

Initial Anticoagulant Treatment of Pulmonary Embolism

How Can We Better Predict Bleeding in the Early Days Rather Than the Early Months?



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Pulmonary embolism (PE) is the most severe clinical presentation of venous thromboembolic disease (VTE).¹ Anticoagulant treatment is the cornerstone of its management, because it reduces the risk of VTE recurrence (including fatal PE recurrence) but at the cost of an increased risk of bleeding. Bleeding negatively affects the patient's outcome in many ways. First, the bleed may be fatal or cause major morbidity (for example, intracerebral bleeding). More commonly, bleeding occurs in the digestive tract, with acute GI bleeding prompting emergency management. In each of these situations, anticoagulant therapy will need to be stopped, exposing the patient to a risk of recurrent VTE, including fatal PE. In an analysis of the RIETE registry, Nieto et al² reported the evolution of 407 patients who presented with major bleeding (defined as if they were overt and required a transfusion of 2 units of blood or more, or were retroperitoneal, spinal, or intracranial, or when they were fatal).² After 30 days, the rates of VTE recurrence were as high as the rate of re-bleeding, with fatal PE being the second cause of death, after fatal bleeding. Hence, a proper assessment of bleeding risk may improve anticoagulant safety, but also efficacy.

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Several scores have been developed.³ Among them, the most commonly used are the RIETE⁴ and VTE-Bleed⁵ scores (Table 1). The RIETE score aims to determine the risk of major bleeding, including fatal bleeding, during the first 3 months of anticoagulant therapy. It includes six items: age >75 years, recent bleeding, cancer, creatinine >1.2 mg/dL, anemia, PE (vs DVT) index event. This score was developed and validated before the direct-acting oral anticoagulant era, drugs associated with a reduced risk of fatal and intracranial bleeding⁶ but also a modified distribution of bleeding episodes.⁷ The VTE-Bleed⁵ score has been developed and validated in populations exposed to direct-acting oral anticoagulants (Table 1). This score includes six items: active cancer, male patient with uncontrolled hypertension, anemia, history of bleeding, age \geq 60 years, and renal dysfunction (CrCl, 30-60 mL/min). Of note, five of the six items cover the same dimensions as RIETE score, and the VTE-Bleed score was developed in populations selected by inclusion in pivotal trials.

Thus, current management guidelines recommend an assessment of the risk (increased risk of bleeding) for prolonged treatment, after at least 3 months of treatment.¹ However, the assessment of bleeding risk is a constant concern for every clinician prescribing anticoagulant therapy, because the risk of bleeding peaks after anticoagulation initiation. Bleeding incidence is twice as high during the first few weeks of anticoagulation as in the period after the third month.³ Then, in this issue of *CHEST*, Chopard et al⁸ provide an important step forward in the prediction of major bleeding during the hospital stay for acute PE. The authors analyzed data of 2,754 patients admitted for PE, of whom 82 presented a major bleed during their hospital stay (median time to event, 2.0 days; 9 were fatal, 28 required surgery, 58 resulted in a decrease of 2.0 g/dL in hemoglobin level). They built a simple score, the Pulmonary Embolism Syncope-Anemia-Renal Dysfunction (PE-SARD) bleeding score, for prediction of early major bleeding: anemia, + 2.5 points; syncope, + 1.5 points; renal dysfunction, + 1 point. Patients were classified according to the score (Table 1): low risk of major bleeding (0 point), intermediate risk (1-2.5 points), and high risk (>2.5 points). Predicted and observed bleeding rates increased according to the score results, from 0.97% (95%CI, 0.53%-1.62%) in the

TABLE 1] Comparisons of the RIETE, VTE-Bleed, and PE-SARD Bleeding Scores

Score (Length of Follow-up)	Items of the Score		Low Risk	Intermediate Risk	High Risk
RIETE score ^a (3 first months)	Age >75 y	+1	0 point → 20% of patients → MB <1%	1-4 points → 74% → MB = 2.6%	≥4 points → 5.8% → MB = 7%
	Recent bleeding	+2			
	Cancer	+1			
	Creatinine >1.2 mg/dL	+1.5			
	Anemia	+1.5			
	PE (vs DVT) index event	+1			
VTE-Bleed ^b (from day 30 to day 180)	Active cancer	+2	1-1 point → 74% of patients → MB <1%	NA	≥ 2 points → 26% → MB = 2%
	Male patient with uncontrolled hypertension	+1			
	Anemia	+1.5			
	History of bleeding	+1.5			
	Age ≥60 y	+1.5			
	Renal dysfunction (CrCl, 30-60 mL/min)	+1.5			
PE-SARD ^c (end of hospital stay)	Syncope	+1.5	0 point → 52% of patients → MB <1%	1-2.5 points → 35% → MB = 4%	>2.5 points → 12.6% → MB = 9%
	Anemia	+2.5			
	Renal Dysfunction (CKD-EPI CrCl <60 mL/min)	+1			

MB = major bleeding.

^aRIETE score: Investigator-reported overt bleeding requiring transfusion of ≥2 units of blood, intracranial or retroperitoneal or spinal location, or leading to death, in a multicenter international registry.

^bVTE-Bleed score: adjudicated ISTH major bleeding in patients selected for RCT.

^cPE-SARD score: adjudicated ISTH major bleeding in a multicenter registry.

low-risk group (corresponding to half of the initial population), 3.82% in the intermediate-risk group (one third of the population), to 8.93% (95%CI, 6.15%-12.44%) in the high-risk group (accounting to 12.6% of the population). Very interestingly, the PE-SARD compared favorably with the RIETE and VTE-Bleed scores, with a better c-stat and a high proportion of bleeding-risk reclassification.

Now that we have a tool with the potential to define patients at high risk of early major bleeding in PE management, what should we do?

Most patients will not experience major bleeding during the hospital stay. Anticoagulant therapy, therefore, remains the cornerstone of PE management.

Although promising, the robustness of PE-SARD still needs to be challenged. Renal dysfunction was defined with the Chronic Kidney Disease - Epidemiology Collaboration (CKD-EPI) formula, although it is known that the Cockcroft-Gault formula (used to select patients in VTE trials) individualizes a completely distinct population, also at risk of bleeding.⁹ Furthermore, renal dysfunction may be transient, because acute kidney injury is diagnosed in one third of PE patients,¹⁰ is

associated with higher risk of bleeding,¹⁰ and may recover within 1 week afterward.¹¹ The absence of cancer and advanced age, two well-validated risk factors for bleeding, still need confirmation. One disputable hypothesis is that their own excess risk of bleeding may take a longer time than the initial hospitalization to operate. Another, raised by the authors, maybe the lack of power. External validation studies of the score will help to assess these hypotheses.

If externally validated, what would be the value of the score in clinical practice? It could encourage the clinician to control even more restrictively the associated factors of bleeding risk, for example, co-prescriptions of antiinflammatory drugs or antiplatelet agents. In patients who remain individualized as high risk, the role of temporary cava filters (whose use in this situation has been associated with a possible survival benefit¹²) may benefit from a dedicated evaluation, subject to international collaboration. Moreover, an improved prediction of GI bleeding is needed, because efficient prophylactic therapies are available.

In conclusion, Chopard et al⁸ should be warmly thanked for their insightful work. Predicting bleeding, in patients

with a clear indication of anticoagulant therapy (as those with acute pulmonary embolism), may have distinct impacts. At the acute phase, it may help the clinician to choose treatment associated with the lowest risk of bleeding, and to pay particular attention to situations in which the risk may be modifiable (lesion at risk of bleeding in the digestive tract, co-prescription). Further research is needed to assess the efficacy and safety of interventional therapies (eg, catheter direct therapy, inferior vena cava filters), in a patient evaluated as having a very high risk of bleeding under anticoagulant therapy.

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