The use of weighted and scored risk assessment models for venous thromboembolism

Alex C. Spyropoulos[1]; Thomas McGinn[2]; Alok A. Khorana[1]

[1]James P. Wilmot Cancer Center and Department of Medicine, University of Rochester Medical Center, Rochester, New York, USA; [2]North Shore/LIJ Health System, Department of Medicine, New York, New York, USA

Summary

Formalised risk assessment models (RAMs) for venous thromboembolism (VTE) using weighted and scored variables have only recently been widely incorporated into international antithrombotic guidelines. Scored and weighted VTE RAMs have advantages over a simplified group-specific VTE risk approach, with the potential to allow more tailored strategies for thromboprophylaxis and an improved estimation of the risk/benefit profile for a particular patient. The derivation of VTE RAMs should be based on variables that are *a priori* defined or identified in a univariate analysis and the predictive capability of each variable should be rigorously assessed for both clinical and statistical significance and internal consistency and completeness. The assessment of the RAM should include the goodness of fit of the model and construction of a prognostic index score. Any VTE RAM which has been derived must undergo validation of that model before it can be used in clinical practice. Validation of the model should be performed in a "deliberate" prospective fashion across several diverse clinical sites using pre-defined criteria using basic standards for performing model validation. We discuss the basic concepts in the derivation of recent scored and weighted VTE RAMs in hospitalised surgical and medical patients and cancer outpatients, the mechanisms for accurate external validation of the models, and implications for their use in clinical practice.

Keywords

Venous thrombosis, risk factors, epidemiological studies

Correspondence to:
Alex. C. Spyropoulos, MD
Department of Medicine, Division of Hematology/Oncology
University of Rochester Medical Center
James P Wilmott Cancer Center
601 Elmwood Ave
Rochester, NY 14642, USA
Tel.: +1 585 276 6103, Fax: +1 585 276 0350
E-mail: Alex_Spyropoulos@URMC.Rochester.edu

Received: July 20, 2012
Accepted after major revision: September 12, 2012
Prepublished online: November 8, 2012
doi:10.1160/TH12-07-0508
Thromb Haemost 2012; 108: 1072–1076

Introduction

The use of formalised risk assessment models (RAMs) for venous thromboembolism (VTE) using weighted scoring systems have only recently seen widespread adaptation into international antithrombotic clinical guidelines such as those of the American College of Chest Physicians (1). A simplified, group-specific strategy that divided patients into low-, moderate-, and high (or very high)-VTE risk based on exposing risk factors (such as surgery type) and predisposing risk factors (such as patient-related medical illnesses) had been the standard approach for VTE risk stratification for the past 30 years (2). The simplicity of a group-specific VTE risk approach, coupled with limited information on the impact of individual risk factors for VTE and the extent that these risk factors interacted in a quantitative manner to determine overall thromboembolic risk, made the utilisation of a group-specific approach attractive. However three major issues using a simplified group-specific approach to VTE have recently emerged: i) the shift to using patient-centered outcomes, such as symptomatic VTE, instead of surrogate outcomes (such as venographic VTE), as the basis for developing evidence-based recommendations for the use of thromboprophylaxis, ii) the inability to adequately risk assess complex patient groups with additive VTE risk factors (such as hospitalised medical and cancer patients), and iii) the complexity of a narrower risk/benefit profile and need for more precise estimations of VTE risk with new paradigms of thromboprophylaxis, such as the extended-duration use of existing antithrombotic agents (low-molecular-weight-heparin) or use of the novel oral anticoagulants.

An ideal RAM for VTE should accurately identify patients who meet a threshold risk of developing a VTE in the absence of prophylaxis, predict a correct risk level (incl. surgical or disease-specific or exposing risk factors and patient-specific or predisposing risk factors) allowing more tailored strategies for thromboprophylaxis, reliably exclude patients without a beneficial risk/benefit ratio, be evidence-based and validated and methodologically transparent, and must be fairly simple to use in clinical practice (2). Although an ideal RAM for VTE is difficult to achieve, an individualised RAM that is scored and weighted based upon specific VTE risk factor indices with possible additional requirements for laboratory criteria and inclusion of novel VTE risk factors comes closest to this ideal RAM. This paper will review the derivation and

Table 1: Risk factors for VTE in hospitalised patients (3, 12–17).

High risk	Probable risk	Possible risk
• History of DVT or PE • Family history of thrombosis	• High-dose estrogen therapy • Obesity (BMI >25)	• Paraproteinaemia • Behcet's disease
• Acute Infection • Malignancy • Age >75 years	• Varicose veins • Heparin-induced thrombocytopenia (HIT	• Disorders of plasminogen and plasminogen activation
	• Congenital or acquired thrombophilia	• Nephrotic syndrome
• Congestive heart failure	• Antithrombin deficiency	• Polycythaemia
• Stroke • Myocardial infarction	• Positive Lupus anticoagulant • Antiphospholipid antibodies	• Paroxysmal nocturnal hemoglobinuria
• Prolonged immobility (=4 days)	• Protein S deficiency	• Elevated serum homocysteine
• Pregnancy or postpartum	• Protein C deficiency	• Dysfibrinogenaemia
• Acute or chronic lung disease • Acute inflammatory disease • Inflammatory bowel disease • Shock	• Positive factor V Leiden • Elevated anticardiolipin antibodies • Positive prothrombin gene mutation 20210A	• Myeloproliferative disorders • Age ≥41 years • Sepsis (<1 month) • Non-type O blood group

validation of individualised RAMs that have used weighted scoring systems for VTE and discuss implications for their use in clinical practice.

Derivation of VTE risk factors used in scoring RAMs

Most of the existing data on individual *exposing* (disease specific) or *predisposing* (patient specific) risk factors for VTE in acutely-ill medical patients are derived from patient subgroups within placebo-controlled randomised clinical trials (3, 4). A group of approximately 15 risk factors, including a history of VTE, age ≥75 years, cancer, and heart disease, are well- established VTE risk factors in this patient population (▶Table 1). When deriving a RAM, it is important to include such well-established risk factors in an *a priori* list of variables. However, it is equally important to conduct preliminary univariate analyses (the so-called "biologically agnostic" approach) to explore additional risk factors that could potentially be of significance in prediction. Indeed, in the development of a RAM for cancer-associated thrombosis led by a co-author (A.A.K.), relatively novel risk factors identified during univariate analysis (platelet and leukocyte counts) eventually were included in the RAM whereas historically better established risk factors (stage of cancer, type of chemotherapy and performance status) were not as significant (5) (▶Table 2). For derivation, all clinically and statistically significant covariates should be included in a multivariate logistic regression model. Predictors that correlate strongly with others may reasonably be excluded. Predictors that are non-significant in univariate analyses, however, need not necessarily be excluded if there is a strong rationale for inclusion (6). However, there should be a solid theoretical biological basis for inclusion of risk factors in the univariate analysis during model derivation. In addition, an evaluation of first-order interaction terms for the primary outcome of VTE needs to be explored. Any significant interactions identified should be incorporated into subsequent model development, using the appropriate interaction term. The predictive capability of each model should be assessed for both clinical and statistical significance. The assessment of the model should include assessment of the goodness of fit of the model, graphical displays based directly on the regression model, and construction of a prognostic index score. To be statistically rigorous, each study measure should be assessed individually for completeness (missing data), consistency and quality. Missing data need to be further evaluated for any relationship with primary outcomes or any of the significant prognostic variables.

The "score" assigned to individual variables within a RAM is important, but there is no consensus on the appropriate approach. Ideally, such scores should be based on the multivariate analysis with some controversy on whether hazard ratios or beta-coefficients should be used. Using empirical scoring systems based on

Table 2: VTE risk assessment model in ambulatory cancer patients undergoing chemotherapy. Adapted from [5].

Patient characteristic	Score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynaecologic, GU excluding prostate)	1
Platelet count ≥350,000/mm^3	1
Hgb < 10 g/dl or use of ESA	1
Leukocyte count >11,000/mm^3	1
BMI ≥35 kg/m^2	1

Hgb, haemoglobin; ESA, erythropoietin stimulating agent; BMI, body mass index.

expert consensus can lead to selection bias and over-fitting to the development dataset. Examples of both data-derived and empiric scoring systems can be seen in ▶Table 3A and B, respectively, which describes VTE RAMs that have been derived in hospitalised medical patient populations.

The definition of the primary endpoint is also quite critical. It is preferable that VTE be measured in a standardised fashion. Underdiagnosis of VTE is quite common in studies conducted for other reasons where VTE was collected as an adverse event or was not part of prespecified outcomes; in one study of metastatic colon cancer patients, 90% of VTE events were missed in an initial reporting of the study and only discovered on separate retrospective cohort analysis (7). In contrast, use of ICD-9 codes or inclusion of upper extremity DVT can lead to inaccuracies when carry-over diagnoses from prior admissions or catheter malfunctions are erroneously classified as VTE (8). Thus, researchers must guard against misclassification bias to avoid under- or over-estimation of risk.

Validation of scored RAMs for VTE

Any VTE RAM which has been derived must undergo validation of that model before it can be used in clinical practice. The method or level of validation considered necessary in order to allow or encourage widespread use of a particular VTE RAM is somewhat controversial. Ideally validation should be performed in a "deliberate" prospective fashion across several diverse clinical sites (9). The term deliberate is used in this situation to indicate that:

- Providers are explicitly applying the RAM.
- Providers are using a predefined prediction model.
- Providers are using the RAM to help determine risk at the point of care which will then direct care.

Deliberate application of a RAM during a validation study differs from a validation study performed by running a large set of predictors in a large data set. Most validations of RAMs for VTE, however, have been performed in the later fashion using large data sets that were collected either prospectively or retrospectively. The data in these sets may not have been collected specifically to predict VTE nor was a given RAM used but rather a long list of predictors. Validation studies are not limited to statistical validation but involve assessing the implementation processes and ideally involve providers explicitly using a previously derived model to predict the likelihood of the outcome event such as DVT and PE. In such studies patients are assessed by providers at the moment of admission for risk for DVT and PE and patients are followed prospectively for possible occurrence of the outcome event. Most studies, however, are performed on large retrospectively collected databases. As an example of this, Bahl et al. performed a validation study by using a large retrospective database looking for many variables not using an *a priori*-derived model with a scoring system (10) (▶Table 4). While this may be a first step towards validation, further validation using a predefined RAM and applying it prospectively is needed before the RAM can be used in clinical settings. Controversy exists, however, when comparing prospective explicit validation versus large databases with thousands of patients which demonstrate high levels of accuracy. In such cases where large data sets exist do we need to perform prospective explicit studies? No such studies have been performed for the $CHADS_2$ RAM for atrial fibrillation, yet it is widely used in clinical practice (11).

Basic standards for performing validation studies includes appropriate blinding of both those assessing the outcome event to the results of prediction model and blinding those assessing the RAM to the outcome. ▶Table 5 outlines the main criteria for performing derivation and validation studies for VTE RAMs is included. An impact analysis represents the most important step in the validation of a clinical prediction rule or RAM, and if this is conducted in a randomised controlled trial setting, it has the potential to change physician behavior or impact patient outcomes using high quality evidence. An important aspect of this validation process is its accuracy, which is not necessarily tested when validated using a large data set.

Table 3A: Risk score points assigned to each independent VTE risk factor in hospitalised acutely ill medical patients. Adapted from [18].

VTE risk factor	Points for the risk score
Previous VTE	3
Thrombophilia	2
Lower limb paralysis	2
Current cancer	2
Immobilisation ≥7 days	1
ICU/CCU stay	1
Age >60 years	1

ICU, intensive care unit; CCU, coronary care unit.

Table 3B: Risk factors for VTE in hospitalised medical patients. Adapted from [19].

Risk factor	Points
Cancer	3
Prior venous thromboembolism	3
Hypercoagulability	3
Major surgery	2
Advanced age	1
Obesity	1
Bed rest	1
Use of hormone replacement therapy or oral contraceptives	1

Conclusion

Individualised VTE RAMs that are scored and weighted using established risk factors for VTE, with incorporation of both labora-

Table 4: Caprini VTE patient risk assessment model in surgical patients. Adapted from [10].

Risk factor – 1 point	Risk factor – 2 points	Risk factor – 3 points	Risk factor – 5 points
Age 41 – 60 years	Age 61 – 74 years	Age 75 years	Stroke (~1 month)
Current swollen legs	Arthroscopic surgery	History of DVT/PE	Elective major lower extremity arthroplasty
Varicose veins	Malignancy (present or previous)	Positive Factor V Leiden	Hip, pelvis, or leg fracture (~1 month)
Obesity (BMI > 25)	Laparoscopic surgery (>45 minutes)	Family history of thrombosis	Acute spinal cord injury (paralysis ~1 month)
Minor surgery	Patient confined to bed (> 72 hours)	Positive Prothrombin 20210A	Multiple trauma (~1 month)
Sepsis (~1 month)	Immobilising plaster cast (< 1 month)	Positive Lupus anticoagulant	
Serious lung disease (~1 month)	Central venous access	Elevated serum homocysteine	
OCP or HRT	Major surgery (>45 min)	HIT	
Pregnancy or post-partum		Elevated anticardiolipin antibodies	
Acute MI		Other congenital or acquired thrombophilia	
CHF (~1 month)			
Medical patient at bed rest			
History of IBD			
History of prior major surgery (~1 month)			
COPD			
History of unexplained stillborn, RPL (3), or growth restriction			

HIT, heparin-induced thrombocytopenia; RPL, recurrent pregnancy loss; OCP/HRT, oral contraceptive/hormone replacement therapy; DVT/PE, deep-vein thrombosis/pulmonary embolism; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; MI, myocardial infarction.

Table 5: Development and testing of a clinical prediction rule. Adapted from [9].

	Step 1: Derivation	Step 2: Validation		Step 3: Impact analysis
		Evidence of reproducible accuracy		
		Narrow validation	Broad validation	
	Identification of factors with predictive power	Application of rule in a similar clinical setting and population as in step 1	Application of rule in multiple clinical settings with varying prevalence and outcomes of disease	Evidence that rule changes physician behaviour and improves patient outcomes and/or reduces costs
Level of evidence	4	3	2	1

tory criteria and the capability to include novel risk factors, have the potential to allow more tailored strategies for thromboprophylaxis and an improved estimation of the risk/benefit profile for a particular patient. As such, the use of weighted and scored RAMs for VTE are being increasingly incorporated into international antithrombotic guidelines for various patient groups such as hospitalised surgical and medical patients and ambulatory cancer patients undergoing chemotherapy. The derivation of VTE RAMs should be based on variables that are *a priori* defined or identified in a univariate analysis and the predictive capability of each variable should be rigorously assessed for both clinical and statistical significance and internal consistency and completeness. The assessment of the RAM should include the goodness of fit of the model and construction of a prognostic index score. The scores assigned to each individual variable within the model may be data-derived or based on expert consensus, but ideally such scores should be based on multivariate analyses to avoid over-fitting of the model and selection bias. Any VTE RAM which has been derived must undergo validation of that model before it can be used in clinical practice. Validation of the model should be performed in a "deliberate" prospective fashion across several diverse clinical sites using pre-defined criteria. Basic standards for performing VTE model validation should be adhered to, incorporating both a blinding process and model accuracy.

Conflicts of interest

A. Spyropoulos has served as consultant to Bayer, Johnson & Johnson, Bristol-Myers Squibb, Pfizer, Eisai, and Boehringer Ingelheim. None of the other authors declares any conflicts of interest.

References

1. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141 (2 Suppl): e227S-277S.
2. Spyropoulos AC. Risk assessment of venous thromboembolism in hospitalized medical patients. Curr Opin Pulm Med 2010; 16: 419–425.
3. Alikhan R, Cohen AT, Combe S, et al. Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. Arch Intern Med 2004; 164: 963–968.
4. Cohen AT, Alikhan R, Arcelus JI, et al. Assessment of venous thromboembolism risk and the benefits of thromboprophylaxis in medical patients. Thromb Haemost 2005; 94: 750–759.
5. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008; 111: 4902–4907.
6. Royston P, Moons KG, Altman DG, et al. Prognosis and prognostic research: Developing a prognostic model. Br Med J 2009; 338: b604.
7. Mandala M, Barni S, Floriani I, et al. Incidence and clinical implications of venous thromboembolism in advanced colorectal cancer patients: the 'GISCAD-alternating schedule' study findings. Eur J Cancer 2009; 45: 65–73.
8. Spyropoulos AC. Upper vs. lower extremity deep vein thrombosis: outcome definitions of venous thromboembolism for clinical predictor rules or risk factor analyses in hospitalized patients. J Thromb Haemost 2009; 7: 1041–1042.
9. McGinn TG, Guyatt GH, Wyer PC, et al. Users' guides to the medical literature: XXII: how to use articles about clinical decision rules. Evidence-Based Medicine Working Group. J Am Med Assoc 2000; 284: 79–84.
10. Bahl V, Hu HM, Henke PK, et al. A validation study of a retrospective venous thromboembolism risk scoring method. Ann Surg 2010; 251: 344–350.
11. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. J Am Med Assoc 2001; 285: 2864–2870.
12. Wu O, Bayoumi N, Vickers MA, et al. ABO(H) blood groups and vascular disease: a systematic review and meta-analysis. J Thromb Haemost 2008; 6: 62–69.
13. Risk of and prophylaxis for venous thromboembolism in hospital patients. Thromboembolic Risk Factors (THRIFT) Consensus Group. Br Med J 1992; 305: 567–574.
14. Clagett GP, Anderson FA, Jr., Geerts W, et al. Prevention of venous thromboembolism. Chest 1998; 114 (5 Suppl): 531S-560S.
15. Turpie AG, Chin BS, Lip GY. ABC of antithrombotic therapy: Venous thromboembolism: treatment strategies. Br Med J 2002; 325: 948–950.
16. Goldhaber SZ, Savage DD, Garrison RJ, et al. Risk factors for pulmonary embolism. The Framingham Study. Am J Med 1983; 74: 1023–1028.
17. Laffan M, Tuddenham E. Science, medicine, and the future: assessing thrombotic risk. Br Med J 1998; 317: 520–523.
18. Spyropoulos AC, Anderson FA, Jr., Fitzgerald G, et al. Predictive and Associative Models to Identify Hospitalized Medical Patients at Risk for VTE. Chest 2011; 140: 706–714.
19. Kucher N, Koo S, Quiroz R, et al. Electronic alerts to prevent venous thromboembolism among hospitalized patients. N Engl J Med 2005; 352: 969–977.

