Risk assessment models for venous thromboembolism in acutely ill medical patients

A systematic review

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Summary

Although the use of thromboprophylaxis is recommended for acutely ill medical patients at increased risk of venous thromboembolism (VTE), it remains unclear which risk assessment model (RAM) should be routinely used to identify at-risk patients requiring thromboprophylaxis. We therefore aimed to describe existing RAMs, and to compare these tools in terms of validity and applicability for clinical decision-making. We performed a comprehensive systematic search in MEDLINE from the date of initiation until May 2016 for studies in acutely ill medical patients investigating validity of RAMs for VTE. Two reviewers independently screened the title, abstract, and full text, and evaluated the characteristics of studies, and the composition, evidence of validation, and results on validity of the RAMs. We included 11 studies assessing eight RAMs: 4-Element RAM, Caprini RAM, a full logistic model, Geneva risk score, IMPROVE-RAM, Kucher Model, a "Multivariable Model", and Padua Prediction Score. The 4-Element RAM, IMPROVE-RAM, Multivariable Model, and full logistic model had derivation by identifying factors with predictive power. The other four RAMs were empirically generated based on consensus guidelines, published data, and clinical expertise. The Kucher Model, the Padua Prediction Score, the Geneva Risk Score and the IMPROVE-RAM underwent multicenter external validation. The Kucher Model, the Padua Prediction Score, and the Geneva Risk Score improved rates of thromboprophylaxis or clinical outcomes. In conclusion, existing RAMs to evaluate the need of thromboprophylaxis in acutely ill medical patients are difficult to compare and none fulfills the criteria of an ideal RAM. Nevertheless, the adequacy of thromboprophylaxis may be improved by implementing one of the validated RAMs.

Keywords

Thrombosis, prophylaxis, review, systematic, clinical prediction rule, inpatients

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Introduction

Venous thromboembolism (VTE) is a major and potentially life-threatening complication among acutely ill medical patients. Hospitalisation accounts for about one fourth of all VTE events in the community (1–3). Evidence clearly demonstrates that anticoagulant prophylaxis significantly reduces the incidence of VTE in this population (4–6). Therefore, current guidelines of the American College of Chest Physicians (ACCP) recommend the use of thromboprophylaxis for acutely ill medical patients at increased risk of developing VTE (1).

Because thromboprophylaxis is insufficiently implemented, multiple risk assessment models (RAM) have been developed for the use in hospitalised medical patients (7). These tools serve as clinical decision aids to risk-stratify patients for VTE, improving the use of adequate anticoagulant prophylaxis in the population at risk. In general, electronic alert systems are useful to implement RAMs into clinical practice. Kucher et al. demonstrated increased use of thromboprophylaxis along with reduced rates of VTE in hospitalised patients using an electronic alert system (8).

However, it is controversial which RAM for VTE in hospitalised medical patients should be applied in clinical practice and to our knowledge, no internationally standardised risk assessment tool is currently being used to assess patient's eligibility for anticoagulant prophylaxis (9).

We therefore aimed to identify and describe existing RAMs for VTE in acutely ill medical patients, and to compare these tools in terms of their validity and applicability for decision-making in clinical practice.

Methods

Data sources and search strategy

For this review, we developed and followed a protocol based on the PRISMA statement for conducting and reporting systematic re-

views (10). We conducted a comprehensive search in MEDLINE from the date of initiation until May 30, 2016, with no language restrictions. Furthermore, we identified additional articles by searching cited references of relevant articles. The detailed search strategy is shown in the Appendix.

Study selection

We included studies in humans on pharmacological thromboprophylaxis in acutely ill medical patients that investigated the validity of risk assessment tool(s). Studies in non-medical, pediatric, pregnant, or psychiatric patients were excluded. Another reason for exclusion was language other than English, German, French, or Italian.

Two investigators (A.K.S. and J.S.) independently screened the titles and abstracts of citations identified by the search strategy and evaluated the full text for study inclusion. The agreement on the study inclusion between the two reviewers was substantial (*k* value 0.86 for screening titles and abstracts). Disagreements on the study inclusion were resolved through discussion.

Data extraction

We abstracted information about the characteristics of studies including study design, number of participating centres and enrolled patients, year of publication, definition of VTE, and inclusion and exclusion criteria using a standardised data extraction tool.

Individual items of RAMs were recorded, together with their cut-offs for risk stratification. Data on the type of validity (derivation, validation, or both), and results on the validity (cumulative rate, hazard ratio, odds ratio, positive/negative likelihood ratio, sensitivity, specificity, negative/positive predictive value, receiver-operating curve, area under the curve) were gathered.

Level of evidence

For each identified RAM, we described the level of evidence. According to Spyropoulus et al. (11), the level of evidence of a clinical prediction rule was classified into the following categories: Level 4 Derivation (Identification of factors with predictive power), Level 3 Validation (Application of rule in a similar clinical setting and popu-

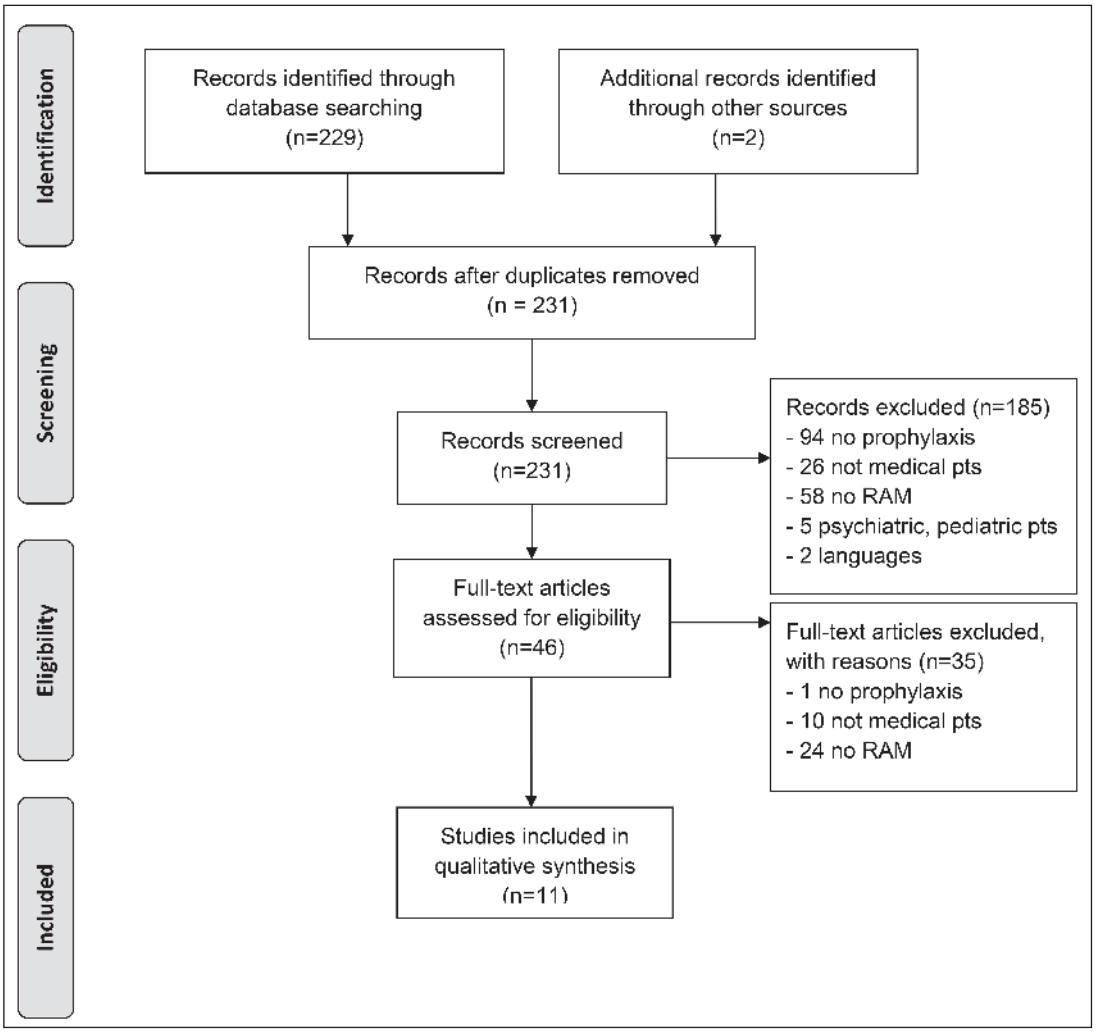

Figure 1: Flow chart according to the PRISMA statement (10).

lation as in step 1), Level 2 Validation (Application of rule in multiple clinical settings with varying prevalence and outcomes of disease), Level 1 Impact analysis (Evidence that rule changes physician behavior and improves patient outcomes and/or reduces costs).

We performed an additional search in MEDLINE for each RAM to identify additional articles with focus on the impact analysis, by showing either improvement of thromboprophylaxis use or improvement of clinical outcomes (e.g. reduction of VTE events), or reduction of costs.

Results

General characteristics of studies and RAMs

We initially identified 231 studies; of which 11 were included in our analysis (►Figure 1). Of these, five (45 %) were performed in multiple centres. ►Table 1 displays a summary of key studies assessing RAMs. Two studies were carried out in Europe, four in the U.S., four in Asia, and one study was intercontinental. Six studies were assessing one single RAM, whereas five studies were comparing two or three RAMs. Time span of performance of included studies ranged between 2000–2013.

Inclusion and exclusion criteria were similar (inclusion criteria: >18 years of age, admission to a medical ward with a minimum stay of >24 hours; exclusion criteria: anticoagulant treatment or indication for therapeutic anticoagulation upon hospital admission or VTE on admission) for all studies except for the fact, that two studies included only a subpopulation of medical patients (one study in cancer patients only and one study in patients with sepsis). VTE was mainly defined as objectively confirmed thrombosis (pulmonary embolism had to be objectively confirmed by contrast-enhanced computer tomography, ventilation perfusion scan or conventional pulmonary angiography, and deep-vein thrombosis by compression ultrasound or venography) (data not shown).

Overall, the following eight RAMs were identified: 4-Element RAM, Caprini RAM, a full logistic model, Geneva risk score, IM-

Table 1: Summary of key studies.

Name of RAM	First author of study (ref.)	Number of centres in Study	Number of patients in study	Proportion of low-risk patients of VTE (%)	Overall VTE incidence at 3 months (%)	VTE incidence in low-risk patients (%)	VTE incidence in high-risk patients (%)
4-Element RAM	Woller (12)[a]	22	143975 (DC) 46846 (VC)	Not indicated	3.7 % (DC) 4.5 % (VC)	N. a.	N. a.[b]
Caprini RAM	Abdel-Razeq (13)[c]	1	606	8.9	3.46 %[d]	0[d]	Moderate risk: 3.38 High risk: 4.2[d]
Full logistic Model	Woller (12)[a]	22	143975 (DC) 46846 (VC)	N. a.	3.7 (DC) 4.5 (VC)	N. a.[e]	N. a.[e]
Geneva Risk Score	Nendaz (16)[c]	8	1478	35	2.3	0.6	3.2
IMPROVE-RAM	Spyropopoulos (17)[f]	358	15156	69	1.2	0 points: 0.4 1 point: 0.6	2 or 3 points: 1.5 ≥4 points: 5.7
	Rosenberg (19)[c]	2	19217	68	N. a.[g]	0.42	1.29
	Mahan (18)[c]	358 (DC) 3 (VC)	20460	63 (VC) 69 (DC)	0.95 (DC) 0.68 (VC)	0.45 (DC) 0.2 (VC)	Intermediate risk: 1.04 (VC), 1.3 (DC) High risk: 4.15 (VC), 4.7 (DC)
Kucher Model	Woller (12)[c]	22	143975 (DC) 46846 (VC)	N. a.	3.7 % (DC) 4.5 % (VC)	N. a.[h]	N. a.[h]
Mulitivariable Model	Rothberg (20)[f]	374	194198 (DC) 48540 (VC)	N. a.	0.46 % (VC)	N. a.[j]	N. a.[j]
Padua Prediction Score	Nendaz (16)[c]	8	1478	52	2.3	1.1	3.5

DC, derivation cohort ; VC, validation cohort ; VTE, venous thromboembolism ; AUC, area under the curve ; N. a., not assessed. [a]Derivation and internal validation. [b]AUC 0.874 (DC), 0.843 (VC). [c]External validation. [d]VTE incidence at 60 days. [e]AUC 0.893 (DC), 0.861 (VC). [f]Derivation. [g]Case control study. [h]AUC 0.781 (DC), 0.756 (VC). [j]Validation cohort: Model discrimination c-statistic 0.75. Multivariable model using a risk threshold of 1 %: sensitivity 28 %, specificity 93 %, positive predictive value 2.2 %, negative predictive value 99.7 %.

PROVE-RAM, Kucher Model, a "Multivariable Model", and Padua Prediction Score. The number of risk factors included in the RAMs ranged between 4 (4-Element RAM) and 86 variables (full logistic model) (▶Table 2).

Descriptive results on validity of RAMs

- The **4-Element RAM** was investigated in one retrospective study differentiating two cohorts (a derivation and a validation cohort). In this study, Woller et al. (12) compared the 4-Element RAM to the Kucher Model and to a full logistic model, that served as a reference model. The area under the curve (AUC) was the highest for the full logistic model (0.86), followed by the 4-Element RAM (0.84), and the Kucher Model (0.76) in the validation cohort.
- The **Caprini RAM** was assessed in three monocentric studies. In cancer patients, Abdel-Razeq et al. (13) demonstrated incidence rates of VTE of 0% in low-risk patients vs. 4.2% in high-risk patients. Zhou H.X. et al. (14) demonstrated that the difference in the VTE recurrence rate among the risk groups was not statistically significant and concluded that the Caprini Model classifies more VTE patients into high or highest risk categories compared to both the Kucher Model and the Padua Prediction Score. Zhou H. et al. (15) performed a case-control study comparing the cumulative risk of inpatients with VTE versus controls by the Caprini and the Padua Prediction Score, respectively. A classification of high-highest risk according to the two RAMs was associated with similar OR for VTE (3.01 Caprini, 2.9 for Padua Prediction Score) compared with low-moderate risk classification. However, the Caprini RAM identified 82.3% of VTE patients as having a high or highest risk, while the Padua Prediction Score identified only 30.1% of VTE patients as being at high risk.
- The **Geneva Risk Score** was examined in a large prospective multicentre study with almost 1500 patients (16). In comparison to the Padua Prediction Score, the Geneva Risk Score predicted VTE and VTE-related mortality favourable, showing a particular benefit to more accurately identify low- risk patients who do not require thromboprophylaxis (negative likelihood ratio 0.28 for the Geneva Risk Score vs. 0.51 for the Padua Prediction Score).
- The **IMPROVE-RAM** was evaluated in three studies (1 retrospective, 1 case control and 1 prospective in 12 countries). The IMPROVE-RAM was not compared to other RAMs. Spyropoulos et al. (17) described that during hospitalisation, the observed VTE rate for an IMPROVE-RAM score of 2 or 3 points (1.5%) and ≥4 points (5.7%) correlated with predicted VTE risk (area of the receiver operating curve, AUC 0.69). The study of Mahan et al. (18) showed an AUC of 0.77 differentiating three risk classes (high, moderate, and low). Rosenberg et al. (19) applied different cut-offs for risk classification, but also found a good discrimination of low-risk and at-risk medical patients with an AUC of 0.70 with more than two thirds in the low-risk group not requiring prophylaxis.
- The **Kucher Model** was evaluated in the study by Woller et al. (12) in comparison to the 4-Element RAM and by Zhou H.X. et al. (14) in comparison to the Caprini RAM and to the Padua Prediction Score (see above).
- The **"Multivariable Model"** was assessed in one study by Rothberg et al. (20) showing sensitivity of 28% and specificity of 93% using a VTE risk threshold of 1%.
- The **Padua Prediction Score** was investigated in five studies. Barbar et al. (21) demonstrated a 32-fold increased VTE risk in patients with high score without prophylaxis compared to patients with a low score. Vardi et al. (22) did not find correlation of the risk categories with incidence of VTE, but with in-hospital death. The authors concluded that the Padua Prediction Score is rather a general co-morbidity and disease severity index. The study of Zhou et al. (14) suggested that the Padua Prediction score classifies more VTE patients into high or highest risk levels in comparison to both the Kucher Model and the Caprini Model. Another Asian study be Zhou et al. (15) found that 82.3% of VTE patients were identified as having high risk, whereas the Padua Prediction Score only identified 30.1% of VTE patients being at high risk. The Padua Prediction Score was further compared to the Geneva Risk Score by Nendaz et al. (16) (see above).

Direct comparison of RAMs

Overall, the 4-Element RAM, the Caprini Model, the Geneva Risk Score, the full logistic model, the Kucher Model, and the Padua Prediction Score feature direct comparison to other RAMs. Thereof, the Geneva Risk Score, the Kucher Model and the Padua Prediction Score had comparison in multicentre studies externally validating RAMs. In contrast, the IMPROVE-RAM and the "Multivariable Model" lack direct comparison to other RAMs.

Level of evidence for RAMs

Derivation (Level 4)

Four RAMs (4-Element RAM, IMPROVE, Multivariable Model, and full logistic model) had derivation by identifying factors with predictive power. Hereby, the 4-Element-RAM was derived in a retrospective cohort study, identifying three variables most predictive for the incidence of VTE, and adding the variable "diagnosis of cancer" to the RAM. The IMPROVE-RAM including seven risk factors was derived in a prospective study. The cut-offs for eligibility for classification into risk groups vary among further studies on the IMPROVE-RAM. The "Multivariable Model" was derived by Rothberg et al. (20) in a retrospective cohort study including 13 variables. Finally, the full logistic model by Woller et al. (12) (86 variables) was derived in a retrospective cohort study.

The other four RAMs (Caprini-RAM, Padua Prediction Score, Kucher Model, and Geneva Risk Score) were empirically generated based on consensus guidelines, published data, and clinical expertise. The Caprini RAM (39 risk factors) was developed from published data and clinical expertise. The Geneva Risk Score (19 risk factors) was derived from VTE prevention trials combined with

Table 2: Characteristics of risk assessment models.

Name of RAM (ref.)	Number of items	Risk factors*	Weighing points of items	Defined cut-off(s) for risk groups
4-Element-RAM (12)	4	• Previous VTE, an order for bed rest, peripherally inserted central venous catheterisation line, cancer diagnosis	1 each	0 low risk ≥1 high risk
Caprini (13–15)	39	• Stroke; Multiple trauma; Elective major lower extremity arthroplasty; Hip, pelvis or leg fracture; Acute spinal cord injury (paralysis) • Age (≥75 years); History of VTE; Positive Factor V Leiden; Positive prothrombin G20210A; Elevated serum homocysteine; Positive Lupus anticoagulant; Other congenital or acquired thrombophilia; Heparin-induced thrombocytopenia (HIT); Family history of VTE; Elevated anticardiolipin antibodies • Age (61–74 years); Central venous access; Arthroscopic surgery; Major surgery; Malignancy; Laparoscopic procedure ≥45 min; Patient confined to bed; Immobilising plaster cast • Age (41–60 years); Acute myocardial infarction; Heart failure; Varicose veins; Obesity (BMI≥25); Inflammatory bowel disease; Sepsis; COPD or abnormal pulmonary function; Severe lung disease; Oral contraceptives or HRT; Pregnancy or postpartum; History of unexpected stillborn infant, recurrent spontaneous abortion (≥3), premature birth with toxaemia or growth-restricted infant; Medical patient currently at bed rest; Minor surgery planned; History of prior major surgery; Swollen legs	5 each 3 each 2 each 1 each	0–1 low risk; 2 intermediate risk; 3–4 high risk; >5 highest risk (According to Zhou HX(14) and Zhou H(15)) ≤2 Low risk; 3–4 moderate risk high; ≥5 high risk (According to Abdel-Razeq (13))
Geneva Risk Score (16)	19	• Cardiac failure, Respiratory failure, Recent stroke (<3 months), Recent myocardial infarction (<4 weeks) • Acute infectious disease (including sepsis), Acute rheumatic disease, Active cancer, Myeloproliferative syndrome, Nephrotic syndrome, Prior VTE, Known hypercoagulable state • Immobilisation (complete bed rest or inability to walk for >30 minutes/day) for >3 days, Recent travel >6 hours, Age >60 years, BMI >30, Chronic venous insufficiency, Pregnancy, Hormonal therapy, Dehydration (assessed subjectively by the treating physician)	2 each 1 each	1–2 low risk ≥ 3 high risk
Kucher Model (12, 14)	8	• Cancer, Prior VTE, Hypercoagulability • Major surgery • Bed rest, Age >70 years, Obesity (BMI >30), Hormone replacement therapy/oral contraceptive pill	3 each 2 1 each	1–3 low risk; ≥4 points high risk (According to Kucher et al. (8)) 1–2 low risk, ≥ 3 high risk (According to Woller SC (12))
Padua Prediction Score (14–16, 21, 22)	11	• Active cancer , Previous VTE (with exclusion of superficial vein thrombosis), Reduced mobility, Already known thrombophilic condition • Recent (≤1 month) trauma and/or surgery • Elderly age (≥70 years), Heart and/or respiratory failure, Acute myocardial infarction or ischaemic stroke, Acute infection and/or rheumatologic disorder, Obesity (BMI≥30), Ongoing hormonal treatment	3 each 2 1 each	<4low risk ≥4 high risk
IMPROVE-RAM (17–19)	7	• Previous VTE • Known thrombophilia, Current lower-limb paralysis, Current cancer • Immobilised ≥ 7 days, ICU/CCU stay, Age >60 years	3 2 each 1 each	0–2 low risk, ≥3 high risk (According to Rosenberg (19)) 0–1low risk, 2–3 intermediate risk, ≥4 high risk (according to Mahan (18))
"Multivariable Model" (20)	13	• Age, Length of stay, gender, primary diagnosis, cancer, inflammatory bowel disease, obesity, central venous catheter, inherited thrombophilia, steroid use, mechanical ventilation, active chemotherapy, and urinary catheters.		No cut-off available
Full logistic model (12)	86	• See reference for all risk factors		No cut-off available

RAM, risk assessment model. *) Several of the scores contain items with a combination of risk factors. The same number of score points are assigned regardless if one or more risk factors within the item are present.

recommendations from the ACCP guidelines (23). The Kucher Model consists of eight factors, and the Padua Prediction Score (11 risk factors) was developed through integration of additional empirically gained risk factors to the Kucher Model.

Validation (Levels 3 and 2)

The 4-Element RAM, the Multivariable Model, and the full logistic model had internal validation without external validation (Level 3). All RAMs with exception of these three models (4-Element RAM, the Multivariable Model and the full logistic model) were externally validated (Level 2). The Kucher Model, the Padua Prediction Score, the Geneva Risk Score and the IMPROVE-RAM underwent even multicentre external validation.

Impact analysis (Level 1)

Three RAMs (Padua Prediction Score, Geneva Risk Score, Kucher Model) were identified to feature impact analyses either on rates of thromboprophylaxis or clinical outcomes. The Padua Prediction Score was shown to improve adequate prophylaxis rates in one monocentric study (24). A multicentre trial showed that the introduction of an e-Alert system with integration of the Geneva Risk Score resulted in an increase of appropriate prophylaxis rates (25). The Kucher Model included in a computer-alert program increased use of prophylaxis and reduced rates of VTE among patients at risk in a monocentric randomised trial (8). Another monocentric study using the Kucher model confirmed that implementation of a computer alert program may increase prophylaxis rates (26). None of the RAMs were investigated in terms of impact on financial aspects.

Discussion

Need for a RAM in clinical practice

Several randomised trials have shown that thromboprophylaxis reduces the rate of VTE among hospitalised medical patients at increased risk of VTE (4–6). In recent years, thromboprophylaxis use among hospitalised medical patients remains inconsistent. A study by Spirk et al. (27) attempted to identify predictors of underuse and overuse of thromboprophylaxis in hospitalised medical patients. Interestingly, bleeding and thrombocytopenia were identified to predict the absence of thromboprophylaxis in high-risk patients, whereas no predictors were found in low-risk patients who received thromboprophylaxis. In the context of evaluating individual risk of VTE among acutely ill medical patients, the risk of bleeding needs to be considered and balanced. According to current guidelines in patients at increased risk of thrombosis who are bleeding or at high risk for major bleeding, the use of mechanical thromboprophylaxis is suggested instead of pharmacological prophylaxis (Grade 2C) (1). A particular challenge towards optimal use of thromboprophylaxis is encountered in the increasing population of elderly patients, as advanced age itself is a risk factor for both VTE and bleeding.

Discussion of existing RAMs

An ideal VTE RAM is properly derived, externally validated for accurate identification of patients who are at increased risk of VTE, improves the rates of appropriate thromboprophylaxis and clinical events, and is cost-effective. An ideal VTE RAM does not contain too many score items and it is easily applicable in routine clinical practice (11). None of the existing VTE RAMs fulfills the criteria of an ideal RAM.

Potential limitations of most RAMs have been described previously, including the lack of prospective validation, applicability to high-risk subgroups only, inadequate follow-up time, and excessive complexity (9). Accordingly, we found in our systematic review several retrospectively designed studies for assessment of validity of RAMs except for the prospectively validated Geneva Risk Score, the Padua Prediction Score and the IMPROVE-RAM.

Due to its simplicity, the 4-Element RAM is an interesting model that was investigated in one large retrospective study differentiating a derivation and a validation cohort. However, the 4-Element RAM lacks external validation. The Geneva Risk Score, Kucher Model, and the Padua Prediction Score are RAMs with multicentre external validation but without formal derivation. The IMPROVE-RAM is an externally validated tool without direct comparison to other RAMs. For validation of the IMPROVE-RAM, two different cut-offs for classification of risk groups were used. The Caprini RAM is a valid model which has been investigated in several independent populations. However, the amount of 39 variables in the Caprini RAM makes it a complex tool to adopt in daily clinical practice. Similarly, the full logistic model includes 86 variables. Evidence identified excessive complexity of a RAM being a major barrier for implementation and use in clinical practice (9). Finally, the "Multivariable Model" by Rothberg et al. (20) was derived in a retrospective study, but did not present clear cut-offs for risk classification during external validation.

Limitations of our review

Comparison of various RAMs was complicated by different aspects. The studies identified to assess validity of the different RAMs showed great methodological heterogeneity. On one hand, different statistical methods were used to validate RAMs (sensitiv-

Medline search strategy

1 Venous Thromboembolism (MESH Term)
2 Venous Thrombosis (MESH Term)
3 Pulmonary Embolism (MESH Term)
4 # 1 OR # 2 OR # 3
5 Risk assessment
6 Hospitalisation
7 # 4 AND # 5 AND # 6

ity, specitifity, receiver operating chararteristics, Cox regression, etc.). On the other hand, different cut-offs for low- and high-risk patients were chosen for the same RAM. Furthermore, different endpoints and follow-up duration was used. Some of the studies assessed rates of VTE irrespective of thromboprophylaxis, others did not consider rates of VTE and compared the use of thromboprophylaxis. In two studies, only subpopulations of medical patients (sepsis and cancer patients) were selected to study validity of RAMs and therefore, results cannot be generalized to all medical patients. Finally, several high risk groups of medical patients were underrepresented, such as patients with chronic kidney disease requiring hemodialysis or obese patients (9).

RAMs in ongoing randomised trials for thromboprophylaxis in the medical ill patients

Few studies investigate whether thromboprophylaxis improves clinical outcomes in medical high-risk patients without the use of a specific RAM. For example, the SYstematic Elderly Medical Patients Thromboprophylaxis: Efficacy on Symptomatic OutcoMeS – Study (SYMPTOMS) investigates whether enoxaparin is superior to placebo in medical patients > 70 years with an anticipated hospital stay of at least four days. The Prophylaxis of Thromboembolism in Critically Ill Patients Using Combined Intermittent Pneumatic Compression and Pharmacologic Prophylaxis Versus Pharmacologic Prophylaxis Alone (PREVENT) trial investigates, without using a RAM, whether the addition of pneumatic compression devices to pharmacological propylaxis improves outcomes in medical intensive care unit patients. Randomised controlled interventional trials may help to establish whether RAMs are helpful to identify high-risk hospitalised medical patients who may benefit from thromboprophylaxis. For example, the Medically Ill Patient Assessment of Rivaroxaban Versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolism Risk (MARINER) trial investigates whether extended rivaroxaban prophylaxis (45 days) is superior to placebo in medical patients with an increased IMPROVE RAM score who where hospitalised for at least three days.

Conclusions

We identified the Geneva Risk Score, the IMPROVE-RAM, the Kucher Model, and the Padua Prediction Score to feature multicentre external validation. Moreover, impact analyses either on improvement of clinical outcomes or on rates of thromboprophylaxis were performed for the Kucher Model, the Padua Prediction Score, and the Geneva Risk Score. The IMPROVE-RAM lacks direct comparison to other RAMs, while the Padua Prediction Score and the Geneva Risk Score were directly compared in a multicentre external validation cohort.

We encourage the implementation of concise guidelines for a standardised VTE risk assessment in hospitalised medical patients. Until further evidence from ongoing randomised thromboprophylaxis trials is available, we suggest that hospitals implement one of the validated RAMs to improve the consistency of thromboprophylaxis among acutely ill medical patients.

What is known about this topic?

- Because thromboprophylaxis is insufficiently implemented, multiple risk assessment models (RAM) have been developed for the use in hospitalised medical patients.
- However, it is controversial which RAM for venous thromboembolism (VTE) in hospitalised medical patients should be applied in clinical practice and to our knowledge, no internationally standardised risk assessment tool is currently being used to assess patient's eligibility for anticoagulant prophylaxis.

What does this paper add?

- None of the existing RAMs fulfills the criteria of an ideal RAM. Several RAMs had multicentre external validation and therefore are applicable in acutely ill medical patients.
- We encourage the implementation of concise guidelines for a standardised VTE risk assessment in hospitalised medical patients.

Author contributions

Conceived and designed the experiments: AKS, NK. Performed the experiments: AKS, JS, DS, NK. Analysed the data: AKS, DS, NK. Wrote the paper: AKS, DS, NK. Obtained funding from the Clinic of Angiology: NK.

Conflicts of interest

Dr. Spirk is an employee of Sanofi-Aventis (Suisse) SA, Vernier, Switzerland. The other authors declare no conflict of interest.

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