Bleeding Risk Assessment in Patients with Venous Thromboembolism

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Abstract

The recommended treatment for patients with venous thromboembolism (VTE) is anticoagulation for at least 3 months. However, anticoagulant treatment increases the risk of bleeding, and patients at high risk for major bleeding might benefit from treatment discontinuation. In this review, we discuss strategies for assessing bleeding risk and compare different bleeding risk tools. Bleeding risk assessment is best viewed as a continuous approach with varying challenges throughout the acute and chronic phase. At diagnosis, bleeding risk factors must be identified and reversible risk factors treated or modified. After initial treatment, repeated bleeding risk assessment is crucial for the decision on extended/long-term anticoagulation. Current clinical prediction models (e.g., HAS-BLED, RIETE, or VTE-BLEED scores) are externally validated tools with relevant differences in specificity and sensitivity, which can aid in clinical decision-making. Unfortunately, none of the current bleeding risk assessment tools has been investigated in clinical trials and provides evidence to withhold anticoagulation treatment based on the score. Nevertheless, the HAS-BLED or RIETE score can be used to identify patients at high risk for major bleeding during the initial treatment phase, while the VTE-BLEED score might be used to identify patients at low risk for bleeding and, therefore, to safely administer extended/long-term anticoagulation for secondary thromboprophylaxis. As clinical prediction scores still lack predictive value, future research should focus on developing biomarker-based risk assessment models.

Keywords

- venous thromboembolism
- anticoagulants
- risk assessment
- hemorrhage

Background

Venous thromboembolism (VTE), a disease entity including deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease, following coronary heart disease and ischemic stroke.[1,2] VTE is associated with significant morbidity due to acute symptoms and long-term complications of DVT and PE, such as the postthrombotic or post-PE syndrome, and contributes to a major global disease burden.[3–5] The incidence of VTE, PE (±DVT), and DVT alone is approximately 1 to 2, 0.6, and 0.9 per 1,000 inhabitants per year, respectively.[1,6,7] VTE affects all age groups; however, the incidence is increasing with age; for example, the yearly incidence in people older than 55 years is 5 to 6 events per 1,000 persons.

The mainstay of VTE treatment is anticoagulation for at least 3 months. In patients with a transient or reversible risk factor, treatment can be stopped after 3 months. Extended anticoagulation therapy is suggested in patients at high risk of VTE recurrence (e.g., patients with a persistent risk factor) and those in whom the index episode occurred in the absence of any identifiable risk factor, the latter referred to as unprovoked

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VTE.[7,8] The main complication of anticoagulation is bleeding, and major bleeding is the complication that limits extended/long-term oral anticoagulation to prevent VTE recurrence.[9] In this narrative review, we aimed at providing an overview of bleeding risk and discuss bleeding risk assessment tools, clinical factors, and biomarkers for prediction of bleeding events in the VTE population.

Balancing Risk of VTE Recurrence versus Risk of Bleeding for Decision-Making

The treatment of choice for the treatment of VTE and prevention of recurrence in patients at high risk of VTE recurrence is anticoagulation. To determine the recurrence risk, VTE is usually categorized into unprovoked and provoked. Provoked VTE events are further divided into those by a transient or persistent risk factor. Recently, there has been an effort in adopting the terminology from "unprovoked VTE" to VTE in the absence of identifiable risk factors.[7] In patients without risk factors, risk of recurrence is approximately 10% at 1 year, 25 to 30% at 5 years, and 30 to 40% at 10 years after stopping oral anticoagulation.[9–12] In patients who had presented with a major transient risk factor, VTE recurrence risk is only 1% after 1 year.[13] Accordingly, international guidelines suggest extended anticoagulation in patients without identifiable risk factors (unprovoked VTE), with persistent risk factors, or a minor transient or reversible risk factor.[7,8]

However, anticoagulation therapy comes at the expense of increasing the risk of bleeding, the most feared complication of all currently available anticoagulants. The management of bleeding may require reversal agents or other interventions and hospitalization, which again may boost risk of VTE recurrence. Overall, occurrence of bleeding may be associated with mortality and increased health care costs.[14]

In clinical practice, the decision to initiate and continue anticoagulation (e.g., for the prevention of VTE recurrence) is based on evaluation and balancing both risk of recurrent VTE and risk of bleeding on anticoagulation. Furthermore, patient preference, which is not further precisely defined yet, is also highlighted as an important factor in the decision of extended/long-term treatment.[8]

To categorize the bleeding events, the International Society on Thrombosis and Haemostasis (ISTH) has established criteria for the definitions of "major bleeding (MB),"[15] "clinically relevant non-major bleeding (CRNMB),"[16] and "non-clinically consequential minor bleeding" to assess the severity of bleedings in nonsurgical studies. Major bleeding is defined as bleeding that occurs in a critical organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome or bleeding that lead to a fall in hemoglobin of 2 g per deciliter or more, or leading to a transfusion of two or more units of whole blood or red blood cells. Fatal bleedings are also categorized as major bleedings.[15] Hemorrhage that does not fit the criteria of major bleeding but requires medical intervention, leads to hospitalization, or requires face-to-face evaluation of a health care professional is defined as CRNMB.[16] Other bleedings are referred to as nonclinically consequential minor bleedings.

Predicting major bleeding is crucial for clinical decision-making. However, CRNMB is also important as patient-centric outcomes resulting in low quality of life may lead to discontinuation of anticoagulation treatment.[15,16] CRNMB has become an important primary or secondary safety endpoint in clinical studies of VTE as it reflects time-consuming management, extended medical care, and increased treatment costs.[16,17] However, CRNMB may not be appropriate as a surrogate parameter for major bleeding.[18]

Patients on anticoagulation for VTE treatment are approximately at a 2% risk to develop major bleeding during the first 3 months according to a meta-analysis published in 2003.[19] The introduction of direct oral anticoagulants (DOACs) in clinical practice has impacted the discussion of bleeding risk. When compared with vitamin K antagonists (VKAs), DOAC showed a better safety profile in randomized-controlled phase III trials, in which consistent definitions of bleeding outcomes were reported across the different studies, with an absolute major bleeding risk of 1.1% during the first 3 to 12 months of treatment period.[20,21] However, in RIETE, a prospective registry study, 19% of patients had at least one criterion (e.g., renal insufficiency, high risk of bleeding, pregnancy), which would have excluded them from the randomized clinical trials of DOAC. Such patients had substantially higher rates of VTE recurrences, major bleedings, and deaths.[22] Consequently, there is a need to further elaborate the bleeding risk in real-world patients on DOAC. Of note, a systematic review even found major bleeding events in patients receiving placebo (incidence: 0.42/100 patient-years), which should be taken into account as the baseline risk of major bleeding without anticoagulation when assessing risk of bleeding.[23]

Case-Fatality Rates of Major Bleeding and VTE Recurrence

Bleeding events most frequently occur during the first 3 to 6 months after the initial event, while the risk of VTE recurrence increases after discontinuation of anticoagulation.[24,25] Interestingly, the majority of fatal events related to both, bleeding and recurrence, are observed within the first month after starting therapy.[26] For clinical decision-making, case-fatality rates of major bleeding events and VTE recurrence are usually taken into consideration. The case-fatality rate is a measure of disease severity representing the proportion of patients who die from a specific condition, over a certain period.

In a meta-analysis, risk of VTE recurrence was higher than major bleeding, while case-fatality rate for both major bleeding and VTE recurrence was 11.3% during the first 3 months of anticoagulation.[27] Accordingly, the initiation of anticoagulation and long-term treatment during the first 3 months after the VTE event is crucial. However, case-fatality rate for recurrence drops after the initial 3 months, while case-fatality remains stable for major bleeding.[19] The RIETE registry, a worldwide "all-comers" registry, found a case-fatality rate of 2% for recurrent VTE and 18% for major bleeding after the first 3 months of anticoagulation in a large cohort of 42,000 patients

with a first VTE event.[26] This highlights the clinical relevance of major bleeding in VTE patients treated in clinical practice. Therefore, extended (i.e., no scheduled stop date) anticoagulation treatment is still a weak recommendation in the current guidelines.[8] Note, data on case-fatality rates after major bleeding in patients on anticoagulants have been mostly reported in patients receiving VKA (mostly warfarin). Direct comparisons of DOAC and VKA showed a better safety profile for DOAC which was also reflected by significantly lower case-fatality rates of bleeding in the phase III trials (10.4 vs. 6.1%).[28]

To exemplify the importance of individual assessment, we provide the following example: A patient suffering from first unprovoked VTE/PE faces a recurrence risk of approximately 25% and a case-fatality rate of 4% within 5 years, according to a recent meta-analysis.[9] Thus, his/her 5-year risk of death due to a recurrent VTE event would be approximately 1%. Given a 10% risk to die of major bleeding, his/her yearly major bleeding risk estimation should be below 2% to show a mortality benefit for anticoagulation treatment. Therefore, tools to predict major bleeding for the decision-making on extended/long-term treatment are essential in clinical practice.

Prediction of Major Bleeding—Risk Factors, Risk Assessment Models, and Biomarkers

While assessment of bleeding risk in patients on anticoagulation is considered a vital element of VTE management, its implementation is challenging. Common risk factors for bleeding are older age, anemia, history of bleeding, abnormal renal function, history of stroke, hypertension, antiplatelet agents, cancer, abnormal liver function, alcohol abuse, female sex, diabetes, labile INR, poor anticoagulant control, thrombocytopenia, increased fall risk, and nonsteroidal anti-inflammatory drugs (NSAIDs; ►Fig. 1).

Current guidelines do not recommend a specific approach to predict major bleeding. The guidelines of the American College of Chest Physicians (ACCP/CHEST) suggest a list of 18 risk factors to indicate high risk of bleeding,[8] while the 2019 European Society of Cardiology (ESC) guidelines lists 8 risk factors and 5 prediction models (OBRI,[29] Kuijer et al,[30] RIETE,[31] HAS-BLED,[32] and VTE-BLEED[33]) to assess bleeding risk.[7] Furthermore, the ESC guidelines implicate to reassess the bleeding risk in high-risk patients every 3 or 6 months. In total, 16 clinical prediction scores for major bleeding are available.[34] Seven were developed specifically in VTE cohorts,[30,31,33,35–37] while 9 were developed in atrial fibrillation (AF)[32,38–42] or mixed cohorts.[29,43,44] The available tools differ in a variety of features. Most of the scores and models are designed to predict major bleeding as defined by the ISTH. However, some were developed to predict clinically relevant bleeding (major bleeding and CRNMB) or bleeding events with different definitions. As some scores were developed in patients with different indications for anticoagulation (e.g., AF), they may lack validity due to different patient demographics and underlying disease. Furthermore, the vast majority of scores had a derivation cohort of patients solely treated with VKA. Only three were derived in a population including patients who were treated with DOAC for VTE.[33,35,45]

Assessment of major bleeding during anticoagulation varies throughout the different stages of anticoagulation treatment and is, therefore, discussed separately.

Initial Bleeding Risk Assessment

In 1960, anticoagulation treatment has been shown to be effective for treating acute VTE and prevent recurrent events for the first time.[46] Given the high case-fatality rate of acute VTE, all guidelines recommend anticoagulation treatment

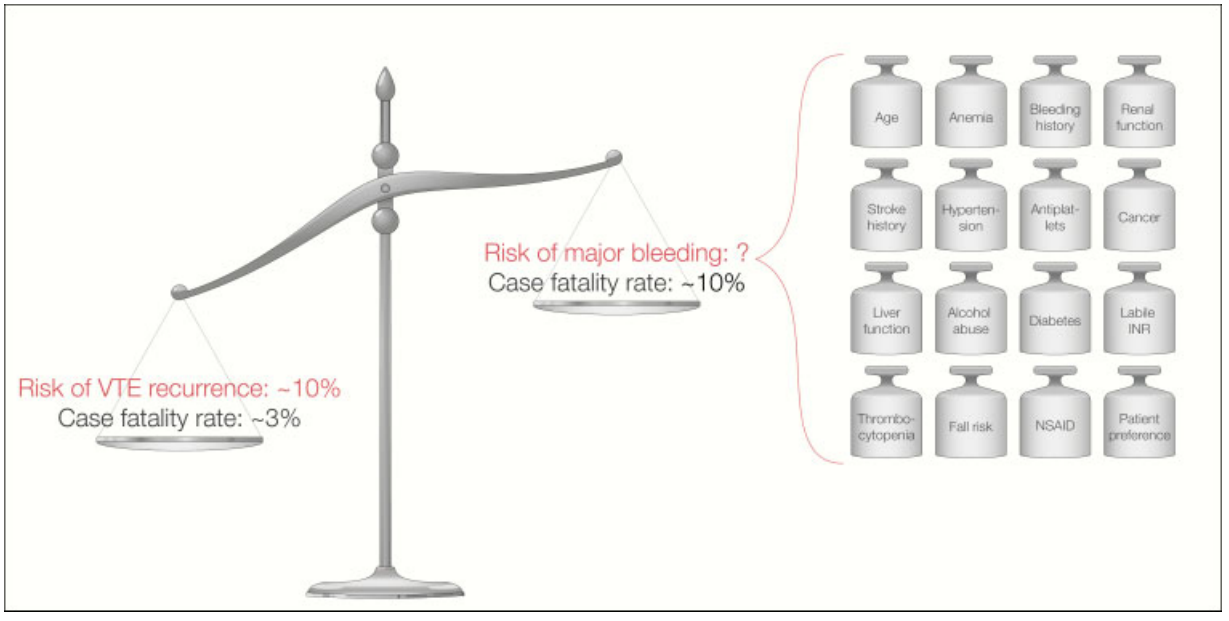

Fig. 1 Bleeding risk assessment—balancing bleeding risk and recurrence risk. Numbers reflect the risks within the first year of a patient suffering from first unprovoked VTE. Risk factors on the right are modified according to the ACCP guidelines.[8]

for at least 3 months.[7,8] Only in patients presenting with subsegmental PE, or isolated distal DVT and without severe symptoms or risk factors for extension, anticoagulation treatment might be withheld. However, bleeding risk assessment in the acute phase is less relevant for the decision to start anticoagulation but might be important to evaluate the use of systemic thrombolysis, choose the appropriate anticoagulant drug,[47] and help identify patients at high risk for major bleeding during anticoagulant treatment and, thereby, improve patient care. The optimal risk model for the initial risk assessment should specifically characterize patients at very high risk of bleeding in which withholding anticoagulation, despite the risk of thrombus extension and recurrent VTE, might be acceptable. However, high risk of bleeding is often accompanied by high risk of VTE recurrence. Therefore, an ideal bleeding risk assessment model would adjust for the VTE recurrence risk and identify those at higher risk for major bleeding.

In the following, we discuss two selected tools for the initial bleeding risk assessment in patients with VTE, which have been extensively studied and validated (►Table 1).

HAS-BLED Score

In clinical practice, the HAS-BLED score is broadly used to assess bleeding risk in patients on anticoagulation treatment. It was originally developed in 3,987 AF patients, who were followed up for 1 year,[32] and has been validated in several AF cohorts, and is decently balanced in terms of sensitivity and

Table 1 Clinical scores to predict major bleeding in patients with venous thromboembolism

	HAS-BLED[32]	RIETE[31]	VTE-BLEED[33]
	Derived in AF population	**Derived in VTE population**	**Derived in VTE population**
Risk factors			
Age ≥ 60 y			1.5 points
Age > 65 y	1 point		
Age > 75 y		1 point	
History of bleeding	1 point		1.5 points
Recent bleeding		2 points	
Active cancer		1 point	2 points
Abnormal renal function	1 point	1.5 points	1.5 points
Abnormal liver function	1 point		
History of stroke	1 point		
Anemia		1.5 points	1.5 points
Hypertension	1 point		1 point
Labile INR	1 point		
Antiplatelets/NSAID	1 point		
Alcohol abuse	1 point		
Clinically overt PE		1 point	
Risk stratification[a]			
Low risk	0 points	0 points	0–2 points
Intermediate risk	1–2 points	1–4 points	
High risk	3–9 points	4.5–8 points	2–9 points
Pros	• Best validated score for major bleeding • Established in clinical practice	• Derived in "real-world" patients • Consistent moderate predictive value throughout validation studies	• Extensively validated and studied in the VTE population
Cons	• Variable "labile INR" is rarely useful in extended VTE treatment • Implementation of the variable "cancer" might be beneficial in VTE population	• Intended to predict bleeding in first 90 days • Not sufficiently validated in DOAC patients	• Poor positive predictive value

Abbreviations: AF, atrial fibrillation; DOAC, direct oral anticoagulant; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drugs; PE, pulmonary embolism; VTE, venous thromboembolism.

[a]Percentage of patients with the respective bleeding outcome in each derivation cohort stratified by risk: HAS-BLED, 0.59% in the low-risk, 1.7% in the intermediate-risk, and 19.6% in the high-risk group; RIETE, 0.3% in the low-risk, 2.6% in the intermediate-risk, and 7.3% in the high-risk group; VTE-BLEED, 2.8% in the low-risk and 12.6% in the high-risk group.

specificity.[48,49] Few studies also evaluated the HAS-BLED score in VTE patients. One study compared 8 bleeding risk scores and showed that HAS-BLED best predicted clinically relevant bleeding (major bleeding and CRNMB) during the first 3 months.[50] However, in this study, none of the scores were better than chance in predicting major bleeding alone. Two other studies showed that patients with a HAS-BLED score $\geq$3 were at increased risk for major bleeding, but major bleeding rates in the high-risk group widely differed between 2.4 and 9.6% within the first 6 months of VTE treatment.[51,52] On the contrary, the HAS-BLED score performed poorly in a study of elderly patients ($\geq$80 years) with a c-statistic of 0.55.[53] Furthermore, the score's cutoff point for high risk of major bleeding is debatable.[54] A score of $\geq$4 indicated a clear delineation for those at high risk for major bleeding with higher positive predictive values but very poor sensitivity.[51,52]

RIETE Bleeding Risk Score

The RIETE bleeding score consists of six variables (age >75 years, recent bleeding, cancer, creatinine levels >1.2 mg/dL, anemia, and PE) and was derived and internally validated in a registry with more than 19,000 VTE patients.[31] A variety of studies already validated the score and found decent discriminative ability between the 3 bleeding risk categories, but poor to moderate predictive value.[50,53,55,56]

Risk Assessment for Extended Anticoagulation Treatment

After the initial treatment phase, extended/long-term anticoagulation is recommended in every patient who suffers from unprovoked VTE or VTE that was associated with a persistent major thrombotic risk factor except in those at high risk for bleeding. Therefore, a bleeding risk assessment for the decision and reevaluation of extended/long-term anticoagulation treatment is of utmost importance for further patient management. However, predictive values of current assessment tools vary substantially throughout validation studies and independent validation studies mostly report c-statistics between 0.5 and 0.6 with most models not predicting better than chance in at least one study.[45,51,57–61] Importantly, most scores were evaluated in studies focusing on the initial 3 or 6 months of the treatment period. Only a few studies evaluated the performance of clinical prediction scores for bleeding after the first months.[35,50,62] We are, therefore, discussing the only adequately validated score for the extended anticoagulation period.

VTE-BLEED

VTE-BLEED, which consists of six clinical variables, is the only rule that was designed and validated to predict bleeding events during "stable" (treatment period of 30 days after the initial event) anticoagulation.[33] It was tested and validated in both patients with DOAC and VKA of two phase III DOAC trials, one cohort, and one registry and showed good to moderate discrimination between risk groups.[33,57,62,63] However, in the validation cohort, the positive predictive value of only 1.5% for the high-risk group of the VTE-BLEED limits the decision to withhold anticoagulation solely based on the score. Due to the high negative predictive value, the strength of this score could lie in identifying patients with very low risk of major bleeding and, therefore, safe administration of extended anticoagulation.

In conclusion, no score showed sufficient discriminative ability throughout the reported studies. Thus, regardless of the predictive value of any bleeding score, withholding anticoagulants is unacceptable in patients with acute VTE, including those with high bleeding risk. Similarly, no currently available bleeding risk score for extended anticoagulation can be recommended without doubts. Therefore, identification of further risk factors and biomarkers for risk of bleeding is needed to improve bleeding assessment.

Nevertheless, bleeding scores can be used to identify patients at high risk and modify and reduce possible risk factors. We suggest elaborating all risk factors listed by the ACCP guidelines and modify or provide adequate treatment of blood pressure; improve INR monitoring and control; stop the long-term use of NSAID or—if appropriate—of platelet inhibitors; and check diabetes, anemia, renal, and liver function. Furthermore, patient education and self-monitoring have been shown beneficial in patients treated with VKA, and could lead to a decrease in bleeding risk.[64,65] Of note, a study of AF patients suggests that continuous bleeding risk assessment better predicts bleeding than baseline assessment only.[66] Given that this may also be the case in VTE patients, continuous assessments might help improve prevention of major bleeding.

Additionally, patient preferences as part of the individual decision-making should be taken into account. A recent study investigated the patients' attitude toward secondary prevention in VTE patients without an identifiable risk factor. Patients reported the willingness to endure four major bleeds to prevent one recurrent event which highlights the considerable fear of VTE in this population.[67] A similar ratio of major bleeding versus stroke was reported by a study conducted in AF patients.[68]

Biomarkers for Risk Prediction

In current bleeding prediction models for VTE patients, simple cutoff values for creatinine clearance, creatinine, hemoglobin, and platelet count are used. However, continuous markers overcome dichotomous variables and may better reflect susceptibility to bleeding. Numerous biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hs-cTnT), markers of renal function, hemoglobin, low platelets, inflammatory markers (e.g., interleukin-6 and C-reactive protein), growth differentiation factor-15 (GDF-15), vitamin E, D-dimer, von Willebrand factor, and genetic polymorphisms have been associated with increased bleeding risk in cardiovascular disease patients.[42,69–74] Only one bleeding risk score, which has been recently developed in AF patients, has implemented continuous biomarkers to predict major bleeding. This new model, termed "ABC-bleeding risk score," includes three biomarkers associated with bleeding risk (e.g., GDF-15, hs-cTnT, and NT-proBNP) and yielded higher c-indices than the HAS-BLED score.[42]

To our knowledge, no predictive biomarker-based model has been developed for VTE patients.[75] However, the biomarkers of the ABC bleeding risk model including GDF-15 might be a promising approach for the evaluation in VTE patients.

Conclusion

Medical care of patients suffering from VTE includes balancing two opposing aims, namely, preventing VTE recurrence while minimizing risk of bleeding. As high risk of bleeding might contradict anticoagulation treatment, clinical decision-making is primarily based on estimating bleeding risk. Unfortunately, we are still far from an optimal bleeding risk assessment tool. Although extensive research in the field identified a variety of risk factors, current risk assessment models lack predictive value and have not been tested in prospective interventional management studies. In patients with acute VTE, anticoagulation is, without a doubt, the treatment of choice. Current bleeding risk scores do not provide enough evidence to withhold anticoagulation. However, they may provide information on critical patients. Such patients should be followed up thoroughly to manage modifiable risk factors for bleeding and to assess changes in bleeding risk over time. After the initial treatment phase, bleeding risk scores (e.g., VTE-BLEED) may help in identifying patients with very low risk of bleeding to safely administer extended anticoagulation, if indicated. Notably, traditional risk factors seem to be simultaneously linked to bleeding and thromboembolic risk. Therefore, repeated individual assessment of both risks, VTE recurrence and bleeding, is key for extended secondary thromboprophylaxis.

Conflict of Interest

The authors declare that they have no conflict of interest.

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