Comparative Performance of Clinical Risk Assessment Models for Hospital-Acquired Venous Thromboembolism in Medical Patients

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Abstract

Background Improved thromboprophylaxis for acutely ill medical patients relies on valid predictions of thrombotic risks. Our aim was to compare the performance of the Improve and Geneva clinical risk assessment models (RAMs), and to simplify the current Geneva RAM.

Methods Medical inpatients from eight Swiss hospitals were prospectively followed during 90 days, for symptomatic venous thromboembolism (VTE) or VTE-related death. We compared discriminative performance and calibration of the RAMs, using time-to-event methods with competing risk modelling of non-VTE death.

Results In 1,478 patients, the 90-day VTE cumulative incidence was 1.6%. Discrimination of the Improve and Geneva RAM was similar, with a 30-day AUC (areas under the curve) of 0.78 (95% CI [confidence interval]: 0.65–0.92) and 0.81 (0.73–0.89), respectively. According to the Improve RAM, 68% of participants were at low risk (0.8% VTE at 90 days), and 32% were at high risk (4.7% VTE), with a sensitivity of 73%.

Keywords
- venous thrombosis
- risk factors
- prophylaxis
- clinical studies

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According to the Geneva RAM, 35% were at low risk (0.6% VTE) and 65% were at high risk (2.8% VTE), with a sensitivity of 90%. Among patients without thromboprophylaxis, the sensitivity was numerically greater in the Geneva RAM (85%) than in the Improve RAM (54%). We derived a simplified Geneva RAM with comparable discrimination and calibration as the original Geneva RAM.

Conclusions We found comparably good discrimination of the Improve and Geneva RAMs. The Improve RAM classified more patients as low risk, but with possibly lower sensitivity and greater VTE risks, suggesting that a lower threshold for low risk (<2) should be used. The simplified Geneva RAM may represent an alternative to the Geneva RAM with enhanced usability.

Introduction

Venous thromboembolism (VTE) is a feared complication of hospital stays and most hospitalization-acquired VTE, including fatalities, occur in medically ill patients.[1] The use of pharmacological thromboprophylaxis (TPX) is cost effective and recognized as a major opportunity to improve patients' outcomes.[2] Its prescription, however, needs to be tailored according to thrombotic and haemorrhagic risks given its associated bleeding complications and use of financial and hospital resources.

The use of TPX is believed to be inappropriate in 30 to 50% of medical inpatients, with a substantial proportion of low-risk patients receiving TPX and high-risk patients not receiving TPX.[3,4] Standardized local protocols are key elements to improve this gap of implementation,[5] including the use of risk assessment models (RAMs) for medical inpatients in daily hospital practice. Not only should such RAMs be valid predictors of clinical risks, but they should also be simple enough to achieve a good usability at the time of implementation.[5]

Out of eight developed RAMs for this purpose, the empirical Geneva[6] and Padua RAMs[7] and the data-derived Improve RAM[8] were validated in multicentre settings.[9] However, the external validation of the Improve RAM relies on administrative data and a case-control study with indirectly estimated incidence rates, and a recent validation within a hospital safety consortium has cast doubts on its discrimination performance.[10] The Improve RAM lacks a direct comparison of its performance with the Geneva RAM, and different cut-offs to define low VTE risk patients have been proposed.[11,12] Finally, the large number of items found in the Geneva RAM limits its implementation.

In view of these limitations, our aims were to externally validate the Improve RAM as an ancillary project in the prospective ESTIMATE cohort study and to simplify the Geneva RAM to enhance its usability.

Methods

This is a post hoc analysis of a multicentre prospective cohort of three academic and five non-academic acute care hospitals in Switzerland.[3] Local ethics committees of all participating hospitals approved the study. Informed consent was obtained at the time of hospital discharge, and it was waived for participants who had died during the in-hospital stay. The study is registered at Clinicaltrials.gov (NCT01277536).

Population

From December 2010 to November 2011, 2,820 patients aged ≥18 years and admitted acutely to a medical ward for ≥24 hours were screened. We excluded 1,342 participants because of ongoing anticoagulation or indication for therapeutic anticoagulation ($n = 522$, 19%), lack of informed consent ($n = 669$, 22%) and other reasons ($n = 151$, 5%). The study started on the day of hospital admission and 99% of living participants had a 90-day telephone follow-up.

Scores and Variables

This analysis evaluated the Geneva,[3] the Padua[7] and the Improve RAMs[8] (►**Table 1**). Data of the Geneva RAM were collected by dedicated study physicians or coordinators on a standardized electronic case report form, without missing data for the calculation of the scores. Scores were calculated after patient discharge, from data recorded at the time of hospital admission. Treating physicians were not informed of the risk scores of their patients during the hospital stay. Thus, the use of TPX was not influenced by the study and reflected current local practices.

A dedicated collection of some items from the Improve score was not performed, because the score was published after this study had started. Therefore, we used 'lower limb paralysis' as a proxy variable for recent or current stroke. Coronary care unit (CCU) admission was not recorded. Therefore, for 'stay in intensive care unit (ICU) or CCU', we used admissions to the ICU or acute coronary syndrome or other cardiovascular disease as a reason for hospitalization when combined with a recent diagnosis of myocardial infarction (MI). Further, immobilization was defined as an inability to walk for more than 30 minutes for more than 3 days in ESTIMATE, instead of 7 days as in the Improve score.

Categories of low and high risks for scores were based on prior publications.[11,12] For the Improve score, we evaluated two previously proposed categorizations: 0 to 2 (low) versus ≥3 points (high)[12] and 0 to 1 (low) versus 2 to 3 (moderate) versus ≥4 (high).[11]

In the effort to simplify the Geneva RAM, we empirically excluded predictors without a strong scientific rationale (such

Table 1 Geneva, improve and Padua risk scores

Geneva risk score Low risk 0–2 High risk ≥3		Padua risk score Low risk 0–3 High risk ≥4		Improve risk score Low risk 0–2 High-risk ≥3	
Malignancy	2	Active cancer (metastasis or treatment <6 mo)	3	Previous VTE	3
Myeloproliferative syndrome	2	Previous VTE	3	Known thrombophilia	2
Previous VTE	2	Reduced mobility (3 d)	3	Cancer	2
Hypercoagulable state	2	Thrombophilia	3	Lower limb paralysis[a]	2
Cardiac failure	2	Recent trauma/surgery (<1 mo)	2	Immobilization > 7 d[a]	1
Respiratory failure	2	Age > 70 y	1	Age > 60 y	1
Recent stroke (<3 mo)	2	Heart/respiratory failure	1	Stay in ICU or CCU[a]	1
Recent myocardial infarction (<1 mo)	2	Acute myocardial infarction/ischaemic stroke	1		
Acute infection	2	Acute infection or rheumatologic disorder	1		
Acute rheumatic disease	2	BMI > 30 kg/m^2	1		
Nephrotic syndrome	2	Hormonal treatment	1		
Immobilization (<30 min/d)	1				
Age > 60 y	1				
BMI > 30 kg/m^2	1				
Hormonal treatment	1				
Recent travel (>6 h)	1				
Chronic venous insufficiency	1				
Pregnancy	1				
Dehydration	1				

Abbreviations: BMI, body mass index; CCU, coronary care unit; ICU, intensive care unit; MI, myocardial infarction; VTE, venous thromboembolism.
[a]Proxy variables and a slightly different definition of immobilization was used in the ESTIMATE study (see section Methods).

as recent travel or dehydration) or that were rare in our patient typology according to our previous studies (such as hormonal treatment, pregnancy and nephrotic syndrome).[3] Besides scientifically derived predictors,[8] we believed it was important to keep variables such acute infection or inflammatory disease, respiratory/cardiac failure, obesity and recent cardiovascular event in the simplified Geneva RAM, based on previous evidence of associations with hospital-associated VTE.[13–15] A history of VTE, the strongest risk factor, was given 3 points instead of 2, because we chose to categorize all such patients at high risk. Points for other variables were mostly kept similar to the Geneva score or slightly modified to keep a similar proportion of the high-risk group.

The use of TPX, collected by in-depth chart review, was defined as any use of unfractionated heparin, low-molecular-weight heparin or fondaparinux (pharmacological TPX) or any use of intermittent compression boots or compression stockings (mechanical TPX), within 48 hours of admission.

Outcomes

The primary outcome was a composite of symptomatic VTE or VTE-related death, at 90 days. In analyses at different time points, the same composite outcome was used. Information on VTE was provided by participants at the 90-day telephone interview. If not accessible, in case of reported VTE event or in case of death, family physicians were contacted. All events were adjudicated by an independent adjudication committee composed of three senior vascular medicine physicians, who were blinded to the VTE scores and the use of TPX. In case of disagreement, a final adjudication was performed by the chairman of the adjudication committee.

Only objectively confirmed VTE diagnoses were included and VTE-related death was defined as death following pulmonary embolism (PE), confirmed by autopsy or imaging test, or death in which VTE was considered a likely cause.

Statistical Analysis

We used time to event with competing risk methods to evaluate the performance of the RAMs, because of the important cumulative risk of overall mortality at 90 days (19.3%), with non-VTE death representing the competing risk.[16]

Cumulative risk of VTE in low- and high-risk scores were evaluated at 30 and 90 days, and depicted graphically as a cumulative incidence function. We assessed the discriminative performance of the scores through a subdistribution hazard model of Fine and Gray, which estimates the relative instantaneous risk of VTE between low- and high-risk participants. These analyses were adjusted for the use of any TPX

(pharmacological and/or mechanical) to evaluate the discrimination of the scores independently of TPX. The sensitivity was defined as the proportion of participants categorized as high risk (or positive) by the score, among those with VTE at 90 days. Discriminative performances of the scores were evaluated by time-dependent ROC (receiver operating characteristic) curve for prognosis of VTE, while also taking competing events into account.[17,18] Secondary analyses included similar analyses in the subcohort of participants who did not receive any TPX within 48 hours of admission, and the exploration of the Improve and simplified Geneva score performances when stratified into three categories (low, intermediate and high). Of note, the subgroup without TPX differs slightly from the subgroup analysed in previous publications, which was defined as not having received any *adequate* TPX.[3,19]

Statistical analyses were conducted with STATA 11 and with R (packages « timeROC » and « pec »).

Results

Among the 1,478 medically ill participants, half were men and the mean age was 64.8 years (►**Table 2**). The most common reasons for hospitalization were infection/sepsis (23.8%), cardiovascular events (17.6%) and malignancies (13.4%). Mean and median durations of hospital stay were 11 and 8 days, respectively. More than half of the sample received some kind of TPX during hospitalization (58.5%): the use of heparin or fondaparinux was much more common (56.4%) than that of mechanical prophylaxis (6.7%).

Table 2 Characteristics of participants

Characteristics ($N = 1{,}478$)	*n* (%)
Men	778 (52.6%)
Age, mean (SD)	64.8 y (16.9)
Obesity	219 (14.8%)
Prior VTE	121 (8.2%)
Known thrombophilia	9 (0.6%)
Recent myocardial infarction or stroke	63 (4.3%)
Hormonal therapy	69 (4.7%)
Acute infection/sepsis	444 (30.0%)
Respiratory failure	182 (12.3%)
Cardiac failure	108 (7.3%)
Renal failure (GFR $<$ 30 mL/min)	135 (9.1%)
Active malignancy (including MP syndromes)	385 (26.1%)
Immobilization	551 (37.3%)
Thrombocytopaenia ($<$100 G/L)	130 (8.8%)
Use of any thromboprophylaxis within 48 h of admission	865 (58.5%)

Abbreviations: GFR, glomerular filtration rate; MP, myeloproliferative; SD, standard deviation; VTE, venous thromboembolism.

Thirty participants developed a VTE in the 90-day follow-up, of which 18 were fatal. Thirteen VTE events occurred in patients who did not receive TPX. The risks of VTE at 30 and 90 days, based on cumulative incidence functions, were 1.1 and 1.6%, respectively (►**Fig. 1**). The risk of overall death at 30 and 90 days were 14.8 and 19.3%.

The proportion of high-risk participants was highest according to the Geneva score (65.0%), lower according to the Padua score (48.3%) and lowest according to the Improve scores (31.7%; ►**Table 3**). The use of TPX was similar in high-risk groups across scores (63.5, 62.3 and 62.6%, respectively)

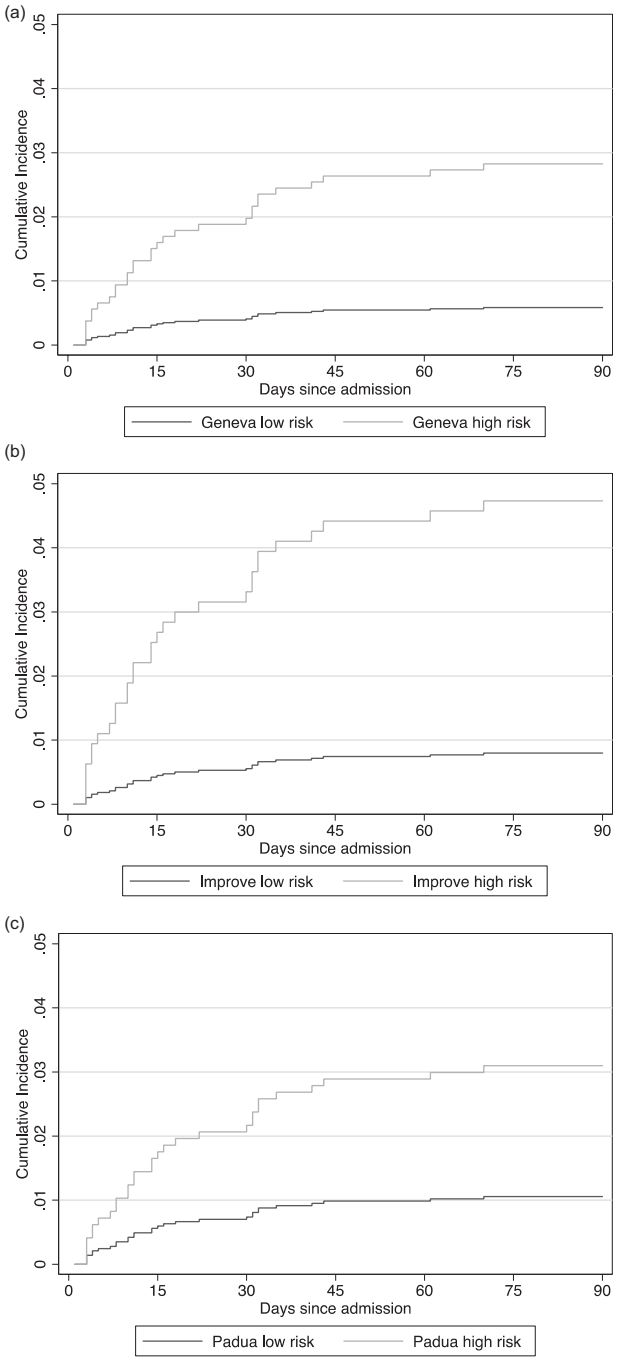

Fig. 1 Cumulative incidence function of venous thromboembolism events (.01 = 1%) (**a**) stratified by binary Geneva risk score, (**b**) stratified by binary Improve risk score, (**c**) stratified by binary Padua risk score.

Table 3 Incidences of VTE and their association with the Geneva, Improve and Padua risk scores

Scores		VTE risk[a]			
	N (%)	Sensitivity	At 30 d	At 90 d	Subdistribution HR (95% CI)[b]
Geneva score					
Low risk (<3)	518 (35%)		0.4%	0.6%	ref.
High risk (≥3)	960 (65%)	90% (27/30)	2.0%	2.8%	5.1 (1.5–16.6)
Improve score					
Low risk (<3)	1,009 (68%)		0.6%	0.8%	ref.
High risk (≥3)	469 (32%)	73% (22/30)	3.6%	4.7%	6.1 (2.7–13.5)
Low-risk (<2)	690 (47%)		0.4%	0.6%	ref.
Intermediate-risk (2–3)	545 (37%)	87% (26/30)	1.5%	2.2%	3.8 (1.2–11.8)
High risk (≥4)	243 (16%)		4.1%	5.8%	10.3 (3.4–30.0)
Padua score					
Low risk (<4)	764 (52%)		0.7%	1.0%	ref.
High risk (≥4)	714 (48%)	73% (22/30)	2.2%	3.1%	3.0 (1.3–6.7)
Simplified Geneva score					
Low risk (<3)	489 (33%)		0.4%	0.6%	ref.
High risk (≥3)	989 (67%)	90% (27/30)	1.9%	2.8%	4.6 (1.4–15.2)
Low-risk (<3)	489 (33%)		0.4%	0.6%	ref.
Intermediate-risk (3–6)	800 (54%)	90% (27/30)	1.2%	1.8%	3.0 (0.8–10.4)
High risk (≥7)	189 (13%)		5.0%	7.1%	12.3 (3.6–42.8)

Abbreviations: CI, confidence interval; HR, hazard ratios; VTE, venous thromboembolism.
[a]Estimated by the cumulative incidence function.
[b]Adjusted for use of any thromboprophylaxis.

and not widely different in low-risk groups (49.2, 54.7 and 56.8%, respectively).

We found good discriminative performance for the Geneva and Improve RAMs, and that of the Padua RAM was somewhat lower. High-risk participants had fivefold, sixfold and threefold greater risks of VTE than low-risk participants for the Geneva, Improve and Padua RAMs, respectively (►**Table 3**). Time-dependent areas under the curve (AUC; C-statistic) were similar (►**Table 4**), with greater discrimination in the first 30 days after admission than in the 2 months thereafter (►**Supplementary Fig. S1** [online only]). Regarding absolute risks, cumulative incidence of VTE at 30 days in low-risk participants were 0.4, 0.6 and 0.7% for the Geneva, Improve and Padua scores, respectively (►**Fig. 1**). High-risk participants had a 2 to 3.6% incidence of VTE at 30 days. When restricting to participants without TPX, low-risk participants had 30-day VTE risk of 0.5, 1.0 and 1.0%, and 90-day VTE risks were 0.7, 1.4 and 1.5%, respectively (►**Supplementary Table S1** [online only]). The sensitivity of the Geneva score (90%) appeared higher than that of the Improve score (73%) and Padua score (73%), albeit without statistically significant difference (Fisher exact test $p = 0.18$; ►**Table 3**). Defining the low-risk as less than 2 points (instead of less than 3 points) for the Improve score increased the sensitivity to 87% and decreased slightly risks of VTE at

Table 4 Discriminative performance of the scores

	All participants (95% CI)		Participants without thromboprophylaxis (95% CI)	
Scores	Time-dependent AUC at 30 d	Time-dependent AUC at 90 d	Time-dependent AUC at 30 d	Time-dependent AUC at 90 d
Geneva score	0.81 (0.73–0.89)	0.72 (0.64–0.81)	0.78 (0.65–0.92)	0.71 (0.59–0.84)
Improve score	0.79 (0.69–0.88)	0.75 (0.70–0.83)	0.74 (0.56–0.91)	0.70 (0.56–0.83)
Padua score	0.76 (0.67–0.86)	0.72 (0.63–0.82)	0.74 (0.56–0.90)	0.70 (0.57–0.82)
Geneva simplified score	0.81 (0.72–0.90)	0.72 (0.62–0.81)	0.80 (0.57–0.90)	0.70 (0.57–0.82)

Abbreviations: AUC, area under the curve; CI, confidence interval.

Table 5 Proposed simplified Geneva RAM

Low risk 0–2 High risk ≥3	
Previous VTE	3
Hypercoagulable state	2
Cancer or myeloproliferative syndrome	2
Cardiac or respiratory failure	2
Acute infection or rheumatic disease	2
Immobilization	2
Age >60 y	1
BMI >30 kg/m^2	1
Recent stroke or myocardial infarction	1

Abbreviations: BMI, body mass index; RAM, risk assessment model; VTE, venous thromboembolism.

30 and 90 days for the low-risk group, while decreasing the proportion of low-risk patients from 68 to 47% (►**Table 3**).

We empirically simplified the Geneva risk score (►**Table 5**); the discrimination and calibration of this score were similar to that of the original Geneva risk score (►**Tables 3** and **4**).

Finally, stratification of participants into three categories for the Improve and the simplified Geneva scores, instead of two categories, allowed identification of approximately 10 to 15% of participants at very high risk, with an incidence of 4 to 5% of VTE at 30 days.

Discussion

In this cohort study of medical inpatients, we confirmed a good performance of the Improve RAM to discriminate between low- and high-risk groups. Incidence rates were low for all low-risk groups (0.4–1.0% at 30 days) in the full cohort, and lowest according to the Geneva RAM.

Importantly, scores differed in the proportion of high-risk patients, and consequently also in their sensitivity (proportion of VTE events identified as high risk). A high sensitivity is critical for these RAMs, in order not to miss patients who should require in-hospital TPX. According to the Geneva RAM, two-thirds of participants were at high-risk, including 90% of those who suffered a VTE event. According to the dichotomous Improve RAM, only one-third were at high risk, including 73% of VTE events. The sensitivity analysis restricted to those without TPX, however, suggested that the lower Improve cut-off may be preferable in the Improve RAM (<2 points instead of <3 points to define low-risk individuals), because of a low sensitivity (54%) and not so low VTE risk at 3 months (1.4%) when using the higher cut-off.

Previous validation studies of the Improve RAM differed in their calibration, due to an overall lower VTE risk at 3 months (0.7–0.9 vs. 1.6% here).[11,12] This is unlikely due to differences in participants, who shared similar clinical characteristics, or to the use of VTE prophylaxis, which appeared similar. Most likely, the prospective design of our study with a formal follow-up allowed for a more complete capture of VTE events than previous retrospective validation efforts. Risks of VTE associated with the Improve RAM were therefore greater in this study than previously reported: in low-risk patients, these were 0.8 to 1.4% instead of 0.2 to 0.4%. Ninety-day discriminative performances were in line with previous studies, with an AUC of approximately 0.70.[8,12] One study suggested a lower AUC and cast doubts on the adequacy of the Improve and Padua RAMs, but this retrospective study had a low proportion of high-risk VTE patients, mainly due to a surprisingly low prevalence of immobility, and a suboptimal follow-up.[10] Interestingly, we observed greater AUC at 30 days (~0.8) than at 90 days (~0.7), reinforcing that these RAMs are adequate tools to identify high-risk VTE patients during and in the short term after hospitalization. A time frame of 30 days may indeed be more adequate than 90 days, because TPX is used for short periods (6–14 days in clinical trials) and its influence on VTE risk beyond 1 month is unlikely.

The simplified Geneva score, which we simplified empirically, had discriminative and calibrative characteristics in line with the original Geneva RAM, but with much greater usability. The lack of certain uncommon risk factors such as pregnancy or exogenous hormones did not affect the results, given that there were no VTE events related to these in our study. Some features may be important in comparison to the Improve RAM: it includes important VTE predictors, such as cardiac failure[14] and does not stratify ICU patients, in which TPX should be universal given the high VTE risk.[20] Further evaluation of this novel RAM is required to assess its external validity.

This study has clinical implications. It demonstrates, in a secondary analysis of a prospective study, the validity of the Improve score. In implementations of VTE prophylaxis strategies, hospital clinicians and VTE leaders can now choose between different RAMs with subtle differences. One such difference is that the Geneva and Padua RAMs have been subject to impact analyses, but not the Improve RAM yet,[9] and because of a possibly lower performance of the Padua RAM, we favour the use of the Geneva RAM. Selecting a RAM, however, remains a hospital-based decision that is influenced by local TPX preferences and goals and implementation challenges. Further, a clear VTE risk threshold at which TPX is beneficial does not exist, given the difficulty of prediction of bleeding consequences, heterogeneous patient preferences, and cost-effectiveness balance. The development of decision analytic models may be of interest in this topic, although experts indicate that the threshold may be around 1%.[21] Finally, the very high-risk groups identified in the three categories of Improve and simplified Geneva scores, representing 10 to 15% of medically ill patients with greater than 5% risk of VTE, deserve a closer attention. Testing of longer, stronger pharmaceutical or multifaceted TPX, including mechanical and pharmaceutical strategies, in these patients would be welcome, and such randomized trials are ongoing (MARINER study, NCT02111564). Finally, biomarkers, such as D-dimer and NT-pro-BNP, may be of interest to further improve the identification of VTE risk, but were not available in our study.[14,22]

Strengths of this study lie in the prospective design and excellent follow-up of participants enrolled in both tertiary and regional hospitals, the validation of VTE events and the direct observation of incidence rates with use of competing risk analytic methods. Our data also need to be interpreted in view of their limitations. There is a potential for misclassification induced by the use of two proxy variables in the Improve RAM, with unpredictable bias. The low number of VTE events limited the power to compare performance of the scores and led to an empirical, and not data-driven, simplification of the Geneva score. Further, the case fatality of VTE was surprisingly high in our study. However, fatal PE is a commonly discrepant diagnosis of in-hospital deaths and likely of deaths after discharge[23] and all VTE fatal events were externally adjudicated as certain or likely by experienced physicians to the best of their ability. Most critically, as in all other derivation or validation studies on this topic, the results of the incidence of VTE (calibration) are biased towards lower risks by the use of TPX. Our sensitivity analysis restricting to participants without TPX may reduce this bias, but we acknowledge that such participants may be in nature different from those who receive prophylaxis. Further, given the lack of important variation in the use of TPX between low- and high-risk patients, the potential for bias for the discrimination results is likely low.[19]

In conclusion, the Improve, Geneva and Padua RAMs validly discriminate between low and high VTE risks in medical inpatients. More patients are classified as low risk in the Improve RAM, but with possibly lower sensitivity and greater VTE risks than the Geneva RAM. A lower threshold to define the low-risk Improve group (<2) may be advisable, and this should be further evaluated in independent cohorts. The simplification of Geneva RAM yielded a simpler RAM with better usability and comparable performance to the original Geneva RAM.

What is known about this topic?

- The use of thromboprophylaxis in medical patients should be tailored to individual thrombotic risks.
- Several clinical risk assessment models (RAMs) exist, but direct comparisons and external validations are scarce.
- Simple RAMs are easier to implement.

What does this paper add?

- The Geneva and Improve RAMs offer overall similar discriminative performances.
- However, these RAMs differ in their stratification of low- and high-risk patients, with a greater proportion of high-risk patients, and of VTE diagnoses identified in the high-risk group with the Geneva RAM.
- We developed a simplified Geneva RAM to improve its implementability.

Conflict of Interest
Dr. David Spirk is an employee of Sanofi-Aventis (Suisse) SA, Vernier, Switzerland.

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