External validation of the IMPROVE Bleeding Risk Assessment Model in medical patients

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Summary

The IMPROVE Bleed Risk Assessment Model (RAM) remains the only bleed RAM in hospitalised medical patients using 11 clinical and laboratory factors. The aim of our study was to externally validate the IMPROVE Bleed RAM. A retrospective chart review was conducted between October 1, 2012 and July 31, 2014. We applied the point scoring system to compute risk scores for each patient in the validation sample. We then dichotomised the patients into those with a score <7 (low risk) vs ≥ 7 (high risk), as outlined in the original study, and compared the rates of any bleed, non-major bleed, and major bleed. Among the 12,082 subjects, there was an overall 2.6 % rate of any bleed within 14 days of admission. There was a 2.12 % rate of any bleed in those patients with a score of < 7 and a 4.68 % rate in those with a score ≥ 7 [Odds Ratio (OR) 2.3 (95 % CI=1.8–2.9), p<0.0001]. MB rates were 1.5 % in the patients with a score of < 7 and 3.2 % in the patients with a score of ≥ 7, [OR 2.2 (95 % CI=1.6–2.9), p<0.0001]. The ROC curve was 0.63 for the validation sample. This study represents the largest externally validated Bleed RAM in a hospitalised medically ill patient population. A cut-off point score of 7 or above was able to identify a high-risk patient group for MB and any bleed. The IMPROVE Bleed RAM has the potential to allow for more tailored approaches to thromboprophylaxis in medically ill hospitalised patients.

Keywords

Risk Assessment Model, validation, bleeding risk, anticoagulants, medical patients

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Introduction

Venous thromboembolism (VTE) remains the number one preventable cause of death in hospitalised patients (1), resulting in approximately 300,000 deaths per year in the United States alone (2). These events are reducible with thromboprophylactic medications (3). However, rates of administration of these medications remain suboptimal, especially in acutely ill hospitalised medical patients (4). This may result, in part, from physicians' fear of bleeding complications that may arise from pharmacologic thromboprophylaxis (5).

Current international guidelines, including those of the American College of Chest Physicians, now call for patients' individualised risk assessment, both for their risk of VTE and their risk of bleeding (6, 7). Numerous VTE risk assessment models (RAMs) focusing on the medically ill hospitalised patient population, have recently been reported in the literature (8-10). The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) Bleeding RAM, remains the only evidence-derived and weighted bleeding RAM in the hospitalised medical population (11). In this study, 11 independent clinical and laboratory factors were used to derive a scoring system. A score of ≥ 7, which occurred in approximately 10 % of patients, predicted an elevated risk of bleeding (11).

The objective of our study was to externally validate the IMPROVE Bleed RAM in a large patient cohort from an academic health system in the United States. Model characteristics, including discrimination and calibration, were also assessed.

Materials and methods

A retrospective chart review was conducted between October 1, 2012 and July 31, 2014, utilising data from our electronic health records (EHR). Inclusion criteria, as described in the original IMPROVE study, were all hospitalised patients over the age of 18, with a length of stay of over three days and with a diagnosis of an "acute medical illness" identified by administrative data (ICD9 codes). "Acute medical illness" was defined as a primary diagnosis of acute infection, respiratory disease, heart failure, cancer, diabetes, pancreatitis, cholecystitis, or rheumatic disease (see Suppl. Material Appendix A, available online at www.thrombosis-online.com). Exclusion criteria included a history of surgery in the three months prior to admission (identified by operative report notes), treatment with therapeutic anticoagulation and a diagnosis of bleeding upon admission. Patients who were admitted with a VTE or a primary obstetric or mental health diagnosis were also

excluded. All of the patients that were included in this cohort are defined as the "validation cohort" for the purposes of this study.

Bleeding outcomes were identified using ICD9 billing codes and EHR data with established accuracy for anticoagulant related complications in hospital discharge abstracts (12) (see Suppl. Material Appendix B, available online at www.thrombosis-online.com). The three outcome events were categorised as major bleed (MB), non-major bleed (NMB) or any bleed defined as MBs or NMBs. These events were included if they occurred within the first 14 days of admission, as discussed in the original study. MB was defined as bleeding associated with a fall in haemoglobin of over 2 g/dl or bleeding associated with a transfusion of at least two units of packed red blood cells, as identified in the ordering and results sections of the EHR. Bleeding within a critical organ i.e. intracranial, retroperitoneal, intraocular, adrenal gland or pericardial bleeding as identified by ICD9 billing codes, was also considered a MB (Suppl. Material Appendix B, available online at www.thrombosis-online.com). These criteria were included in the original derivation study and also from the International Society on Thrombosis and Haemostasis definition of MB in non-surgical patients (13). NMB was defined as gross haematuria, gastrointestinal (GI) bleeding (excluding insignificant haemorrhoid bleeding) epistaxis, intra-articular bleeding, menorrhagia, menorrhagia, extensive haematoma or bruising, or any other bleeding as identified by ICD9 billing code that did not fall under a "major bleed" category. The 11 IMPROVE clinical and laboratory risk factors were pulled from the EHR (test orders and results, nursing documentation, past medical history, patient demographics, problem list and discharge diagnoses). All patients who received standard pharmacologic prophylaxis were identified, including subcutaneous unfractionated heparin 5000 U every 12 or 8 hours and enoxaparin 30 mg or 40 mg daily.

In the original IMPROVE study data was prospectively collected on 15,126 acutely ill hospitalised medical patients from 12 countries and 52 hospitals. This population of patients is defined as the "derivation cohort". Using the derivation cohort, the IMPROVE study developed a Bleed RAM consisted of 11 clinical and laboratory features that were independently associated with in-hospital bleeding (►Table 1). Each factor was valued between 1 and 5 points, and the weighted score was based on the sum of those 11 factors. The bleeding risk began to increase exponentially in patients with a risk score of ≥7. In the derivation study, a score of 7 was used to divide the groups into high and low risk of bleeding. In order to validate the IMPROVE Bleed RAM, we applied the point scoring system to compute risk scores for each patient in our validation sample. The total bleed risk score was then dichotomized into two groups (<7 vs ≥ 7 points). Lastly, we compared the frequencies/rates of bleeding in the derivation and our validation samples at this cut-off point. The Positive Predictive Value (PPV) and Negative Predicted Value (NPV) for both samples were directly computed using standard binomial methods. Secondly, since PPV and NPV depend, in part, on prevalence of a bleed outcome, Bayes' Rule was used to compute PPV and NPV for a variety of prevalence rates. Odds ratios (OR) for a bleeding event according to the bleed risk score cut-off point were computed along with their 95% confidence intervals (CI). Associated p-values were computed using the Chi-square test and results were considered statistically significant at $p<0.05$. Receiver-operating characteristic (ROC) curves were created to compare the overall diagnostic accuracy of the original derivation set and our validation set. All analyses were carried out in SAS Version 9.3 (Cary, NC, USA).

The procedures used were reviewed and approved as being in compliance with ethical standards of the responsible institutional review committee at the authors' institution.

Table 1: IMPROVE Bleed Score. List of 11 risk factors that were included in the IMPROVE bleed RAM.

Risk factors	Points
Moderate renal failure (GFR 30–59 vs ≥60 ml/min/m^2)	1
Male vs Female	1
Age, 40–84 vs <40	1.5
Current cancer	2
Rheumatic disease	2
Central venous catheter	2
ICU/CCU	2.5
Severe Renal Failure (GFR < 30 vs ≥60 ml/min/m^2)	2.5
Hepatic failure (INR>1.5)	2.5
Age ≥85 vs <40	3.5
Platelet count <50 × 10^9	4
Bleeding in the three months before admission	4
Active gastroduodenal ulcer	4.5

Results

There were 14,796 patients that met inclusion criteria and the updated pool of subjects was reduced to a final number of 12,082 patients after excluding subjects with missing or inaccurate EHR data (►Figure 1).

Compared to the derivation cohort, our validation sample identified an older population of patients, with a mean age of 70 years old, a higher incidence of comorbid disease, and a two-fold increase in the number of patients in the higher bleed risk category (≥ 7) compared to the original derivation sample (►Table 2). There were also a greater number of patients with hepatic failure, severe renal disease, and bleed within 90 days prior to admission in the validation sample compared to the derivation cohort. There was a greater proportion of patients receiving VTE prophylaxis in the validation sample compared to the original IMPROVE derivation cohort.

Bleeding rate

Among the 12,082 patients, there was a 2.6% rate of any bleed within 14 days. There was a MB rate of 1.8% and NMB rate of

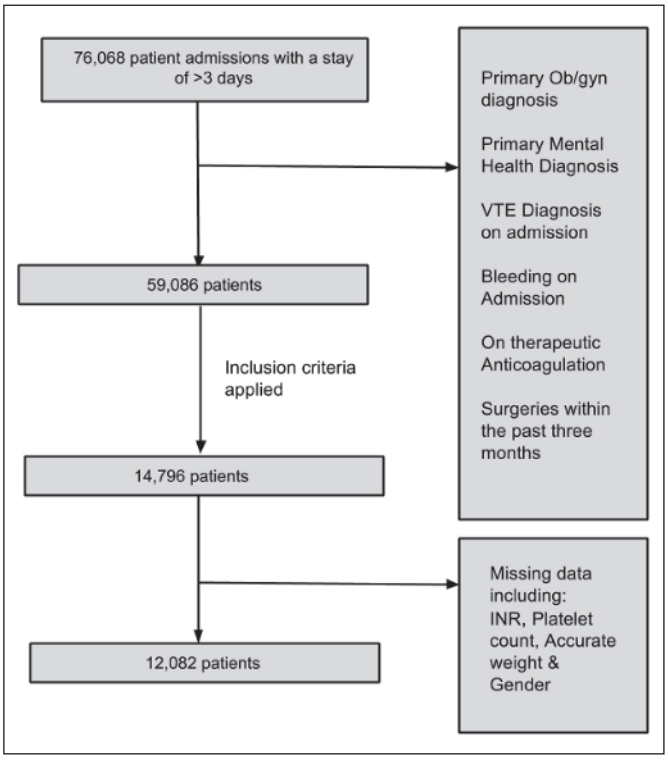

Figure 1: Subjects included in the validation analysis. Figure 1 summarises the selection process used in this study which resulted in a final n=12,082.

Table 2: Comparison of the demographic and clinical factors. Demographic characteristics in both the validation and derivation samples.

Risk factor	Derivation sample (%)	Validation sample (%)
Age≥85	11 %	21 %
Gastroduodenal ulcer	2.2 %	0.9 %
Hepatic failure (INR>1.5)	2.0 %	9.2 %
Bleed within 90 days prior to admission	2.2 %	0.5 %
GFR<30 ml/min/m^2	11 %	20.3 %
Rheumatic disease	6.8 %	15.3 %
ICU/CCU stay	8.5 %	12.5 %
Cancer	10.7 %	12.5 %
Catheterisation	7.5 %	13.8 %
Median LOS	7 (IQR 5–12 days)	6 (IQR 4–10 days)
VTE prophylaxis	48 %	82 %
Proportion of patients with a bleed risk score ≥7	10 %	19 %

ICU/CCU: Intensive Care Unit/Critical Care Unit; GFR: Glomerular Filtration Rate; VTE: Venous thromboembolism; LOS: Length of Stay.

1.6 % in the validation sample. There was a 0.9 % rate of both a MB and NMB in the validation sample, which were categorised as a MB. The rates of any bleed, MB and NMB in the original derivation cohort was 3.2 %, 1.2 % and 2.1 %, respectively.

Bleeding risk score analysis

The bleed risk scores ranged from 0–20, with 81 % of patients having a bleed risk score < 7 and 19 % with a score ≥ 7, compared to 90.3 % and 9.7 % of patients seen in the original derivation sample. In our population, any bleeding rates were 2.1 % in those with a score < 7 and 4.7 % with a score of ≥7, [OR 2.3 (95 % CI: 1.78–2.87), p<0.0001]. MB rates increased from 1.5 % in patients with a score of < 7 to 3.2 % in patients with a score of ≥ 7 [OR 2.3 (95 % CI: 1.6–2.9), p<0.0001]. In the original derivation cohort, the rates for any bleed and MB were 1.5 % and 0.4 % in the low bleed risk patients and 7.9 % and 4.1 % in the high bleed risk patients.

The calculated sensitivity and specificity for any bleed in the validation sample were 34.0 % and 81.5 %, respectively. The observed PPV and NPV for any bleed were 4.7 % and 97.9 %, respectively. Using only MB as an outcome resulted in a sensitivity of 33.3 %, specificity of 81.3 %, PPV of 3.2 % and NPV of 98.5 % (▶Table 3). The sensitivity and specificity for any bleed in the derivation sample were 35.9 % and 90.9 %, respectively. Using the computed sensitivity and specificity from the validation sample, PPVs and NPVs for any bleed, were computed for a range prevalence estimates to elucidate how the bleed risk tool may perform in patient populations with increasing rates of any bleeding outcome.

Model calibration to the extent that estimated risks corresponded to observed event rates revealed that increasing bleed score increased the incidence of any bleed and MB, at increment levels. The cumulative patient percentage and incidence of any bleed and MB at each interval midpoint score level is summarised in ▶Table 4.

Model discrimination

The ROC analysis for both our validation sample and the derivation cohort is shown in ▶Figure 4 and ▶Figure 5, in which the area under the ROC curve is 0.63 in our validation set and 0.71 in the original derivation sample. The data that was used to construct the ROC curve was based on the original derivation cohort's risk of any bleed at the interval midpoint level for each score grouping.

Venous thromboprophylaxis and model characteristics

In our validation sample 82 % of patients received VTE prophylaxis, versus 48 % in the original derivation sample. The proportion of patients in the low and high bleed risk category that received thromboprophylaxis were 84 % vs 75 %, respectively. The sensitivity of the score for any bleeding did not change significantly when applied to those on pharmacologic prophylactic medications with heparin/low-molecular-weight heparin, but the specificity and

Table 3: Sensitivities, specificities, NPV & PPV of model. Sensitivities, specificities, NPV & PPV of the derivation and validation sample for both a MB and any bleed outcome.

	Derivation (%)	Validation (%)
Sensitivity for predicting any bleed	35.9	34
Specificity for predicting any bleed	90.9	81.5
PPV for predicting any bleed	2.6	4.7
NPV for predicting any bleed	98.2	97.9
Sensitivity for predicting a major bleed	51	33.3
Specificity for predicting a major bleed	90	81.3
PPV for predicting a major bleed	4	3.2
NPV for predicting a major bleed	99	98.5

NPV: Negative Predictive Value; PPV: Positive Predicted Value.

NPV of the model were significantly increased with thromboprophylaxis use (►Table 5).

Discussion

This validation study of the IMPROVE Bleed RAM represents the largest external, validation study of a bleed risk score in a medically ill patient population of over 12,000 patients. The bleed RAM using a bleed risk score of ≥ 7 as in the original derivation model was able to identify approximately 19% of patients with a two-fold increased risk in major bleeding and thus a population whose risk of bleed may outweigh the benefit of pharmacologic thromboprophylaxis. Conversely the 81% of patients which the model defined as low risk and the high NPV for any bleed and MB indicate that the RAM predicts that the majority of medical patients are at low risk of a bleed.

We found only one other recently published study by Hostler et al 2015, that validated this bleed RAM (14). Although the study involved a smaller proportion of patients (n=1668), the study used similar retrospective ICD9 coding and manual chart review methods to validate the IMPROVE RAM in an external population of patients. Their results were similar to our current study in that the sample of patients differed from the original study on key demographic and clinical factors, a common finding in external validation studies. As in our study, they identified that a score of ≥7 predicted a similar and significant over two-fold increased risk of MB, from 1.6% to 5.4%. However, the small sample size of the study precluded robust model discrimination and calibration characteristics, and the study was not able to assess ROC characteristics of the IMPROVE Bleed RAM. However, data from these two external validation studies reveals that the IMPROVE Bleed RAM appears to accurately predict increased MB and any bleed risk when applied to patients that are uniquely different than the population of patients it was derived from using the cut-off score of ≥ 7. Considering that the incidence of MB within 14 days of admission seen in large randomised trials in the medical population is ~1.2% (15-17), a threshold MB rate of ~1.5% appears clinically appropriate to distinguish high versus low bleed risk, as our study has shown.

The ROC of the validation sample of 0.63, reveals that the IMPROVE Bleed RAM shows moderate discriminatory characteristics when applied to external populations and less optimistic than the calculated ROC of the original derivation sample of 0.71.

Table 4: Application of the bleeding risk score in the patient population included in the risk factor analysis. Calibration statistics for the derivation and validation sample, which predicted both increasing incidence of any bleed and MB, at increment levels.

Risk score grouping (interval midpoint)	Derivation sample			Validation sample		
	Patients included in risk factor analysis, n	Incidence of any bleeding, n (%)	Incidence of major bleeding, n (%)	Patients included in risk factor analysis, n	Incidence of any bleeding, n (%)	Incidence of major bleeding, n (%)
0–1 (0.5)	778	3 (0.4)	0 (0.0)	352	1 (0.3)	1 (0.3)
1.5–2 (1.75)	1,448	11 (0.8)	3 (0.2)	1,102	13 (1.2)	10 (0.9)
2.5 (2.5)	2,340	33 (1.4)	3 (0.1)	1,829	39 (2.1)	39 (1.6)
3–4 (3.5)	1,539	24 (1.6)	6 (0.4)	2,062	37 (1.8)	26 (1.3)
4.5–5 (4.75)	1,466	27 (1.8)	8 (0.5)	2,472	48 (1.9)	34 (1.4)
5.5–6.5 (6)	905	28 (3.1)	11 (1.2)	2,004	70 (3.5)	48 (2.4)
7 (7)	300	13 (4.3)	9 (3.0)	677	26 (3.8)	16 (2.4)
7.5–8 (7.75)	220	13 (5.9)	6 (2.7)	571	22 (3.8)	15 (2.6)
8.5–9.5 (9)	226	17 (7.5)	9 (4.0)	597	26 (4.4)	16 (2.7)
10–12 (11)	130	22 (16.9)	9 (6.9)	322	24 (7.5)	22 (6.8)
12.5 and up	36	7 (19.4)	4 (11.1)	73	8 (11)	5 (6.8)
Total	9,388	198	68			

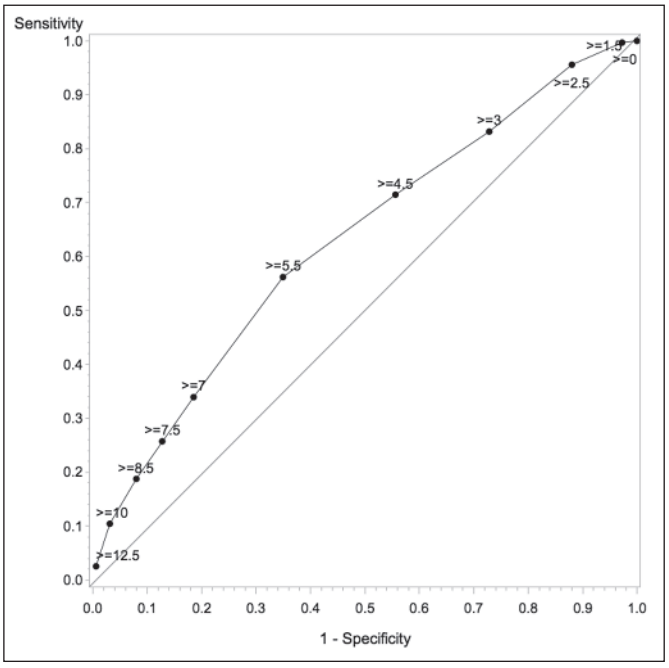

Figure 2: Validation sample ROC curve. The data that was used to construct this ROC curve was based on the validation cohort's risk of any bleed at the interval midpoint level for each score grouping.

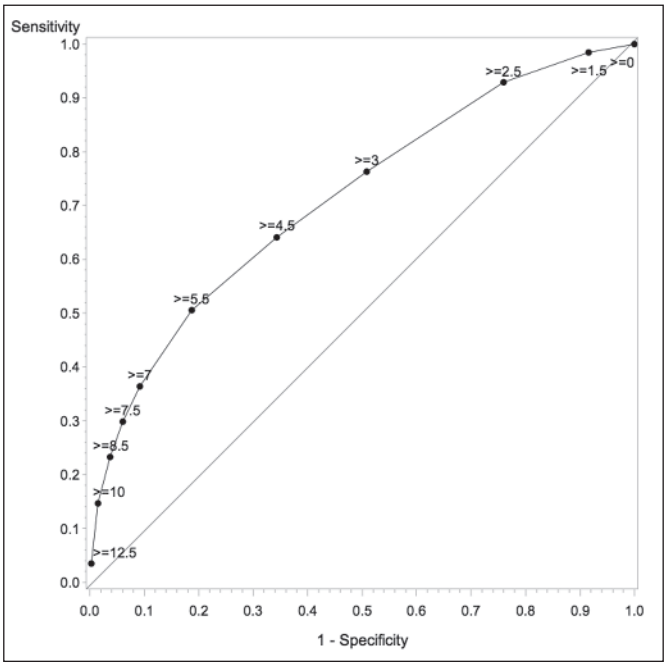

Figure 3: Derivation sample ROC curve. The data that was used to construct this ROC curve was based on the original derivation cohort's risk of any bleed at the interval midpoint level for each score grouping.

The result of a less optimistic ROC for the validation sample of an external validation study compared to the original derivation sample is expected as estimates using the derivation sample will tend to be biased optimistically, given the fact that the tool was derived in that same population. Lastly an analysis of thromboprophylaxis revealed greater use in the validation sample compared to the derivation sample (82 % vs 48 %) and did not affect certain model characteristics, such as model sensitivity. However, there was an increase in model specificity and NPV, suggesting that the model can be used with caution in those patients already receiving heparin thromboprophylaxis as a possible confounder. Furthermore, the model can be useful for predicting patients' risk of bleed at admission, before the initiation of thromboprophylaxis.

The strengths of the present study include a large database of electronic health records from two large acute care hospitals in a setting different from the original derivation cohort population. In addition, standardised abstraction instruments were used by trained personnel to extract the relevant independent clinical risk factors in the validation population. Moreover, the number of bleeding events were sufficiently robust to allow assessment of both the discrimination and the calibration of bleed risk factors as they applied to the Bleed RAM. Despite being an external population, the study results are close to those of the derivation cohort as well as the previous validation study, suggesting validity of the model across different populations. Lastly and importantly, we were also able to obtain ROC curves for both the original derivation cohort as well as the validation sample, which has not been done before.

Limitations of this study include its retrospective design and its use of administrative database analysis based on ICD-9 codes. In addition, claims data may have had decreased sensitivity in capturing NMB and as a result there appears to be a reduced number of these events compared to the original derivation study. These results also showed that there was a decline in the specificity of the risk scoring system from the derivation sample to the validation sample. Whether or not this drop in specificity and its corresponding effect on the other operating characteristics of the tool are clinically significant remains to be determined. Reasons for the differences in the tool's performance from the derivation cohort to the validation sample may include the well-known phenomenon that the estimated sensitivity, specificity, PPV and NPV, and misclassification rates for the derivation cohort, from which these operating characteristics are derived, will tend to be biased optimistically, given the fact that the tool was derived in that same

Table 5: Effects of Thromboprophylaxis. Effects the use of thromboprophylaxis had on the model's sensitivity, specificity, NPV and PPV for any bleed.

	Thromboprophylaxis	No Thromboprophylaxis	P-value
Sample size	9922	2160	n/a
Sensitivity	37.3 %	30.2 %	0.18
Specificity	83.0 %	73.9 %	<0.0001
PPV	3.6 %	7.9 %	<0.0001
NPV	98.7 %	93.5 %	<0.0001

What is known about this topic?

- The risk of venous thromboembolism (VTE) in hospitalised medical patients remains high and pharmacologic thromboprophylaxis remains suboptimal.
- Current international guidelines, including those of the American College of Chest Physicians, call for patients' individualised risk assessment for bleeding prior to the administration of VTE prophylaxis.
- The IMPROVE Bleeding Risk Assessment Model (RAM), remains the only evidence-derived and weighted bleeding RAM in the hospitalized medical population. However, it had not been extensively validated in an external population of patients.

What does this paper add?

- The present study represents the largest external validation of an evidence-derived and weighted bleed RAM in a hospitalised medically ill patient population.
- Using the 11 clinical and laboratory factors in the IMPROVE Bleed RAM, a cut-off of 7 or more points was able to identify approximately 20% of the medically ill hospitalised patient population whose individual risk of any and major bleeding bleed is over two-fold higher than the low bleed risk patient groups. In high bleed risk groups the harms of pharmacologic thromboprophylaxis may outweigh the benefits.
- Validation of this rule in an external population will allow for a more tailored approach to pharmacologic thromboprophylaxis in acutely ill hospitalized medical patients.

population. In addition, there were observed differences in the distribution of demographics and prognostic factors of the derivation and validation samples. Although our definitions of MB were identical to the validation sample, the definition of NMB may have varied across the two samples leading to different point estimates and model characteristics. As previously discussed, the use of heparin thromboprophylaxis may have been a confounder with certain model characteristics. Lastly, it is possible that certain inclusion/exclusion criteria or other factors make the case mix in the original study different from the validation population, which would also influence the validation results.

The results of this study speak toward the importance of using an evidence-based RAM to predict an acutely ill medical patient's risk of bleeding while in the hospital. This information, combined with the knowledge of the same patient's risk of VTE will allow physicians to make more tailored, specific, and evidence-based decisions regarding pharmacologic thromboprophylaxis. Specifically, providers can establish net clinical benefit of pharmacologic VTE prophylaxis for individual medical patients using both the IMPROVE Bleed RAM and the previously validated IMPROVE VTE RAM (which was derived on the same population of patients as the IMPROVE Bleeding RAM) (8, 9). Providers can directly compare each patient's risk of bleed to their risk of symptomatic VTE, more accurately identifying an individual patient that will benefit from pharmacologic thromboprophylaxis. Towards this end a clinical calculator that analyses an individual patient's risk of VTE and bleeding using the IMPROVE RAMs is available at http://www.outcomes-umassmed.org/improve/.

The next steps include prospective validation of the IMPROVE Bleed RAM in medical patients and the ability to conduct large-scale impact/management studies. Future studies should also focus on analysing the effects of standardising physician practice regarding VTE prophylaxis by integrating the VTE and bleed score RAMs into existing clinical workflows.

To conclude, this study represents the largest, external validation study of the only evidence-derived and weighted bleed risk score in hospitalised medical patients, the IMPROVE Bleed RAM. The model predicted a high bleed risk group of patients with a score of ≥ 7 that comprised ~20% of the hospitalised medical patient population. This group, whose risk of MB was over 3%, would likely not benefit from pharmacologic thromboprophylaxis. The model showed moderate discriminatory characteristics in the validation sample and high NPV, suggesting that the majority of medical patients would benefit from thromboprophylaxis. This advances the field of hospital-based VTE prevention by allowing more specific and tailored approaches to benefit/risk assessment when considering thromboprophylaxis in this difficult patient group. Additional prospective validation studies as well as management and impact studies are necessary for the IMPROVE Bleed RAM in the medical patient group before widespread adaptation of the model.

Conflicts of interest
None declared.

References

1. Tapson VF, Hyers TM, Waldo AL, et al. Antithrombotic therapy practices in US hospitals in an era of practice guidelines. Arch Intern Med 2005; 165: 1458–1464.
2. Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost 2007; 98: 756–764.
3. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med 1999; 341: 793–800.
4. Cohen AT, Tapson VF, Bergmann JF, et al; ENDORSE Investigators. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet 2008; 3719610: 387–394.
5. Douketis JD. Prevention of venous thromboembolism in hospitalised medical patients: addressing some practical questions. Curr Opin Pulm Med 2008; 145: 381–388.
6. Qaseem A, Chou R, Humphrey LL, et al. Venous thromboembolism prophylaxis in hospitalised patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2011; 155: 625–632.
7. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence Based Clinical Practice Guidelines. Chest 2012; 141: e195S-e226S.
8. Spyropoulos AC, Anderson FA, Fitzgerald G, et al. Predictive and associative models to identify hospitalised medical patients at risk for VTE. Chest 2011; 140: 706–714.

9. Rosenberg D, Eichorn A, Alarcon M, et al. External validation of the risk assessment model of the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) for medical patients in a tertiary health system. J Am Heart Assoc 2014; 3: e001152.
10. Huang W, Anderson FA, Spencer FA, et alJ. Risk-assessment models for predicting venous thromboembolism among hospitalised non-surgical patients: a systematic review. J Thromb Thrombolysis 2013; 35: 67–80.
11. Decousus H, Tapson VF, Bergmann JF, et al. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. Chest 2011; 139: 69–79.
12. Arnason T, Wells PS, Van Walraven C, et al. Accuracy of coding for possible warfarin complications in hospital discharge abstracts. Thromb Res 2006; 118: 253–262.
13. Meijer K, Schulman S. The absence of 'minor' risk factors for recurrent venous thromboembolism: a systematic review of negative predictive values and negative likelihood ratios. J Thromb Haemost 2009; 7: 1619–1628.
14. Hostler DC, Marx ES, Moores LK, et al. Validation of the IMPROVE Bleeding Risk Score. Chest 2015; Epub ahead of print.
15. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med 1999; 341: 793–800.
16. Leizorovicz A, Cohen AT, Turpie AG, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 2004; 110: 874–879.
17. Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. Br Med J 2006; 332: 325–329.