

BMJ Open Risk assessment models for venous thromboembolism in hospitalised adult patients: a systematic review

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ABSTRACT

Introduction Hospital-acquired thrombosis accounts for a large proportion of all venous thromboembolism (VTE), with significant morbidity and mortality. This subset of VTE can be reduced through accurate risk assessment and tailored pharmacological thromboprophylaxis. This systematic review aimed to determine the comparative accuracy of risk assessment models (RAMs) for predicting VTE in patients admitted to hospital.

Methods A systematic search was performed across five electronic databases (including MEDLINE, EMBASE and the Cochrane Library) from inception to February 2021. All primary validation studies were eligible if they examined the accuracy of a multivariable RAM (or scoring system) for predicting the risk of developing VTE in hospitalised inpatients. Two or more reviewers independently undertook study selection, data extraction and risk of bias assessments using the PROBAST (Prediction model Risk Of Bias ASsessment Tool) tool. We used narrative synthesis to summarise the findings.

Results Among 6355 records, we included 51 studies, comprising 24 unique validated RAMs. The majority of studies included hospital inpatients who required medical care (21 studies), were undergoing surgery (15 studies) or receiving care for trauma (4 studies). The most widely evaluated RAMs were the Caprini RAM (22 studies), Padua prediction score (16 studies), IMPROVE models (8 studies), the Geneva risk score (4 studies) and the Kucher score (4 studies). C-statistics varied markedly between studies and between models, with no one RAM performing obviously better than other models. Across all models, C-statistics were often weak (<0.7), sometimes good (0.7–0.8) and a few were excellent (>0.8). Similarly, estimates for sensitivity and specificity were highly variable. Sensitivity estimates ranged from 12.0% to 100% and specificity estimates ranged from 7.2% to 100%.

Conclusion Available data suggest that RAMs have generally weak predictive accuracy for VTE. There is insufficient evidence and too much heterogeneity to recommend the use of any particular RAM.

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Strengths and limitations of this study

- This systematic review provides an up-to-date comprehensive review of risk assessment models for predicting venous thromboembolism in patients admitted to hospital.
- The newly developed PROBAST (Prediction model Risk Of Bias ASsessment Tool) tool was used to evaluate the risk of bias and applicability of the available evidence.
- Heterogeneity in the included studies (participants, inclusion criteria, clinical condition, outcome definition and measurement) and variable reporting of items precluded meta-analysis.
- Limitations of the existing evidence and areas of future research are highlighted.

INTRODUCTION

Venous thromboembolism (VTE) is an important and life-threatening complication of hospitalisation and illness, and is associated with significant morbidity and mortality.^{1 2} Globally, an estimated 10 million VTE episodes are diagnosed each year; over half of these episodes are associated with hospital inpatients stays and result in significant loss of disability-adjusted life years.^{3 4} Consequently, there has been a substantial and sustained focus on VTE prevention over the last three decades, with good evidence indicating a reduction in morbidity with primary thromboprophylaxis in hospitalised patients.^{5–8} Despite this evidence, thromboprophylaxis remains either underused or inappropriately applied.⁹

Risk assessment models (RAMs) have been developed to help stratify the risk of VTE among hospitalised patients.¹⁰ These models use clinical information from the patient's history and examination to identify those with an increased risk of developing VTE who are most likely to benefit from pharmacological prophylaxis. Inappropriate use of VTE



prophylaxis may not reduce VTE rates and may cause unnecessary harm.¹¹ While RAMs could improve the ratio of benefit to risk and benefit to cost, it is unclear which VTE RAM should be applied to guide decision-making for prophylaxis in clinical practice and thereby optimise patient care.

The current review extends and updates three broadly overlapping existing reviews.^{10 12 13} While these reviews identified the use of various (derived and validated) RAMs for VTE in hospitalised patients, they did not find any evidence to suggest which RAM was superior. The aim of this systematic review was to identify primary validation studies (as derivation studies may give an overoptimistic assessment of model performance measures) and determine the accuracy of individual RAMs for predicting the risk of developing VTE in hospital inpatients.

METHODS

A systematic review was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁴ This review was part of a larger project on VTE RAMs for hospital inpatients¹⁵ and was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020165778).

Eligibility criteria

We sought studies evaluating RAMs which could be applied to a general inpatient population (medical, surgical or trauma) rather than disease-specific models. All primary validation studies that evaluated the accuracy (eg, sensitivity, specificity, C-statistic) of a multi-variable RAM (or scoring system) for predicting the risk of developing VTE were eligible for inclusion. We selected studies that included validation of the model in a group of patients that were not involved in model derivation. This involved either splitting the study cohort (internal) or using a new cohort (external). The study could have reported derivation of the model but we only used the validation data to estimate accuracy. The study population consisted of hospital inpatients including those who required medical care, undergoing any surgery (excluding day surgery) or received care following an injury. Studies that primarily focused on children (aged under 16 years), women admitted to hospital for pregnancy-related reasons and any patient admitted to a level 2 or above critical care environment (eg, patients requiring more detailed observation or intervention including support for a single failing organ system or postoperative care and those 'stepping down' from higher levels of care) were excluded. These patient groups have VTE risk profiles that differ markedly from the general inpatient population, making the use of a generic model inappropriate.

Data sources and searches

Potentially relevant studies were identified through searches of five electronic databases including MEDLINE (with MEDLINE In-process and Epub Ahead of Print), EMBASE and the Cochrane Library. The search strategy used free text and thesaurus terms and combined synonyms relating to the condition (eg, VTE in medical inpatients) with risk prediction modelling terms. No language restrictions were used. However, as the current review updated three previous systematic reviews,^{10 12 13} searches were limited by date from 2017 (last search date from earlier reviews)¹⁰ to February 2021. Searches were supplemented by hand-searching the reference lists of all relevant studies (including existing systematic reviews); forward citation searching of included studies; contacting key experts in the field; and undertaking targeted searches of the World Wide Web using the Google search engine. Further details on the search strategy can be found in online supplemental appendix S1.

Study selection

All titles were examined for inclusion by one reviewer (KS) and any citations that clearly did not meet the inclusion criteria (eg, non-human, unrelated to VTE inpatients) were excluded. All abstracts and full-text articles were then examined independently by two reviewers (KS and AP). Any disagreements in the selection process were resolved through discussion or if necessary, arbitration by a third reviewer (SG) and included by consensus.

Data extraction and quality assessment

Data relating to study design, methodological quality and outcomes were extracted by one reviewer (KS) into a standardised data extraction form and independently checked for accuracy by a second (AP or MT). Any discrepancies were resolved through discussion to achieve agreement. Where differences were unresolved, a third reviewer's opinion was sought (SG). Where multiple publications of the same study were identified, data were extracted and reported as a single study.

The methodological quality of each included study was assessed using PROBAST (Prediction model Risk Of Bias ASsessment Tool).^{16 17} This instrument evaluates four key domains: patient selection, predictors, outcome and analysis. Each domain is assessed in terms of risk of bias and the concern regarding applicability to the review (first three domains only). To guide the overall domain-level judgement about whether a study is at high, low or an unclear (in the event of insufficient data in the publication to answer the corresponding question) risk of bias, subdomains within each domain include a number of signalling questions to help judge with bias and applicability concerns. An overall risk of bias for each individual study was defined as low risk when all domains were judged as low; and high risk of bias when one or more domains were considered as high. Studies were assigned an unclear risk of bias if one or more domains were unclear and all other domains were low.

Data synthesis and analysis

We were unable to perform meta-analysis due to significant levels of heterogeneity between studies (participants, inclusion criteria, clinical condition) and variable reporting of items. As a result, a prespecified narrative synthesis approach^{18 19} was undertaken, with data being summarised in tables with accompanying narrative summaries that included a description of the included variables, statistical methods and performance measures (eg, sensitivity, specificity and C-statistic (a value between 0.7 and 0.8 and >0.8 indicated good and excellent discrimination, respectively; and values <0.7 were considered weak²⁰), where applicable. All analyses were conducted using Microsoft Excel V.2010 (Microsoft Corporation, Redmond, Washington, USA).

Patient and public involvement

Patients and the public were not involved in the design or conduct of this systematic review.

RESULTS

Study flow

Figure 1 summarises the process of identifying and selecting relevant literature. Of the 6355 citations identified, 51 studies investigating 24 unique RAMs met the inclusion criteria. The majority of the articles were excluded primarily for not using a RAM for predicting the risk of developing VTE, having no useable or relevant outcome data or an inappropriate study design (eg, derivation study, reviews, commentaries or editorials). A

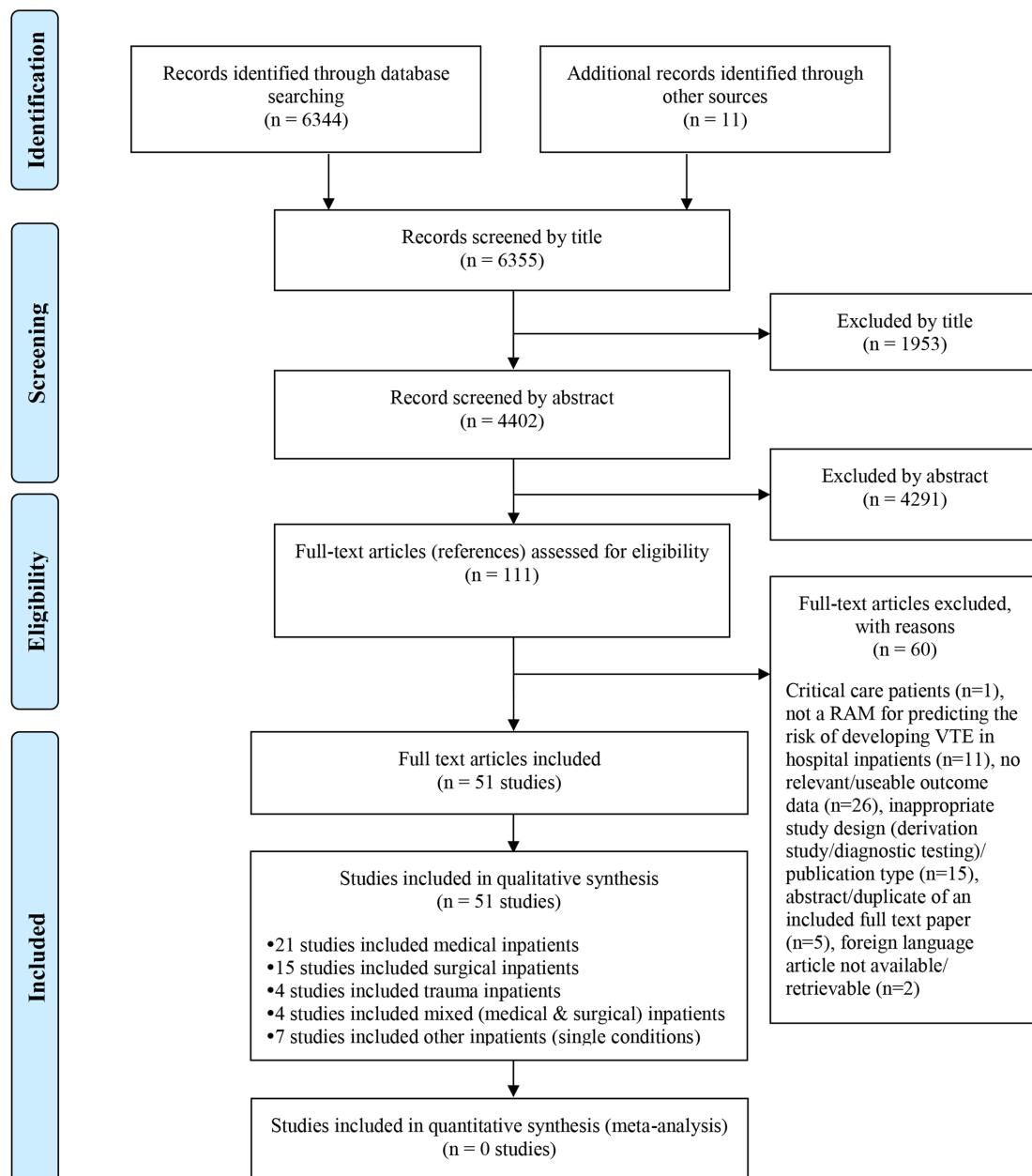


Figure 1 Study flowchart. RAM, risk assessment model; VTE, venous thromboembolism.

Table 1 Study and population characteristics

Author, year	Country	Design	Single/ Multicentre	Sample size	Population	Mean age (years)	VTE prophylaxis	RAMs	Target condition (risk period)	Incidence	Validation methodology	
Autar, 2003 ²²	UK	P,CS	Single	148	Hospitalised patients from orthopaedic, medical and surgical specialities	NR	NR	50%	► Novel (Autar, 2003)	DVT, not defined (90 days)	18.9%	External
Rogers et al, 2007 ⁵⁸	USA	P,CS	Multi	91 308	Hospitalised surgical patients (undergoing vascular and general surgery)	NR	NR	NR	► Novel (Rogers et al, 2007)	VTE (30 days)	0.6%	Internal: split (half)
Abdel-Razeq et al, 2010 ²¹	Jordan	P,CS	Single	606	Hospitalised (>24 hours) cancer patients aged ≥18 years	51	51%	55%	► Caprini (modified)	VTE, symptomatic (60 days)	3.5%	External
Bahl et al, 2010 ²³	USA	R,CS	Multi	8216	Hospitalised surgical patients (undergoing general, vascular and urologic surgery)	NR	NR	NR	► Caprini	VTE (30 days)	1.4%	External
Barbar et al, 2010 ²⁴	Italy	P,CS	Single	1180	Hospitalised medical patients	NR	47%	16%	► Padua	VTE, symptomatic (90 days)	3.1%	External
Rothberg et al, 2011 ⁵⁸	USA	R,CS	Multi	48 540	Hospitalised (≥3 days) medical patients aged ≥18 years	NR	NR	30%	► Novel (Rothberg et al, 2011)	VTE, hospital associated (NR)	0.5%	Internal: split (20%)
Woller et al, 2011 ⁶⁹	USA	R,CS	Multi	46 856	Hospitalised medical patients aged ≥18 years	61	46%	NR	► Intermountain ► Kucher	VTE, defined by ICD-9 codes (90 days)	4.5%	Internal: split (25%)
Pannucci et al, 2012 ⁵³	USA and Canada	R,CS	Multi	5761	Hospitalised (>2 days) patients with a burn injury aged ≥18 years	46	69%	NR	► Novel (Panunucci et al, 2012)	VTE; not defined (NR)	1.0%	Internal: split (25%)
Rogers et al, 2012 ⁵⁵	USA	R,CS	Multi	234 032	Hospitalised trauma patients	NR	NR	NR	► TESS	VTE (NR)	NR	Internal: split
Billimoria et al, 2013 ⁵⁵	USA	R,CS	Multi	88 053	Hospitalised surgical patients (undergoing colorectal surgery)	NR	NR	NR	► ACS NSQIP—Colon specific ► ACS ► ACS NSQIP—Universal	DVT, not defined (30 days)	2.3%	External: split (by year)
Hegsted et al, 2013 ³⁹	USA	R,CS	Single	2281	Hospitalised (≥2 days) trauma patients aged ≥13 years	45	70%	NR	► RAP	DVT, not defined or PE (NR)	► DVT: 10.5% ► PE: 1.5%	External
Vardi et al, 2013 ⁶⁴	Israel	P,CS	Single	1080	Hospitalised (≥2 days) sepsis patients aged >18 years	75	52%	18%	► Padua	VTE, hospital associated (NR)	1.3%	External
Ho et al, 2014 ⁴¹	Australia	R,CS	Single	357	Hospitalised major trauma patients	NR	75%	NR	► TESS	VTE, symptomatic (NR)	20.7%	External
Liu et al, 2014 ⁴⁴	China	P,CS	Single	287	Hospitalised acute stroke patients aged >18 years	NR	63%	22%	► Post-stroke DVT prediction system	DVT (14±3 days)	10.5%	Internal: split (33%)

Continued

Table 1 Continued

Author, year	Country	Design	Single/ Multicentre	Sample size	Population	Mean age (years)	VTE prophylaxis	RAMS	Target condition (risk period)	Incidence	Validation methodology
Mahan <i>et al</i> , 2014 ⁴⁷	USA	CC	Multi	417	Hospitalised (≥3 days) medical patients aged ≥18 years	NR	49% NR	▲ IMPROVE (7-factor)	VTE, hospital associated (92 days)	NA	External
Nendaz <i>et al</i> , 2014 ⁵¹	Switzerland	R,CS	Multi	1478	Hospitalised (>24 hours) medical patients aged ≥18 years	65	53% 57%	▲ Geneva ▲ Padua	VTE, symptomatic including PE or DVT (90 days)	2.0%	External
Pannucci <i>et al</i> , 2014 ⁵²	USA	R,CS	Multi	3576	Hospitalised surgical patients aged ≥18 years	NR	NR 66%	▲ Novel (Panunucci <i>et al</i> , 2014)	VTE (90 days)	1.4%	Internal: split (35%)
Rosenberg <i>et al</i> , 2014 ⁵⁷	USA	CC	Multi	19217	Hospitalised (≥3 days) medical patients aged ≥18 years	NR	47% 43%	▲ IMPROVE (7-factor)	VTE, defined by ICD-9 codes (90 days)	NA	External
Zhou <i>et al</i> , 2014 ¹	China	CC	Single	998	Hospitalised (≥2 days) medical patients aged >18 years	NR	58% 15%	▲ Caprini ▲ Padua	VTE, defined by ICD-10 codes (NR)	NA	External
Hewes <i>et al</i> , 2015 ⁴⁰	USA	R,CS	Single	70	Hospitalised cancer patients (undergoing oesophagectomy)	NR	83% 96%	▲ Caprini (modified)	VTE (60 days)	14.3%	External
de Bastos <i>et al</i> , 2016 ³²	Brazil	R,CS	Single	11 091	Hospitalised medical patients aged >18 years	50	61% 0%	▲ Caprini	VTE, symptomatic (NR)	0.3%	External
Grant <i>et al</i> , 2016 ³⁶	USA	R,CS	Multi	63 548	Hospitalised (≥2 days) medical patients aged ≥18 years	66	45% 61%	▲ Caprini	VTE, hospital associated (90 days)	1.1%	External
Greene <i>et al</i> , 2016 ³⁷	USA	R,CS	Multi	63 548	Acutely ill, hospitalised (≥2 days) medical patients aged ≥18 years	66	45% 61%	▲ IMPROVE (4-factor) ▲ Intermountain ▲ Kucher ▲ Padua	VTE, hospital associated (90 days)	1.1%	External
Hachey <i>et al</i> , 2016 ³⁸	USA	R,CS	Single	232	Hospitalised surgical patients (undergoing segmentectomy, lobectomy or pneumonectomy for lung cancer)	NR	43% 92%	▲ Caprini	VTE (60 days)	5.2%	External
Lui <i>et al</i> , 2016 ⁴⁵	China	CC	Single	640	Hospitalised (>2 days) medical patients aged ≥18 years	NR	52% NR	▲ Caprini ▲ Padua	VTE (NR)	N/A	External
Lobastov <i>et al</i> , 2016 ⁶	Russia	R,CS*	Multi	140	Hospitalised high-risk emergency surgery patients (undergoing general and neurosurgery)	69	49% 100%	▲ Caprini	DVT or PE, new (NR)	27.9%	External
Shaikh <i>et al</i> , 2016 ⁵⁹	USA	R,CS	Multi	1598	Hospitalised surgical patients (undergoing plastic surgery)	50	19% 34%	▲ Caprini	VTE, not defined (30 days)	1.5%	External

Continued

Table 1 Continued

Author, year	Country	Design	Single/ Multicentre	Sample size	Population	Mean age (years)	Male	VTE prophylaxis	RAMs	Target condition (risk period)	Incidence	Validation methodology
Elias <i>et al</i> , 2017 ⁵⁴	USA	R,CS	Single	30726	Hospitalised (>2 days) medical and surgical patients	NR	44%	21%	▶ Padua (automated)	VTE, defined by ICD-9 codes (NR)	0.8%	External
Frankel <i>et al</i> , 2017 (abstract) ³⁵	USA	CC	NR	149	Hospitalised surgical patients aged ≥18 years (undergoing robotic- assisted laparoscopic prostatectomy)	NR	NR	NR	▶ Caprini	VTE, not defined (90 days)	NA	External
Krasnow <i>et al</i> , 2017 (abstract) ⁴³	USA	R,CS	Multi	1 099 093	Hospitalised surgical patients (major urological cancer surgery)	NR	NR	NR	▶ Caprini	VTE, symptomatic (90 days)	1.2%	External
Patell <i>et al</i> , 2017 ⁵⁴	USA	R,CS	Single	2780	Hospitalised (>24 hours) cancer patients aged >18 years	62 (median)	56%	65%	▶ Khorana	VTE, defined by ICD-9 codes (NR)	3.8%	External
Winoker <i>et al</i> , 2017 ⁶⁸	USA	R,CS	Multi	300	Hospitalised surgical patients (undergoing urological surgery using robot-assisted partial nephrectomy)	61 (median)	62%	NR	▶ ACS NSQIP—Universal	VTE, not defined (NR)	0.3%	External
Blondon <i>et al</i> , 2018 ²³	Switzerland	R,CS	Multi	1478	Hospitalised (>24 hour) medical patients aged ≥18 years	65	53%	59%	▶ IMPROVE (7-factor) ▶ Geneva † ▶ Padua †	VTE, symptomatic including PE or DVT (90 days)	2.0%	External
Chen <i>et al</i> , 2018 ³⁰	China	CC	Single	390	Hospitalised (>2 days) patients aged ≥18 years with and without DVT	NR	51%	41%	▶ Caprini ▶ Padua	DVT (NR)	NA	External
Dombus <i>et al</i> , 2018 (abstract) ³³	USA	R,CS	NR	2830	Hospitalised surgical patients (undergoing neurosurgery)	NR	NR	NR	▶ Caprini	VTE, not defined (NR)	NR	External
Vaziri <i>et al</i> , 2018 ⁶⁵	USA	R,CS	Single	1006	Hospitalised surgical patients (undergoing neurosurgery)	NR	46%	NR	▶ ACS NSQIP—Universal	VTE, not defined (NR)	1.3%	External
Vincentelli <i>et al</i> , 2018 ⁶⁶	Italy	CC	Multi	1215	Acutely ill, hospitalised medical patients aged >18 years	NR	44%	NR	▶ Chopard ▶ Kucher ▶ Padua	VTE (NR)	NA	External
Zhou <i>et al</i> , 2018 ⁷⁰	China	CC	Single	1804	Hospitalised (≥2 days) medical patients aged >18 years	NR	59%	5%	▶ Caprini ▶ Padua	VTE, defined by ICD-10 codes (NR)	NA	External
Blondon <i>et al</i> , 2019a ²⁶	Italy	R,CS*	Single	1180	Hospitalised medical patients	72	47%	20%	▶ Geneva (simplified)	VTE, symptomatic (90 days)	3.1%	External
Blondon <i>et al</i> , 2019b (abstract) ²⁷	Switzerland	R,CS*	Multi	991	Hospitalised elderly medical patients	75	55%	NR	▶ Geneva (simplified) ▶ IMPROVE (NR) ▶ Padua	VTE, symptomatic (NR)	15.0%	External

Continued

Table 1 Continued

Author, year	Country	Design	Single/ Multicentre	Sample size	Population	Mean age (years)	Male	VTE prophylaxis	RAMs	Target condition (risk period)	Incidence	Validation methodology
Cobben <i>et al</i> , 2019 ³¹	Netherlands	CC	Multi	556	Hospitalised (>24 hours) medical patients	NR	52%	NR	<ul style="list-style-type: none"> ▲ Caprini ▲ Geneva ▲ IMPROVE (4-factor) ▲ IMPROVE (7-factor) ▲ Intermountain ▲ Kucher ▲ Lecumberri ▲ NAVAL ▲ NICE Guideline ▲ Padua ▲ PRETEMED guideline ▲ Zakai <i>et al</i> (model 2) 	VTE (NR)	NA	External
Tachino <i>et al</i> , 2019 ³²	Japan	R,CS	Multi	859	Hospitalised (>24 hours) trauma patients aged ≥18 years	NR	64%	NR	<ul style="list-style-type: none"> ▲ RAP ▲ Quick RAP 	VTE (NR)	3.0%	External (RAP)/ internal (qRAP)
Tian <i>et al</i> , 2019 ⁶³	China	R,CS	Single	533	Hospitalised surgical patients (undergoing thoracic surgery)	53	53%	0%	<ul style="list-style-type: none"> ▲ Caprini ▲ Khorana ▲ Padua ▲ Novel (Rogers <i>et al</i>, 2007) 	VTE (NR)	8.4%	External
Bo <i>et al</i> , 2020 ²⁹	China	P,CS	Multi	24 524	Hospitalised (≥2 days) patients from medical and surgical specialties aged ≥18 years	57	57	NR	▲ Caprini	DVT (NR)	0.9%	External
Hu <i>et al</i> , 2020 ⁴²	China	CC	Single	442	Hospitalised (≥2 days) cancer patients aged ≥18 years	NR	62	3.8	<ul style="list-style-type: none"> ▲ Caprini ▲ Khorana 	VTE, defined by ICD-10 codes (NR)	NA	External
Mlaver <i>et al</i> , 2020 ⁴⁸	USA	CC	Single	189	Hospitalised surgical patients (undergoing hepatobiliary, colorectal, endocrine, plastic, transplant or general surgery)	NR	NR	NR	<ul style="list-style-type: none"> ▲ Caprini ▲ Padua 	VTE, not defined (NR)	NA	External
Mourmneh <i>et al</i> , 2020 ⁴⁹	France	R,CS*	Multi	14 660	Acutely ill, hospitalised (≥2 days) medical patients aged ≥40 years	73	50	46.1	<ul style="list-style-type: none"> ▲ Caprini ▲ Padua ▲ IMPROVE (7 factor) 	VTE, symptomatic including PE or DVT (90 days)	1.8%	External
Nafee <i>et al</i> , 2020 ⁵⁰	35 countries	R,CS*	Multi	6459	Hospitalised medical patients	76	45	100	<ul style="list-style-type: none"> ▲ IMPROVE (NR) ▲ Novel (Nafee <i>et al</i>, 2020a) ▲ Novel (Nafee <i>et al</i>, 2020b) 	VTE (77 days)	6.3%	External

Continued

Table 1 Continued

Author, year	Country	Design	Single/ Multicentre	Sample size	Population	Mean age (years)	Male	VTE prophylaxis	RAMs	Target condition (risk period)	Incidence	Validation methodology
Shang <i>et al</i> , 2020 ⁶⁰	China	CC	Single	2878	Hospitalised (≥2 days) cancer patients aged ≥18 years	56	47	NR	▲ Caprini (2009) ▲ Caprini (2013)	VTE, (NR)	NA	External
Shen <i>et al</i> , 2020 ⁶¹	China	CC	Single	148	Hospitalised (≥2 days) medical patients aged ≥18 years	NR	NR	0	▲ Novel (Shen <i>et al</i> , 2020)	VTE, not defined (NR)	NA	Internal: split (by time, months)
Wang <i>et al</i> , 2020 ⁶⁷	China	CC	Single	1579	Hospitalised (≥3 days) medical patients aged ≥18 years	53	57	NR	▲ Padua	VTE, (NR)	NA	Internal: split (by year, months)

*Prospective cohort study with retrospective analysis, thus classified as retrospective cohort study.

†Data overlap with Nendaz *et al*.⁵¹

ACS NSQIP; American College of Surgeons National Surgical Quality Improvement Program; CC, case-control; CS, cohort study; DVT, deep vein thrombosis; NA, not applicable; NR, not reported; P, prospective; PE, pulmonary embolism; R, retrospective; RAMs, risk assessment models; RAP, Risk Assessment Profile; TESS, Trauma Embolic Scoring System; VTE, venous thromboembolism.

full list of excluded studies with reasons for exclusion is provided in online supplemental appendix S2.

Study and patient characteristics

The design and participant characteristics of the 51 included studies^{21–71} are summarised in table 1. All studies were published between 2003 and 2020 and were undertaken in North America (n=24),^{232533–4043474852–59656869} Asia (n=13),^{29304244–4660–63677071} Europe (n=9),^{22 24 26–28 31 49 51 66} the Middle-East (n=2),^{21 64} South America (n=1),³² Australia (n=1)⁴¹ and one study was intercontinental.⁵⁰ Sample sizes ranged from 70⁴⁰ to 1 099 093⁴³ patients in 37 observational cohort studies (11 prospective²¹²²²⁴²⁸²⁹³²⁴⁴⁵¹⁵²⁵⁶⁶⁴ (5 of which were multicentre) and 26 retrospective^{23 25–27 33 34 36–41 43 46 49 50 53–55 58 59 62 63 65 68 69} (16 of which were multicentre) in design). Sample sizes in 14 case-control studies^{30 31 35 42 45 47 48 57 60 61 66 67 70 71} (4 of which were multicentre) ranged from 148⁶¹ to 19 217⁵⁷ patients.

The vast majority of studies evaluated VTE risk assessment in hospital inpatients who required medical care (n=21),^{24 26–28 31 32 36 37 45 47 49–51 57 58 61 66 67 69–71} were undergoing surgery (n=15)^{23 25 33 35 38 40 43 46 48 52 56 59 63 65 68} or were a mixed medical and surgical cohort (n=4).^{22 29 30 34} The remaining studies focused on patients receiving care for trauma (n=4),^{39 41 55 62} cancer (n=4),^{21 42 54 60} stroke (n=1),⁴⁴ burn injuries (n=1)⁵³ and sepsis (n=1).⁶⁴ The mean age ranged from 45 years³⁹ to 76 years⁵⁰ (not reported in 29 studies)^{22–25 30 31 33–35 38 40–45 47 48 52 55–58 61 62 65 66 70 71} and the proportion of female subjects ranged from 17%⁴⁰ to 81%⁵⁹ (not reported in 12 studies).^{22 23 25 33 35 43 48 52 55 56 58 61}

VTE definition and case ascertainment

The majority of studies (n=37)^{21 23 24 26–32 36–38 40–47 49–52 55–58 60 62–64 66 67 70 71} defined the VTE endpoint (DVT and/or PE) as being objectively confirmed. Of the remainder, 3 studies^{34 54 69} had no objective confirmation of VTE and 11 studies^{22 25 33 35 39 48 53 59 61 65 68} did not report the methods for diagnosis confirmation. In terms of VTE risk period, half of the studies (n=23)^{21–26 28 35–38 40 43 44 47 49–52 56 57 59 69} used the RAMs to predict the occurrence of VTE within 3 months of the index hospitalisation. The remaining studies did not report the VTE risk period. The reported incidence of VTE ranged widely from 0.3%^{32 68} to 27.9%,⁴⁶ depending on definition, study design and study participants (eg, medical, surgical or trauma).

RAMs

The studies included in this review evaluated 24 validated unique RAMs. The most widely evaluated models were the Caprini RAM (22 studies),^{21 23 29–33 35 36 38 40 42 43 45 46 48 49 59 60 63 70 71} Padua prediction score (16 studies),^{24 27 28 30 31 34 37 45 48 49 63 64 66 67 70 71} IMPROVE models (8 studies),^{27 28 31 37 47 49 50 57} the Geneva risk score (4 studies)^{26–28 31} and the Kucher score (4 studies).^{31 37 66 69} A summary of their associated characteristics and composite clinical variables is provided in online supplemental appendix S3.

Table 2 Summary of each study's risk of bias and applicability concern using the PROBAST (Prediction model Risk Of Bias ASsessment Tool) tool—review authors' judgements

Author, year	Risk of bias				Concern regarding applicability			Overall	
	1. Participant selection				1. Participant selection	2. Predictors	3. Outcomes	Risk of bias	Applicability
	1. Participant selection	2. Predictors	3. Outcome	4. Analysis	1. Participant selection	2. Predictors	3. Outcomes	Risk of bias	Applicability
Abdel-Razeq et al, 2010 ²¹	High	High	High	High	High	High	High	High	High
Autar, 2003 ²²	High	High	High	High	High	High	High	High	High
Bahl et al, 2010 ²³	High	High	High	High	Unclear	Unclear	Unclear	High	Unclear
Barbar et al, 2010 ²⁴	Low	Unclear	Unclear	High	Low	Unclear	Unclear	High	Unclear
Bilimoria et al, 2013 ²⁵	Low	Low	Low	High	Low	Low	Low	High	Low
Blondon et al, 2019a ²⁶	Low	Unclear	High	High	Low	Low	Low	High	Low
Blondon et al, 2019b (abstract) ²⁷	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Blondon et al, 2018 ²⁸	Low	Unclear	Unclear	High	Unclear	Low	Unclear	High	Unclear
Bo et al, 2020 ²⁹	Low	Unclear	Unclear	Unclear	High	Low	Low	Unclear	High
Chen et al, 2018 ³⁰	High	High	High	High	Unclear	High	High	High	High
Cobben et al, 2019 ³¹	Unclear	Unclear	High	High	Unclear	Low	Unclear	High	Unclear
de Bastos et al, 2016 ³²	High	Low	High	High	High	Low	Low	High	High
Dornbus et al, 2018 (abstract) ³³	High	Unclear	High	Unclear	Unclear	Unclear	Unclear	High	Unclear
Elias et al, 2017 ³⁴	High	Unclear	High	High	Low	Low	High	High	High
Frankel et al, 2017 (abstract) ³⁵	High	Unclear	Unclear	High	High	Unclear	Unclear	High	High
Grant et al, 2016 ³⁶	High	Unclear	Unclear	Unclear	Low	Low	Low	High	Low
Greene et al, 2016 ³⁷	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear	Low
Hachey et al, 2016 ³⁸	High	Unclear	Unclear	High	High	Low	High	High	High

Continued



Table 2 Continued

Author, year	Risk of bias				Concern regarding applicability				Overall									
	1. Participant selection		2. Predictors		3. Outcome		4. Analysis		1. Participant selection		2. Predictors		3. Outcomes		Risk of bias		Applicability	
Hegsted <i>et al</i> , 2013 ³⁹	High	Unclear	High	High	High	High	High	High	High	Low	Unclear	Unclear	High	High	High	High	High	High
Hewes <i>et al</i> , 2015 ⁴⁰	High	Unclear	Unclear	High	High	Unclear	High	High	High	Unclear	Low	Unclear	High	High	High	High	High	High
Ho <i>et al</i> , 2014 ⁴¹	Unclear	Unclear	Unclear	High	High	Unclear	High	High	High	Unclear	Unclear	Unclear	High	High	High	High	High	High
Hu <i>et al</i> , 2020 ⁴²	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Krasnow <i>et al</i> , 2017 (abstract) ⁴³	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Liu <i>et al</i> , 2014 ⁴⁴	Low	Low	Unclear	Unclear	High	Unclear	Unclear	Unclear	High	High	High	High	Unclear	Unclear	Unclear	Unclear	Unclear	High
Liu <i>et al</i> , 2016 ⁴⁵	High	Unclear	High	High	High	High	High	High	High	Low	Low	Low	High	High	High	High	High	High
Lobastov <i>et al</i> , 2016 ⁴⁶	Unclear	Unclear	Unclear	High	High	Unclear	High	High	High	Low	High	High	High	High	High	High	High	High
Mahan <i>et al</i> , 2014 ⁴⁷	Low	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	High	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Mlaver <i>et al</i> , 2020 ⁴⁸	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Moumneh <i>et al</i> , 2020 ⁴⁹	High	Unclear	Unclear	Low	High	Unclear	Low	Low	High	Low	Low	Low	High	High	High	High	High	High
Nafee <i>et al</i> , 2020 ⁵⁰	Unclear	Low	Low	Low	Unclear	Low	Low	Low	Unclear	Low	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Nendaz <i>et al</i> , 2014 ⁵¹	Low	Unclear	Low	High	High	Unclear	High	High	Low	Unclear	Low	Low	High	High	High	High	High	Unclear
Pannucci <i>et al</i> , 2012 ⁵³	High	Unclear	Unclear	High	High	Unclear	High	High	High	High	High	Unclear	High	High	High	High	High	High
Pannucci <i>et al</i> , 2014 ⁵²	Low	Unclear	High	High	High	Unclear	High	High	High	Low	Low	Low	High	High	High	High	High	High
Patell <i>et al</i> , 2017 ⁵⁴	High	Unclear	Unclear	High	High	Unclear	High	High	High	High	Unclear	Unclear	High	High	High	High	High	High
Rogers <i>et al</i> , 2007 ⁵⁶	Unclear	Unclear	Unclear	High	High	Unclear	High	High	Low	Unclear	Unclear	Unclear	High	High	High	High	High	Unclear
Rogers <i>et al</i> , 2012 ⁵⁵	High	High	Unclear	High	High	Unclear	High	High	High	High	High	High	High	High	High	High	High	High
Rosenberg <i>et al</i> , 2014 ⁵⁷	Low	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Continued

Table 2 Continued

Author, year	Risk of bias				Concern regarding applicability			Overall	
	1. Participant selection		4. Analysis		1. Participant selection	2. Predictors	3. Outcomes	Risk of bias	Overall
	1. Participant selection	2. Predictors	3. Outcome	4. Analysis	1. Participant selection	2. Predictors	3. Outcomes	Risk of bias	Applicability
Rothberg <i>et al</i> , 2011 ⁵⁸	High	Unclear	Unclear	High	Low	Unclear	Unclear	High	Unclear
Shaikh <i>et al</i> , 2016 ⁵⁹	High	Unclear	High	High	High	Unclear	High	High	High
Shang <i>et al</i> , 2020 ⁶⁰	Low	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	High
Shen <i>et al</i> , 2020 ⁶¹	Unclear	High	Unclear	Unclear	High	Unclear	Unclear	High	High
Tachino <i>et al</i> , 2019 ⁶²	High	Unclear	Unclear	High	High	Unclear	Unclear	High	High
Tian <i>et al</i> , 2019 ⁶³	High	Unclear	High	High	High	High	High	High	High
Vardi <i>et al</i> , 2013 ⁶⁴	Unclear	Low	Low	High	High	Low	Low	High	High
Vaziri <i>et al</i> , 2018 ⁶⁵	Unclear	Unclear	Unclear	High	High	Unclear	Unclear	High	High
Vincentelli <i>et al</i> , 2018 ⁶⁶	High	Low	Unclear	High	High	Low	Unclear	High	High
Wang <i>et al</i> , 2020 ⁶⁷	Low	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	High
Winoker <i>et al</i> , 2017 ⁶⁸	High	Unclear	Unclear	High	High	High	High	High	High
Woller <i>et al</i> , 2011 ⁶⁹	High	High	Unclear	High	Unclear	Unclear	Unclear	High	Unclear
Zhou <i>et al</i> , 2014 ⁷¹	Unclear	Unclear	Unclear	High	High	Unclear	Unclear	High	High
Zhou <i>et al</i> , 2018 ⁷⁰	Low	High	High	High	High	Unclear	Unclear	High	High

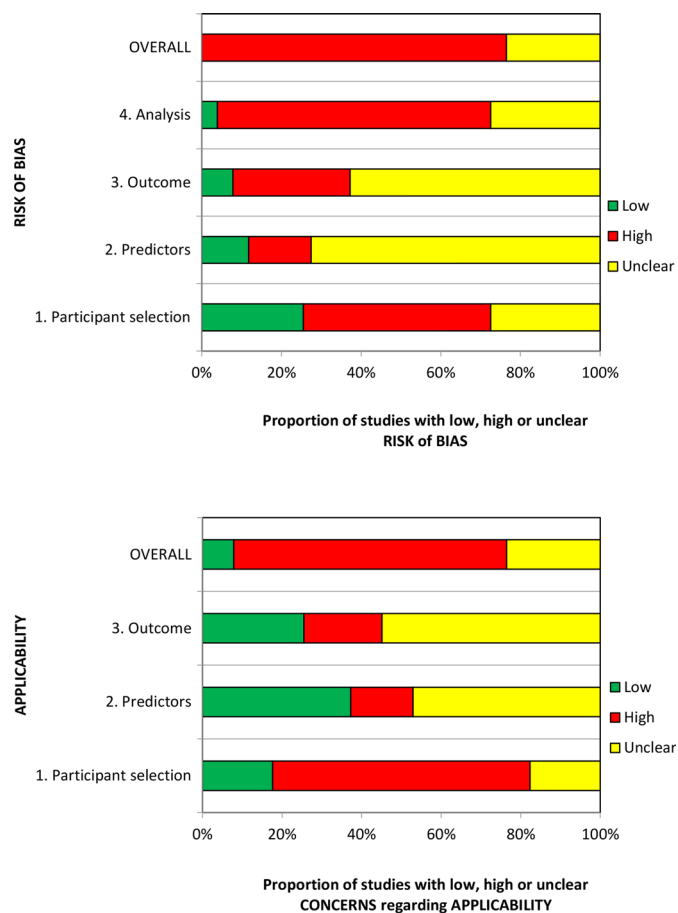


Figure 2 PROBABST (Prediction model Risk Of Bias ASsessment Tool) assessment summary graph—review authors' judgements.

Statistical methods

Statistical methods varied significantly between studies. Most studies reported the discrimination of the RAMs using a combination of the C-statistic and sensitivity or specificity. A minority reported calibration measures, such as the Hosmer-Lemeshow test.^{23 40 41 50}

Risk of bias and applicability assessment

The overall methodological quality of the 51 included studies^{21–71} is summarised in table 2 and figure 2. The methodological quality of the included studies was variable, with most studies having high or unclear risk of bias in at least one item of the PROBABST tool. The main sources of potential bias were related to the following domains:

1. Patient selection factors, such as retrospective data collection, incomplete patient enrolment or unclear criteria for patients receiving VTE prophylaxis.
2. Predictor and outcome bias arising from inappropriate inclusion of predictors within RAMs, unclear methods of outcome definition, low event rates and missing predictor or outcome data.
3. Analysis factors, such as small sample sizes, inappropriate handling of missing data and failure in reporting relevant performance measures such as calibration.

Assessment of applicability to the review question led to the majority of studies being classed either as high ($n=35$)^{21 22 29 30 32 34 35 38–49 52–55 59–68 70 71} or unclear ($n=12$)^{23 24 27 28 31 33 50 51 56–58 69} risk of inapplicability. These assessments were generally related to patient selection (highly selected study populations, eg, single pathologies, single site settings), predictors (inconsistency in definition, assessment or timing of predictors) and outcome determination.

Predictive performance of VTE RAMs (summary of results)

As there were a reasonable number of studies to compare, a summary of the C-statistics for studies involving medical, surgical and trauma patients respectively is presented in figure 3a–c, with the results grouped by RAM. Results of other hospital inpatients are presented in online supplemental appendix S4. C-statistics varied markedly between these studies and between models, with no RAM performing obviously better than other models. In studies evaluating a single model, C-statistics²⁰ were sometimes weak (<0.7 ; 10 studies with 17 data points), often good ($0.7–0.8$; 17 studies with 20 data points) and a few were excellent (>0.8 ; 5 studies with 5 data points). There was marked heterogeneity between multiple studies evaluating the same model. Studies evaluating multiple (more than 3) models^{31 37} tended to report weak accuracy across all the models (C-statistic <0.7 ; 2 studies with 16 data points).

Table 3 shows the sensitivity and specificity at various thresholds for studies involving medical, surgical and trauma patients respectively, with the results grouped by RAM. Interpretation was again limited by marked heterogeneity, which was exacerbated when different thresholds were reported by different studies evaluating the same model. Model accuracy was generally poor, with high sensitivity usually reflecting a threshold effect, as evidenced by corresponding low specificity (and vice versa).

DISCUSSION

Summary of results

In this systematic review of 51 observational studies evaluating RAMs for predicting the risk of developing VTE in hospital inpatients, we found that VTE RAMs have generally weak predictive accuracy. The studies validating these models are heterogeneous and most have a high risk of bias. Lack of methodological clarity was common, leading to difficulty in assessing the applicability of the individual study results.

Interpretation of results

We were unable to undertake meta-analysis or statistical examination of the causes of the observed heterogeneity. Potential sources of heterogeneity include variation in study design, the study population, how RAMs are implemented, outcome definition and measurement, and the use of thromboprophylaxis.

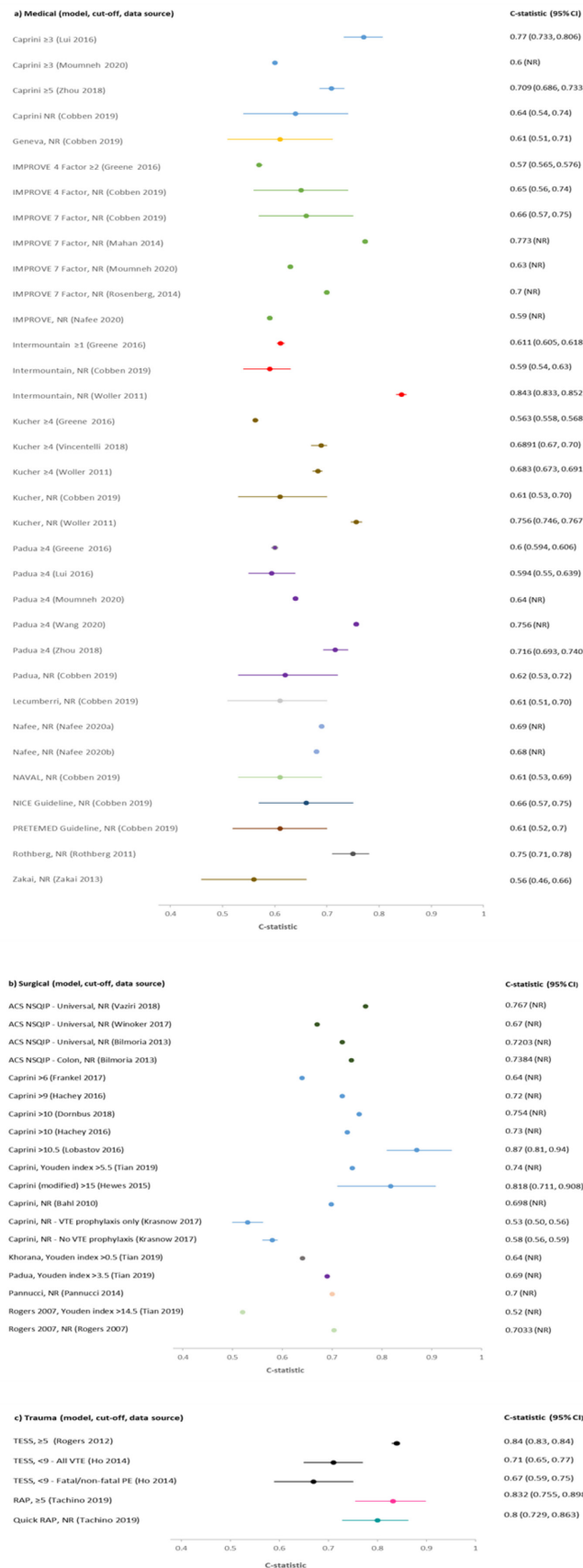


Figure 3 C-statistics by model for studies involving (a) medical, (b) surgical and (c) trauma inpatients. ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program; CI, confidence interval; DVT, deep vein thrombosis; NR, not reported; PE, pulmonary embolism; RAP, Risk Assessment Profile; TESS, Trauma Embolic Scoring System; VTE, venous thromboembolism.

**Table 3** Sensitivity and specificity for studies involving medical, surgical and trauma inpatients

Risk assessment models	Threshold or cut-off	Endpoint	Data source	Sensitivity (95% CI)	Specificity (95% CI)
MEDICAL INPATIENTS					
Caprini (7 studies)	Risk score ≥ 3	VTE	Lui <i>et al</i> , 2016 ⁴⁵	70.9% (NR)	73.4% (NR)
	Risk score ≥ 3	VTE	Moumneh <i>et al</i> , 2020 ⁴⁹	98.1% (95.6 to 99.4)	7.5% (7.1 to 8.0)
	Risk score ≥ 3	VTE	Zhou <i>et al</i> , 2014 ⁷¹	82.3% (NR)	60.4% (NR)
	Risk score ≥ 3	VTE	Zhou <i>et al</i> , 2018 ⁷⁰	84.3% (NR)	66.2% (NR)
	Risk score ≥ 5	VTE	Zhou <i>et al</i> , 2018 ⁷⁰	57.1% (NR)	24.6% (NR)
	Risk score ≥ 5	VTE	Grant <i>et al</i> , 2016 ³⁶	69.7% (NR)	50.28% (NR)
	Risk score ≥ 7	VTE	Grant <i>et al</i> , 2016 ³⁶	42.69% (NR)	74.71% (NR)
	Risk score ≥ 9	VTE	Grant <i>et al</i> , 2016 ³⁶	18.51% (NR)	89.03% (NR)
	NR*	VTE	de Bastos <i>et al</i> , 2016 ³²	86.5% (NR)	47.0% (NR)
	NR	VTE	Cobben <i>et al</i> , 2019 ³¹	88.6% (NR)	21.4% (NR)
Chopard (1 study)	Risk score ≥ 3	VTE	Vincentelli <i>et al</i> , 2018 ⁶⁶	64.2% (38.4 to 81.9)	57.7% (63.9 to 79.4)
Geneva models (4 studies)	Risk score ≥ 3	VTE	Blondon <i>et al</i> , 2018 ²⁸ ; Nendaz <i>et al</i> , 2014 ⁵¹	All patients: 90.0% (73.5 to 97.9) No prophylaxis: 85% (NR)	All patients: 35.3% (32.8 to 37.8) No prophylaxis: NR
	NR	VTE	Cobben <i>et al</i> , 2019 ³¹	75.0% (NR)	34.1% (NR)
	Simplified model: Risk score ≥ 3	VTE	Blondon <i>et al</i> , 2019a ²⁶	95.0% (NR)	44.0% (NR)
	Simplified model: NR	VTE	Blondon <i>et al</i> , 2019b (abstract) ²⁷	86.4% (NR)	NR
	IMPROVE models (4 studies)	4-factor model: NR	VTE	Cobben <i>et al</i> , 2019 ³¹	27.9% (NR)
	7-factor model: Risk score ≥ 2	VTE	Moumneh <i>et al</i> , 2020 ⁴⁹	73.8% (68.0 to 79.0)	47.1% (46.3 to 47.9)
	7-factor model: Risk score 2–3	VTE	Blondon <i>et al</i> , 2018 ²⁸ ; Nendaz <i>et al</i> , 2014 ⁵¹	All patients: 87% (NR) No prophylaxis: 85% (NR)	All patients: NR No prophylaxis: NR
	7-factor model: Risk score ≥ 3	VTE	Blondon <i>et al</i> , 2018 ²⁸ ; Nendaz <i>et al</i> , 2014 ⁵¹	All patients: 73% (NR) No prophylaxis: 54% (NR)	All patients: NR No prophylaxis: NR
	7-factor model: Risk score ≥ 4	VTE	Moumneh <i>et al</i> , 2020 ⁴⁹	24.7% (19.6 to 30.4)	85.5% (84.9 to 86.1)
	7-factor model: NR	VTE	Cobben <i>et al</i> , 2019 ³¹	63.3% (NR)	70.7% (NR)
	NR	VTE	Blondon <i>et al</i> , 2019b (abstract) ²⁷	57.6% (NR)	NR
	Intermountain (1 study)	NR	VTE	Cobben <i>et al</i> , 2019 ³¹	26.4% (NR)
Kucher (2 studies)	Risk Score ≥ 4	VTE	Vincentelli <i>et al</i> , 2018 ⁶⁶	25.1% (17.0 to 55.1)	92.9% (81.0 to 95.4)
	NR	VTE	Cobben <i>et al</i> , 2019 ³¹	28.0% (NR)	85.7% (NR)
Lecumberri (1 study)	NR	VTE	Cobben <i>et al</i> , 2019 ³¹	61.6% (NR)	46.3% (NR)
NAVAL (1 study)	NR	VTE	Cobben <i>et al</i> , 2019 ³¹	19.0% (NR)	92.7% (NR)
NICE Guidelines (1 study)	NR	VTE	Cobben <i>et al</i> , 2019 ³¹	77.6% (NR)	39.0% (NR)
Padua (10 studies)	Risk score ≥ 4	VTE	Barbar <i>et al</i> , 2010 ²⁴	94.6% (NR)	62.0% (NR)

Continued

Table 3 Continued

Risk assessment models	Threshold or cut-off	Endpoint	Data source	Sensitivity (95% CI)	Specificity (95% CI)
	Risk score ≥ 4	VTE	Blondon <i>et al</i> , 2018 ²⁸ ; Nendaz, 2014 ⁵¹	All patients: 73.3% (54.1 to 87.7) No prophylaxis: 62% (NR)	All patients: 51.9% (49.3 to 54.5) No prophylaxis: NR
	Risk score ≥ 4	VTE	Lui <i>et al</i> , 2016 ⁴⁵	23.4% (NR)	85.6% (NR)
	Risk score ≥ 4	VTE	Moumneh <i>et al</i> , 2020 ⁴⁹	91.6% (87.6 to 94.7)	25.6% (24.9 to 26.3)
	Risk score ≥ 4	VTE	Zhou <i>et al</i> , 2014 ⁷¹	30.1% (NR)	12.7% (NR)
	Risk score ≥ 4	VTE	Zhou <i>et al</i> , 2018 ⁷⁰	49.1% (NR)	16.2% (NR)
	Risk score ≥ 4	VTE	Vincentelli <i>et al</i> , 2018 ⁶⁶	52.4% (38.4 to 81.9)	72.3% (63.9 to 79.4)
	Risk score ≥ 4	VTE	Wang <i>et al</i> , 2020 ⁶⁷	76.2% (NR)	61.6% (NR)
	NR	VTE	Blondon <i>et al</i> , 2019b (abstract) ²⁷	72.7% (NR)	NR
	NR	VTE	Cobben <i>et al</i> , 2019 ³¹	61.8% (NR)	48.8% (NR)
PRETEMED guidelines (1 study)	NR	VTE	Cobben <i>et al</i> , 2019 ³¹	81.6% (NR)	24.4% (NR)
Shen 2020 (1 study)	NR	VTE	Shen <i>et al</i> , 2020 ⁶¹	77.8% (NR)	84.7% (NR)
Zakai 2013 (1 study)	Model 2: NR	VTE	Cobben <i>et al</i> , 2019 ³¹	63.8% (NR)	31.7% (NR)
SURGICAL INPATIENTS					
Caprini (8 studies)	Risk score >5	VTE	Hachey <i>et al</i> , 2016 ³⁸	100% (100 to 100)	7.2% (4.1 to 11.0)
	Risk score ≥ 5	VTE	Mlaver <i>et al</i> , 2020 ⁴⁸	88.9% (NR)	32.7% (NR)
	Risk score >5	VTE	Shaikh <i>et al</i> , 2016 ⁵⁹	70.8% (48.9 to 87.4)	39.39% (37.0 to 41.9)
	Youden index >5.5	VTE	Tian <i>et al</i> , 2019 ⁶³	76.0% (NR)	64.0% (NR)
	Risk score >6	VTE	Frankel <i>et al</i> , 2017 (abstract) ³⁵	61.5% (NR)	59.8% (NR)
	Risk score >6	VTE	Shaikh <i>et al</i> , 2016 ⁵⁹	58.3% (36.6 to 77.9)	60.1% (57.6 to 62.5)
	Risk score >7	VTE	Hachey <i>et al</i> , 2016 ³⁸	100% (100 to 100)	31.4% (25 to 37.3)
	Risk score >9	VTE	Hachey <i>et al</i> , 2016 ³⁸	83.3% (58.3 to 100)	60.5% (54.4 to 67.3)
	Risk score >9	VTE	Shaikh <i>et al</i> , 2016 ⁵⁹	16.7% (NR)	93.3% (NR)
	Risk score >10	VTE	Hachey <i>et al</i> , 2016 ³⁸	75.0% (50 to 100)	69.6% (64.6 to 76.4)
	Risk score >10	VTE	Dornbus <i>et al</i> , 2018 (abstract) ³³	78.9% (NR)	60.9% (NR)
	Risk score >10.5	DVT or PE	Lobastov <i>et al</i> , 2016 ⁴⁶	95.0% (NR)	73.0% (NR)
	Risk score >15 †	VTE	Hewes <i>et al</i> , 2015 ⁴⁰	100% (100 to 100)	66.7% (55.0 to 78.3)
Khorana (1 study)	Youden index >0.5	VTE	Tian <i>et al</i> , 2019 ⁶³	78.0% (NR)	48.0% (NR)
Padua (2 studies)	Risk score ≥ 4	VTE	Mlaver <i>et al</i> , 2020 ⁴⁸	61.1% (NR)	47.4% (NR)
	Youden index >3.5	VTE	Tian <i>et al</i> , 2019 ⁶³	36.0% (NR)	93.0% (NR)
Rogers 2007 (1 study)	Youden index >14.5	VTE	Tian <i>et al</i> , 2019 ⁶³	53.0% (NR)	54.0% (NR)
TRAUMA PATIENTS					
RAP (2 studies)	Risk score ≥ 5	VTE	Tachino <i>et al</i> , 2019 ⁶²	100% (86.8 to 100)	37.9% (34.6 to 41.3)
	Risk score 5 to ≤ 14	DVT or PE	Hegsted <i>et al</i> , 2013 ³⁹	► DVT: 82.0% (77 to 87) ► PE: 71.0% (55 to 86)	► DVT: 57.0% (55 to 59) ► PE: 53.0% (51 to 56)

Continued



Table 3 Continued

Risk assessment models	Threshold or cut-off	Endpoint	Data source	Sensitivity (95% CI)	Specificity (95% CI)
	Risk score >14	DVT or PE	Hegsted <i>et al</i> , 2013 ³⁹	▶ DVT: 15.0% (11 to 20) ▶ PE: 12.0% (1 to 23)	▶ DVT: 97.0% (97 to 98) ▶ PE: 96.0% (95 to 97)
TESS (2 studies)	Risk score ≥5	VTE	Rogers <i>et al</i> , 2012 ⁵⁵	77.4% (NR)	75.6% (NR)
	Risk score <9	VTE	Ho <i>et al</i> , 2014 ⁴¹	▶ All VTE: 97.0% (91 to 99)	▶ All VTE: 27.0% (22 to 32)
	Risk score <9	VTE	Ho <i>et al</i> , 2014 ⁴¹	▶ Fatal and non-fatal PE: 97.0% (87 to 99)	▶ Fatal and non-fatal PE: 24.0% (20 to 29)
	Risk score <9	VTE	Ho <i>et al</i> , 2014 ⁴¹	▶ Fatal PE only: 100% (81 to 100)	▶ Fatal PE only: 20.0% (13 to 28)

*Paper states 'moderate and high risk'.

†Modified Caprini model.

.DVT, deep vein thrombosis; NR, not reported; PE, pulmonary embolism; RAP, Risk Assessment Profile; TESS, Trauma Embolic Scoring System; VTE, venous thromboembolism.

The latter point warrants further attention. Thromboprophylaxis was employed in about half (n=25) of the studies,^{21 22 24 26 28 30 34 36–38 40 42 44 46 49–52 54 57–59 64 70 71} with the proportion receiving thromboprophylaxis ranging from 3.8%⁴² to 100%.^{46 50} It was not employed in 3 studies,^{32 61 63} and 23 studies^{23 25 27 29 31 33 35 39 41 43 45 47 48 53 55 56 60 62 65–69} did not report on thromboprophylaxis use. The use of thromboprophylaxis may lead to underestimation of predictive accuracy if a given RAM were to predict VTE events that were subsequently prevented by thromboprophylaxis. Limited reporting of thromboprophylaxis use precludes further analysis of its impact on the performance of the RAMs.

Comparison to the existing literature

The present review is the largest and most comprehensive systematic review in this field to date. It includes 18 recent studies^{26–31 33 42 48–50 60–63 66 67 70} published since the completion of the previous systematic review.^{10 12 13} These studies are consistent with the previous literature in that they report modest performance of the assessed RAMs, with limitations in methodology and reporting preventing further analysis. The conclusion of this review therefore concurs with previous systematic reviews: there is insufficient evidence to recommend one RAM over another.

Strengths and limitations

This systematic review has a number of strengths. The review was conducted with robust methodology in accordance with the PRISMA statement and the protocol was registered with the PROSPERO register. Clinical experts were involved throughout as checkers and to assess the validity and applicability of research during the review. We reported descriptive statistics to provide insight into the limited evidence base applicable to the subject matter, and the scientific concerns regarding validity of

the data. However, there are a number of potential weaknesses. Decisions on study relevance, information gathering and validity were unblinded and could potentially have been influenced by pre-formed opinions. However, masking is resource intensive with uncertain benefits. The studies of risk prediction were a combination of prospective cohorts and retrospective health database registries. Both have significant limitations. Retrospective studies of health database registries may have large numbers but may be limited by poor data quality and failure to accurately ascertain outcomes. Prospective cohorts may have better quality data but with smaller numbers lack statistical power. The included studies demonstrated high levels of heterogeneity so we were unable to undertake any meta-analysis.

Implications for policy, practice and future research

Guidelines from the American College of Chest Physicians (ACCP)^{72 73} and the UK National Institute for Health and Care Excellence (NICE)¹⁰ suggest using a validated RAM to guide the decision on whether to prescribe thromboprophylaxis. This review identifies all relevant RAMs and their validation studies. The reported results are insufficient to recommend one RAM over another. A RAM with weak predictive accuracy may still be better than no RAM at all but it is unclear whether RAMs predict VTE risk better than unstructured clinical assessment. Further research is clearly needed but routine use of thromboprophylaxis may present an insurmountable barrier to generating accurate and precise estimates of the prognostic accuracy of RAMs. The evidence that thromboprophylaxis is effective means that it is unethical to withhold thromboprophylaxis when a significant risk of VTE is identified. This inevitably reduces the number of VTE events in any study and confounds the association

between risk factors and VTE events. Further studies of RAM accuracy will add little to our review unless they can address this issue.

Alternative approaches therefore need to be considered. Decision-analytic modelling can use existing data to explore the trade-off between the benefits and harms of thromboprophylaxis and identify key uncertainties for future primary research. The data presented in our review show how well RAMs predict VTE but do not tell us the threshold score on the RAM at which thromboprophylaxis should be given to maximise prevention of VTE and minimise harm from bleeding. This may be a more important determinant of RAM effectiveness than predictive accuracy for VTE. Le *et al*⁷⁴ suggested thromboprophylaxis is beneficial and cost-effective if a patient's VTE risk exceeds 1%. Further work to improve RAMs to help stratify the risk of VTE in different types of hospitalised patients could focus on using decision-analytic modelling to compare the effects, harms and costs of giving thromboprophylaxis to patients with varying risk of VTE. This would allow determination of the risk threshold at which thromboprophylaxis provides optimal overall benefit.

Findings from decision-analytic modelling would require validation through primary research. The limitations of undertaking accuracy studies in populations where thromboprophylaxis is routinely used mean that future research should focus on research that compares the effectiveness of different risk assessment approaches. Observational studies could draw on variation in practice to compare outcomes between different risk assessment methods. Alternatively, a controlled trial could compare risk assessment methods in low-risk patients where existing evidence (synthesised using decision-analytic modelling) suggests the benefits of thromboprophylaxis are uncertain.

CONCLUSIONS

We identified a number of validated RAMs for potential risk stratification of hospitalised inpatients. The available evidence is insufficient to recommend one over another.

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