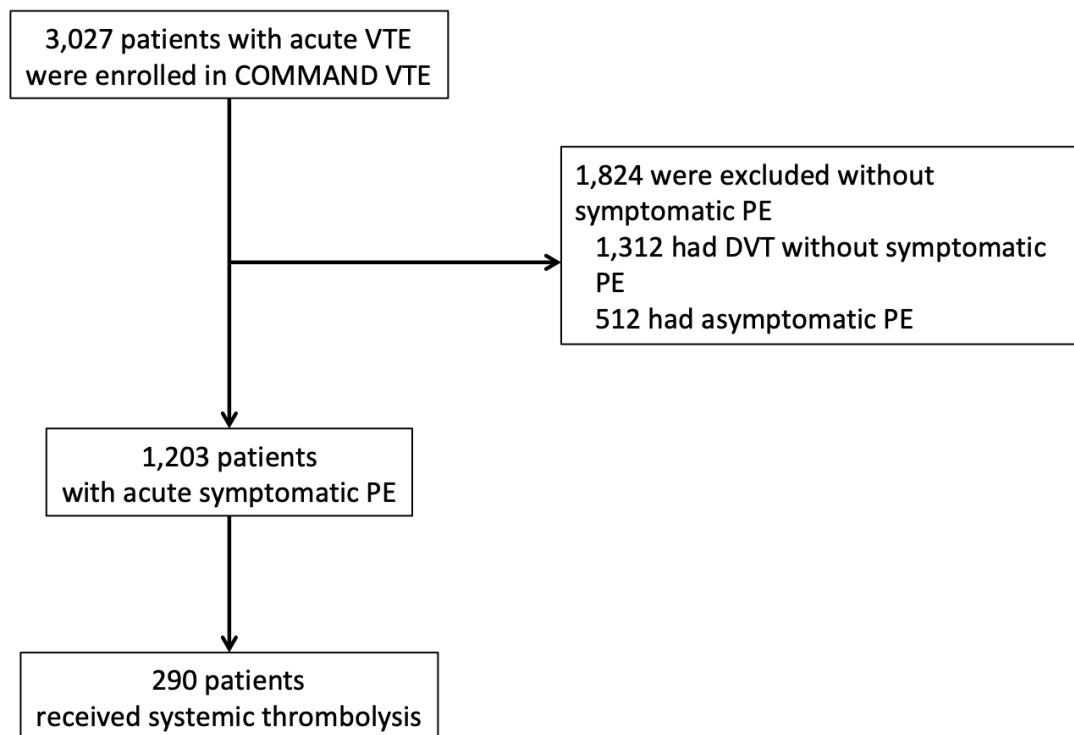
Figure 1.

A) RIETE derivation cohort



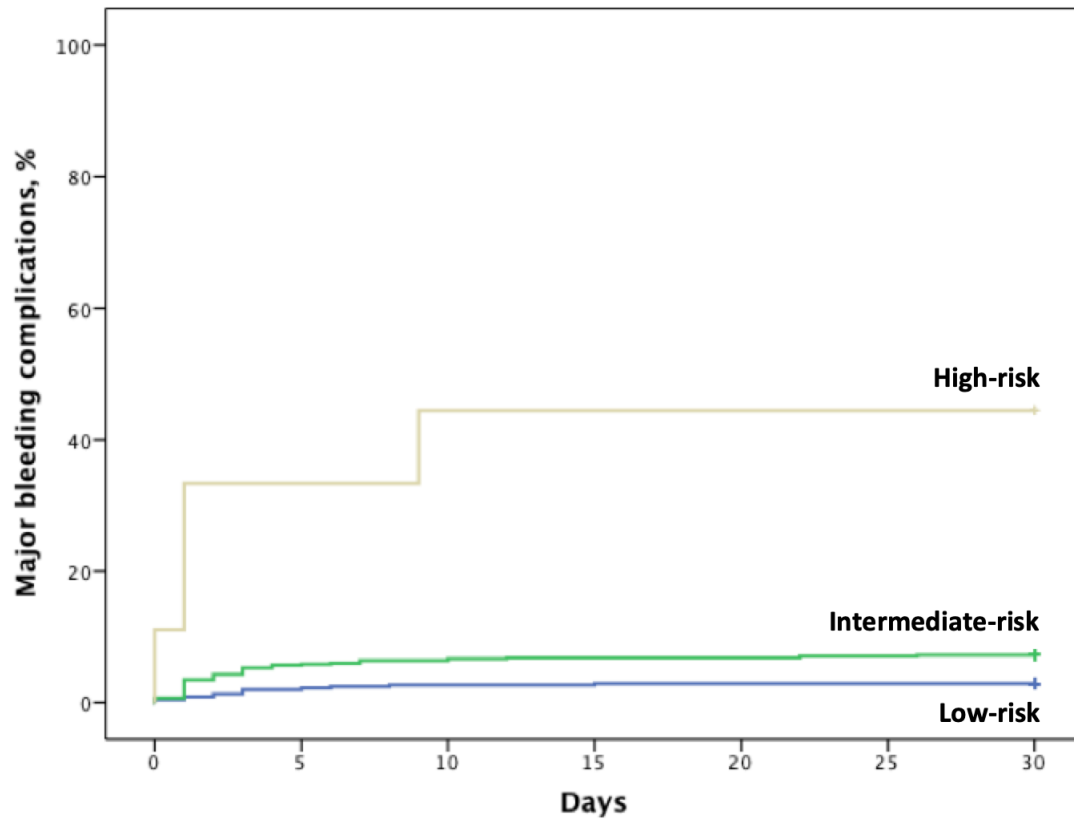
Abbreviations: VTE, venous thromboembolism; RIETE, Registro Informatizado de la Enfermedad Tromboembólica; PE, pulmonary embolism; DVT, deep vein thrombosis.

B) COMMAND VTE validation cohort



Abbreviations: VTE, venous thromboembolism; COMMAND VTE, COntemporary ManageMent AND outcomes in patients with Venous ThromboEmbolism; PE, pulmonary embolism; DVT, deep vein thrombosis.

Figure 2.

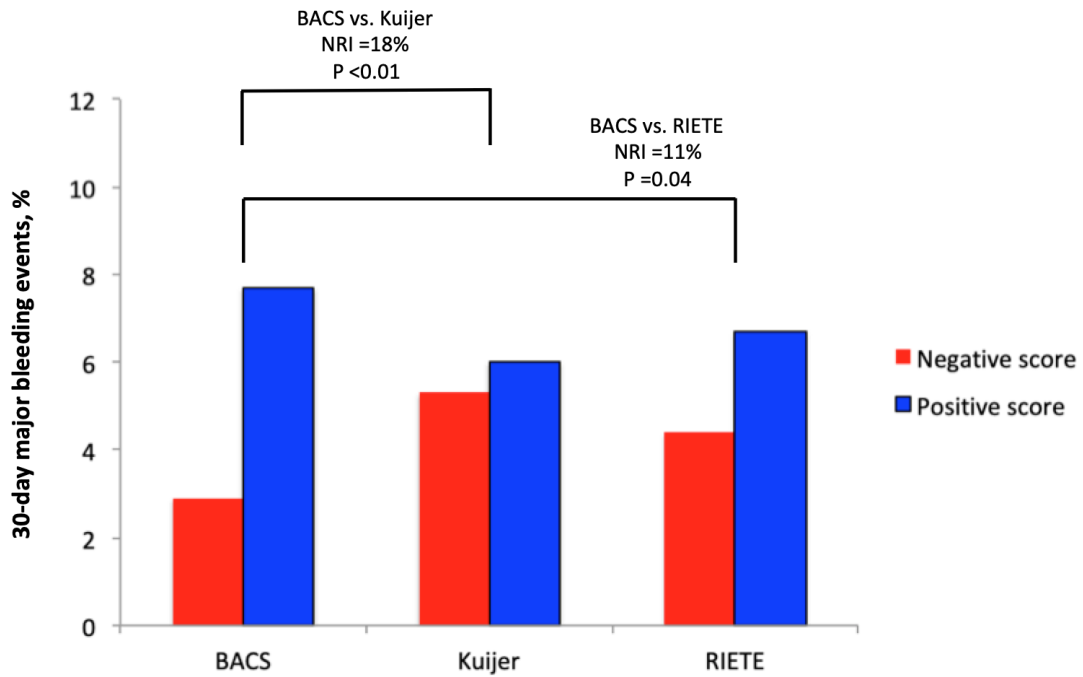


BACS score: recent major bleeding: 3 points; age >75 years: 1 point; active cancer: 1 point; syncope: 1 point. Points are assigned for the presence of each variable. The sum of the variable points produces the total point score (range, 0–6). BACS risk staging increased with point totals: low-risk (0 points), intermediate-risk (1–3 points), or high-risk (>3 points).

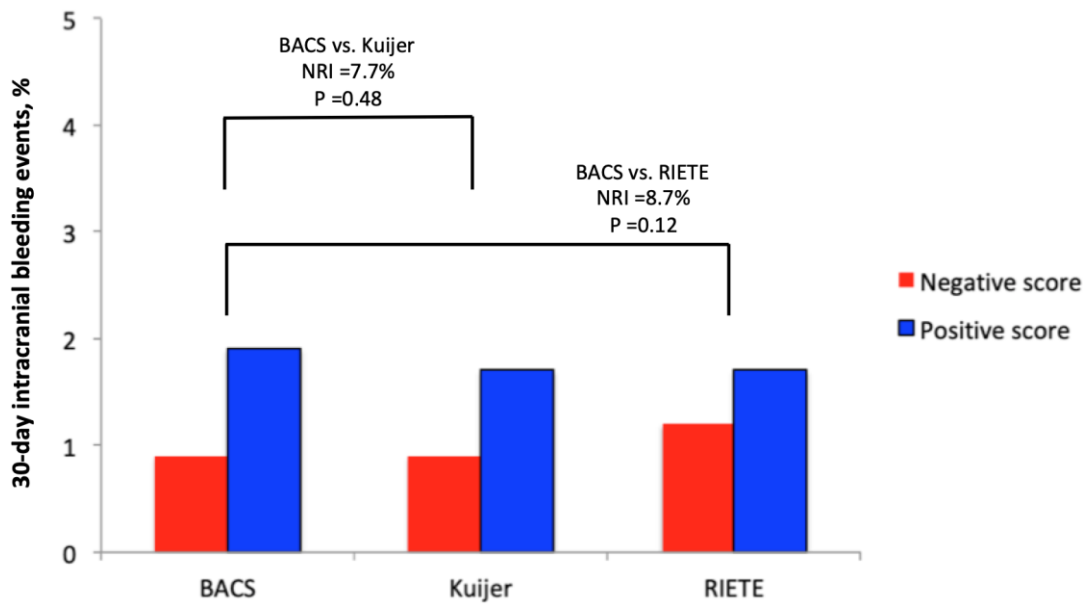
Figure 3.

NRI, net reclassification improvement.

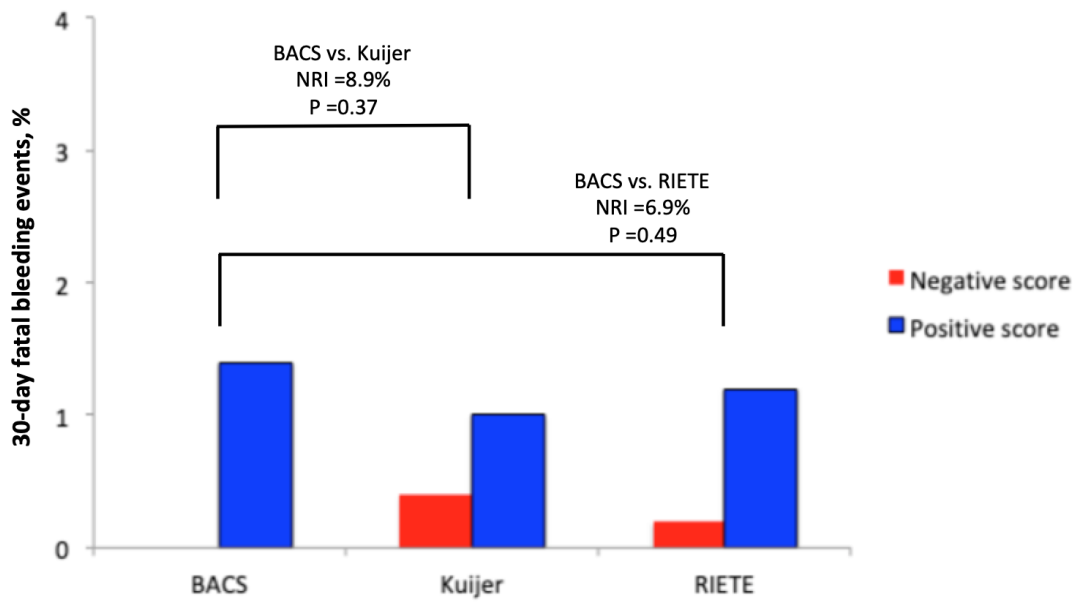
A)



B)



C)



Supplementary Appendix

Contents:

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Table S1. Kuijer and RIETE scores and staging systems for risk of major bleeding complications within 30 days of anticoagulation for PE

A) Kuijer score

Predictor variable	Points
Age >60 year	1.6
Female sex	1.3
Active malignancy	2.2

Points are assigned for the presence of each variable. The sum of the variable points produces the total point score (Kuijer risk score; range, 0–5.1). Kuijer risk staging increased with point totals: low-risk (0 points), intermediate-risk (1-3 points), or high-risk (>3 points).

B) RIETE score

Predictor variable	Points
Recent bleeding	2
Abnormal renal function	1.5
Anemia	1.5
Age >75 years	1
Active malignancy	1
PE diagnosis*	1

Abbreviations: PE, pulmonary embolism.

Points are assigned for the presence of each variable. The sum of the variable points produces the total point score (RIETE risk score; range, 0–8). RIETE risk staging increased with point totals: low-risk (0 points), intermediate-risk (1-4 points), or high-risk (>4 points).

*This variable was not considered for the present analysis.

Table S2. Observed proportion of major bleeding events for each of the risk score points

Point(s)	Patients N (%)	Major bleeding events* N (%)
0	446 (38.1)	13 (2.9)
1	517 (44.1)	30 (5.8)
2	174 (14.8)	19 (10.9)
3	26 (2.2)	3 (11.5)
4	7 (0.6)	2 (28.6)
5	2 (0.2)	2 (100)

*Per risk stratum

Table S3. Test and performance characteristics of the BACS score in the subgroup of 858 patients with complete data on renal function

Risk classification	Low	Intermediate	High
Points	0	1-3	>3
RIETE derivation cohort			
(N =858)			
Patients, %	37.2	61.9	0.9
30-day major bleeding, %	3.4	7.3	50.0
30-day intracranial bleeding, %	0.6	1.7	12.5
30-day fatal bleeding, %	0	1.1	25.0

Table S4. Reclassification of patients who bled or who did not bleed

A) Comparison with Kuijer score

Patients who did not bleed			
(N =1,103)			
		<i>Kuijer score</i>	
		Low-risk	High-risk
<i>BACS score</i>	Low-risk	120 (56%)	313 (35%)
<i>N (%)</i>	High-risk	95 (44%)	575 (65%)
Patients who bled			
(N =69)			
		<i>Kuijer score</i>	
		Low-risk	High-risk
<i>BACS score</i>	Low-risk	4 (33%)	9 (16%)
<i>N (%)</i>	High-risk	8 (67%)	48 (84%)

B) Comparison with RIETE score

Patients who did not bleed			
(N =1,103)			
		<i>RIETE score</i>	
		Low-risk	High-risk
<i>BACS score</i>	Low-risk	236 (60%)	197 (28%)
<i>N (%)</i>	High-risk	157 (40%)	513 (72%)
Patients who bled			
(N =69)			
		<i>RIETE score</i>	
		Low-risk	High-risk
<i>BACS score</i>	Low-risk	9 (50%)	4 (7.8%)
<i>N (%)</i>	High-risk	9 (50%)	47 (92%)

Table S5. Bleeding definition per some of the commonly used criteria

	Major	Minor	Comment
RIETE	Bleeding episodes that require a transfusion of at least 2 units of blood, are retroperitoneal, spinal or intracranial, intraocular, intrapericardial, or are fatal	All non-major bleeds	The RIETE bleeding definition has been in use since 2001
TIMI	Intracranial, clinical signs of hemorrhage with a hemoglobin decrease greater than 5 g/dL	Observed blood loss and decrease in hemoglobin level of 3 to 5 g/dL	Initially developed for cardiovascular diseases other than pulmonary embolism
GUSTO	Intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention	Bleeding that requires blood transfusion but does not result in hemodynamic compromise	Initially developed for cardiovascular diseases other than pulmonary embolism
ISTH	Fatal bleeding and/or symptomatic bleeding in critical area or organ, and/or bleeding causing fall in hemoglobin to 2 g/dL leading to transfusion of two or more units of whole blood or red cells	Clinically relevant: hospital admission for bleeding, physician guidance for bleeding, or change in antithrombotic therapy	Similar to the RIETE bleeding definition