 UNCERTAINTIES

Which is the best model to assess risk for venous thromboembolism in hospitalised patients?

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What you need to know

• Venous thromboembolism in hospitalised patients can be potentially prevented through patient education and pharmacological thromboprophylaxis

• Risk assessment models (RAMs) help clinicians decide who should be offered pharmacological thromboprophylaxis, but variation exists in their composition of risk factors and thresholds for high and low risk

• Uncertainty exists over which RAM is optimal for hospitalised patients and whether any complex RAM outperforms simple criteria or subjective clinical opinion

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major global health burden. North American data report a 30 day case fatality rate of 10.6% following VTE. Between 30% and 50% of survivors go on to have long term complications. 1,2 About half of VTE episodes occur during hospitalisation for surgery or acute medical illness, or within 90 days from discharge. These events are classified as hospital acquired thrombosis (HAT). 3

HAT events are potentially preventable through patient education and pharmacological thromboprophylaxis. A meta-analysis (seven trials, 15 095 hospitalised patients) showed greater than 50% risk reduction for VTE with heparins compared with control. 4 In many elective surgical settings, thromboprophylaxis has become established practice. 5,6

However, pharmacological thromboprophylaxis is not suitable for all patients admitted to hospital in an emergency. It can increase the baseline risk of major bleeding by approximately 0.4%. 6-10 When given inappropriately, the consequences can be potentially harmful, notably for patients with occult bleeding on admission or those undergoing emergency procedures.

VTE risk assessment models (RAMs) aim to minimise unnecessary pharmacological thromboprophylaxis and reduce the associated harm and costs. They can also potentially provide individualised and reproducible evaluation of VTE risk, independent of seniority, expertise or bias of the assessing clinician. Fifteen published RAMs were identified in a recent overview of systematic reviews. 11 RAMs overlap on individual risk factors but vary in composition and threshold for high VTE risk. For example, application of different RAMs to a similar cohort of patients could result in recommendations for pharmacological thromboprophylaxis ranging from 32% to 90% of patients (fig 1). 12

This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is Nai Ming Lai, clinical editor. You can read more about how to prepare and submit an Education article on our Instructions for Authors pages: https://www.bmj.com/about-bmj/resources-authors/article-types
International guidance currently allows substantial variation in practice regarding VTE risk assessment. The National Institute for Health and Care Excellence (NICE) recommends the use of any RAM published by a national body, professional network, or in a peer reviewed journal. American and Australasian guidelines...
acknowledge the limited evidence to support use of any particular RAM.\textsuperscript{13-16}

Uncertainty exists regarding the optimal method of risk assessment and whether any RAM outperforms subjective clinical assessment. It is also unclear whether a validated RAM in one healthcare system will be of use in others owing to international variability in models.

**What is the evidence of uncertainty?**

Use of RAMs has been shown to discriminate between patients at high risk for VTE who may be suitable for thromboprophylaxis, and patients at low risk who do not require thromboprophylaxis. Studies of individual RAMs also show improved rates of appropriate pharmacological thromboprophylaxis prescribing, compared with historical care.\textsuperscript{12,17-20} Systematic reviews, however, note a lack of generalisability and adequate validation of available RAMs for hospitalised emergency medical and surgical patients.\textsuperscript{6,12,21} Variability in methods and outcome measurement preclude pooled estimates of effectiveness in predicting VTE or bleeding risk. NICE guidelines concluded that “none of the tools demonstrated sufficiently accurate performance for predicting VTE or bleeding risk.” Table 1 lists comparative characteristics of five widely evaluated models\textsuperscript{11} and the Department of Health RAM (in common use in the UK).
### Table 1 | Comparative RAM characteristics, thresholds, variables, and attempted validation

| RAM characteristics | UK Department of Health VTE risk assessment tool | Caprini score for VTE | Padua prediction score | Improve predictive score | IMPROVE Associative | Geneva risk score | Kucher score |
|---------------------|------------------------------------------------|-----------------------|------------------------|--------------------------|---------------------|-------------------|--------------|
| Author and year     | NICE 2018<sup>2</sup> | Caprini 2005<sup>2,3</sup> | Barbar 2010<sup>1</sup> | Tapson 2007<sup>2</sup> | Spyropoulos 2011<sup>1</sup> | Chopard 2006<sup>3</sup> | Kucher 2005<sup>3</sup> |
| Applicable cohort   | Surgical and medical | Surgical and medical | Medical | Medical | Medical | Medical | Surgical and medical |
| Design              | Dichotomous variables and threshold | Ordinal variables with cumulative score | Dichotomous variables with cumulative score | Dichotomous variables with cumulative score | Dichotomous variables with cumulative score | Dichotomous variables with cumulative score | Dichotomous variables with cumulative score |
| Number of VTE risk variables | 19 | 39 | 11 | 4 | 7 | 19 | 8 |
| C-statistic (range) | 0.66 (1 study) | 0.53-0.87 (11 studies) | 0.594-0.716 (4 studies) | 0.57-0.65 (2 studies) | 0.66-0.7731 (3 studies) | 0.61 (1 study) | 0.563-0.756 (4 studies) |
| When is pharmacological thromboprophylaxis recommended (high risk identified)? | Any thrombosis risk factor identified<sup>A</sup> | Score ≥5 | Score ≥4 | Score ≥1 | Score ≥3 | Score ≥3 | Score ≥4 |
| What proportion of patients is likely to be classified as high risk?<sup>2,3</sup> | 80% | 82% | 48% | 67% | 32% | 65% | NR |

### Clinical variables

**Patient related**

- **Active cancer**: Yes
- **Age**: Yes (<60)
- **Dehydration**: Yes (≥70)
- **Thrombophilia**: Yes (generic)
- **Obesity**: Yes (≥30 kg/m²)
- **Comorbidity**: Yes (one or more)

**Prior VTE**

- Yes (first degree relative)

**Use of hormone replacement treatment**

- Yes

**Use of oestrogen containing contraceptive therapy**

- Yes

**Varicose veins**

- Yes (with phlebitis)

**Pregnancy or postpartum period**

- Yes

**Unexplained stillbirth or miscarriage**

- No

**Current swollen legs**

- No

**Current central venous access**

- No

**Recent major surgery**

- No

**Recent use of plaster cast immobilisation**

- No

**Lower limb paralysis**

- No

**Travel related**

- No

**Admission related**

- Reduced mobility: Yes (≥3 days)

**Arthroplasty surgery**

- Yes

**Hip fracture**

- Yes

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<sup>A</sup> When is pharmacological thromboprophylaxis recommended (high risk identified)?

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External validation studies show weak prognostic performance for all RAMs for symptomatic VTE at 3 month follow-up, and variable sensitivity, ie, proportion of VTE events accurately predicted by a “high risk” score at proposed threshold (supplementary table 1). Evidence of safety is limited; three validation studies report major bleeding rates, ranging from 0.7% to 3.4% (supplementary table 1). All validation studies have a high risk of bias. Observational studies commonly include patients who have received thromboprophylaxis at clinical discretion. This will likely reduce the incidence of VTE in the at-risk population and may lead to underestimation of RAM accuracy.

Complex RAMs appear to compare unfavourably with simple, reproducible criteria. A secondary analysis (14 910 patients) of the Prevenu study across 25 French hospitals compared the performance of age ≥70 as a single variable with the Padua, Caprini, and Improve RAMs for predicting VTE risk. No statistically significant difference was seen in performance between groups and overall weak prognostic performance was noted for all methods of risk assessment.

Recent studies have investigated the use of biomarkers to improve the accuracy of risk assessment. Evidence of moderate certainty shows a probable association between VTE risk in hospitalised medical patients and elevated C reactive protein, D dimer, and fibrinogen levels as per a systematic review and meta-analysis. In a retrospective analysis of a multicentre randomised trial, the addition of a raised D dimer (more than twice the upper limit of normal) to the Improve score identified a threefold higher VTE risk in a subgroup of hospitalised acutely ill medical patients. These findings have not yet been evaluated in prospective studies and the additive value of biomarkers remains uncertain.

Integration of risk assessment into electronic records has also been explored. A well conducted randomised controlled trial (2506 patients) showed that a computer alert program based on risk factors increased physicians’ use of prophylaxis and reduced the rates of DVT and PE at 90 days by 41% (hazard ratio, 0.59; 95% confidence interval, 0.43 to 0.81; P=0.001) amongst hospitalised patients at risk.

If ongoing research likely to provide relevant evidence?
We searched the EU Clinical Trials Register, ISRCTN Registry, and ClinicalTrials.gov and identified two ongoing randomised controlled trials comparing existing risk models, bleeding risk scores, and clinical judgement for VTE prevention (supplementary table 2). One of these will evaluate the use of an embedded risk assessment process within an electronic healthcare record. The UK National Institute for Health Research has commissioned a project assessing the cost effectiveness of VTE risk assessment tools for hospital inpatients (NIHR127454).

These studies will add to the evidence on clinical and cost effectiveness of using RAMs in practice, but are not likely to conclude on the optimal model to be used in hospitalised patients. External validation research on current RAMs remains challenging, given national VTE prevention programmes.

Derivation and validation of any new RAM through prospective research would necessitate withholding pharmacological prophylaxis from patients identified at risk of VTE, which would be unethical.

What should we do in light of the uncertainty?
Current evidence strongly supports the use of pharmacological thromboprophylaxis in hospitalised general medical and surgical patients identified as at risk of VTE. Patients identified at lower risk of VTE using a RAM should be individually counselled, and provided with supporting information throughout hospital stay and on discharge. Given the temporal changes in risk during hospitalisation (dependent on clinical progress), repeated risk assessment and patient education are crucial.

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**Table 1 | Comparative RAM characteristics, thresholds, variables, and attempted validation** (Continued)

| UK Department of Health VTE risk assessment tool | Caprini score for VTE | Padua prediction score | Improve predictive score | IMPROVE Associative score | Geneva risk score | Kucher score |
|---|---|---|---|---|---|---|
| Pelvic or lower limb surgery | Yes (total anaesthetic and surgical time ≥60 mins) | Yes (arthroscopic) | No | No | No | No |
| Total anaesthetic and surgical time | Yes (≥90 mins) | Yes (≥45 mins) | No | No | No | No |
| Acute surgical admission | Yes (inflammatory or intra-abdominal condition) | No | No | No | No | No |
| Acute infection | Yes (within 7 days) | Yes | No | Yes | No | No |
| Acute rheumatological disorder | Yes (within 7 days) | No | Yes | Yes | Yes | No |
| Critical care admission | Yes | No | No | No | Yes | No |
| Surgery leading to reduced mobility | Yes | Yes | No | No | No | No |
| ‘Other risk factors’ | No | Yes | No | No | No | No |

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**Search strategy**
We searched five electronic databases including MEDLINE (with MEDLINE in-process and Epub ahead of print), EMBASE, and the Cochrane Library for relevant studies using terms relating to the condition (eg, VTE in medical inpatients) and risk prediction modelling. No language restrictions were used. Our search was limited by date from 2017 (last search date from earlier systematic reviews) to March 2021. We supplemented our search by 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 using Google.
Multiple options for risk assessment should not necessarily lead to national variation in clinical practice or outcomes. For example, NHS England has used a single recommended risk assessment tool and supporting guidance to achieve a consistent reduction in HAT and overall mortality from VTE.\(^3\)\(^3\) These results undoubtedly owe as much to the use of a nationally endorsed RAM, coordinated metrics, local quality improvement practice, and contractual obligations as they do to original research.

The NHS results also likely arise from use of a RAM which has a low threshold for recommending pharmacological thromboprophylaxis. The recent pandemic has drawn further attention to this issue, with multiple national guideline documents recommending pharmacological thromboprophylaxis for all patients hospitalised with covid-19, without use of a RAM, unless contraindicated by bleeding risk.\(^3\)\(^3\)

**Education into practice**

- How do you perform a VTE risk assessment for patients you admit to hospital and why do you use that particular method?
- Think about the last time you talked to a patient about their VTE risk. How did you counsel them regarding the signs and symptoms of VTE, irrespective of risk? How might you alter your discussion next time?

**What patients need to know**

- Blood clots can be one of the most serious complications associated with an operation and/or hospital stay.
- Any hospital admission for more than 24 hours or major surgical procedure can increase your risk of developing a blood clot. This increased risk can persist for up to 90 days after hospital discharge.
- Having clear and accurate information, increasing your fluid intake, early mobilisation, and use of preventive therapies can reduce this risk of a blood clot.
- If you are admitted to hospital, your doctor will assess your risk for blood clots and offer blood thinning medication if appropriate. This risk assessment can be repeated when the clinical situation changes and at the point of hospital discharge. You will be informed about signs of blood clots, so you know when and how to seek help.

**Recommendations for further research**

Future research should determine whether any validated RAM provides additional clinical or cost effectiveness compared with a default option of pharmacological thromboprophylaxis for all hospitalised general medical and surgical patients, subject to contraindications. Future work should also consider the effectiveness and safety of increased prophylaxis dosing for hospitalised patients identified at very high risk of VTE, and withholding pharmacological thromboprophylaxis in those patients identified as very low risk. Such research could also compare the clinical and cost effectiveness of different RAMs to identify levels of risk. Outcomes for this research must identify symptomatic VTE events up to 90 days following hospital discharge, including objectively diagnosed VTE and/or fatality attributable to VTE. Safety outcomes should include major bleeding and clinically relevant non-major bleeding.

**How patients were involved in the creation of this article**

A patient co-author of this article made suggestions to emphasise the importance of repeated patient education, advice on individualised risk reduction, and safety netting alongside routine clinical risk assessment. We are grateful for his input.

**Contributorship:** The authors were involved as follows: SG and DH (conception), all (execution, analysis, drafting manuscript and critical discussion, revision, and final approval of the manuscript). All authors had full access to all of the data (including statistical reports and tables) in the guideline and can take responsibility for the integrity of the data and the accuracy of the data analysis.

DH acts as guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

**Competing interests:** We have read and understood the BMJ policy on declaration of interests and declare that we have no competing interests. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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