Evaluation of venous thromboembolism risk assessment models for hospital inpatients: the VTEAM evidence synthesis

Daniel Edward Horner[1,2,3*] Sarah Davis[3] Abdullah Pandor[3] Helen Shulver[3] Steve Goodacre[3] Daniel Hind[3] Saleema Rex[3] Michael Gillett[3] Matthew Bursnall[3] Xavier Griffin[4] Mark Holland[5] Beverley Jane Hunt[6] Kerstin de Wit[7,8] Shan Bennett[3] and Robin Pierce-Williams[9]

[1]Emergency Department, Northern Care Alliance NHS Foundation Trust, Salford, UK
[2]Division of Infection, Immunity and Respiratory Medicine, University of Manchester, Oxford Road, Manchester, UK
[3]School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK
[4]Barts Bone and Joint Health, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[5]School of Clinical and Biomedical Sciences, Faculty of Health and Wellbeing, University of Bolton, Bolton, UK
[6]Thrombosis & Haemophilia Centre, St Thomas' Hospital, King's Healthcare Partners, London, UK
[7]Department of Emergency Medicine, Queens University, Kingston, ON, Canada
[8]Department of Medicine, McMaster University, Hamilton, ON, Canada
[9]Thrombosis UK, Llanwrda, UK

[*]Corresponding author daniel.horner@srft.nhs.uk

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/AWTW6200.

Primary conflicts of interest: Steve Goodacre was Deputy Programme Director of the NIHR Health Technology Assessment (HTA) programme and chair of the NIHR HTA commissioning committee up to 31/12/2020, which included membership of the HTA Remit and Competitiveness Group, HTA Post-Funding Committee teleconference, HTA Funding Committee Policy Group and HTA Prioritisation Group. Daniel Hind is a current member of the NIHR HTA Clinical Evaluation and Trials Committee, and NIHR HTA Fast Track Committee. Mark Holland has received honorariums from Pfizer for conference presentations. Kerstin de Wit has received an unrestricted grant from Bayer. Dan Horner has previously acted as a paid subject matter expert on venous thromboembolic disease for the Healthcare Safety

Investigation Branch. Beverley Hunt, Dan Horner and Xavier Griffin were previously involved in developing relevant National Institute for Health and Care Excellence (NICE) guidance on prevention and management of venous thromboembolic disease.

Published April 2024
DOI: 10.3310/AWTW6200

Scientific summary

Evaluation of venous thromboembolism risk assessment models for hospital inpatients: the VTEAM evidence synthesis

Health Technology Assessment 2024; Vol. 28: No. 20
DOI: 10.3310/AWTW6200

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Venous thromboembolism (VTE) is a composite diagnosis including deep-vein thrombosis (DVT) and pulmonary embolism (PE). The condition is a global health burden, affecting over 1:1000 adults worldwide, every year. Previous epidemiological studies have shown more than half of all VTE events to be hospital-associated (or acquired) thrombosis (HAT), occurring during admission or within 90 days of discharge.

Current evidence suggests that many HAT events are potentially preventable. Pharmacological prophylaxis in medical and surgical inpatients has been shown to be clinically effective in several large studies and meta-analyses. However, although prophylaxis reduces the risk of VTE for hospital inpatients, it also incurs costs and potentially increases the risk of bleeding. As such, international guidelines recommend a process of individualised VTE risk assessment at the point of hospital admission. Several risk assessment models (RAMs) have been developed to aid this process. The accuracy and cost-effectiveness of these models are uncertain.

Further prospective studies in this area are challenging due to national guidance, contract standards and high rates of routine prescribing (> 70%). We sought to assess the clinical and cost-effectiveness of VTE RAMs through secondary research methods, by conducting a systematic review of RAM accuracy and subsequent decision-analytic modelling. In addition, we sought to evaluate the accuracy of routine data sources to identify core VTE and bleeding outcomes and estimate key clinical parameters for any future implementation study.

Objectives

The prespecified and combined project objectives were as follows:

1. Update existing systematic reviews to identify VTE RAMs for hospital inpatients and determine their comparative accuracy for predicting the risk of VTE.
2. Undertake decision-analytic modelling to determine the cost-effectiveness of pharmacological prophylaxis guided by a RAM, compared to prophylaxis for all and prophylaxis for none.
3. Use the decision-analytic model to identify key areas of uncertainty and determine the value of gathering additional information to reduce uncertainty.
4. Pilot the use and evaluate the accuracy of efficient methods to measure core clinical VTE and bleeding outcomes.
5. Estimate key parameters for planning a future implementation study.

Methods

Workstream 1 used a systematic review and economic analysis to address objectives 1, 2 and 3. We extended and updated overlapping systematic reviews of available RAMs, performed quality assessment of relevant studies and synthesised performance measures (e.g. sensitivity, specificity and concordance (*C*) statistics) to evaluate the prognostic accuracy of individual RAMs. We subsequently used this information to inform decision-analytic modelling. The target population for the conceptual model was hospital inpatients, including medical, surgical and trauma patients but excluding critical care patients, children and women admitted to hospital for pregnancy-related reasons. Patients at increased risk of bleeding were assumed not to receive pharmacological prophylaxis under any strategy and were

excluded from the model. We compared strategies of using no pharmacological prophylaxis, pharmacological prophylaxis for all and pharmacological prophylaxis given in accordance with validated RAMs. The use of mechanical prophylaxis was considered out of scope for the modelling. We used a lifetime horizon and reported primary outcomes of costs and quality-adjusted life-years (QALYs). Multiple scenario and sensitivity analyses were conducted by subgroup.

Workstream two used primary research to address objectives four and five. We conducted a multicentre observational cohort study across four hospitals to compare prespecified methods of efficient data collection to formal case note review. We identified a target population hospitalised during 2019 and extracted data from prospectively completed VTE risk assessments, when available. Research assistants undertook further retrospective case note review for each patient episode. We used electronic health records to evaluate additional risk characteristics and record all relevant clinical outcomes, including the subsequent diagnosis of HAT, major bleeding and clinically relevant non-major bleeding events. We then collated multiple routine data sources for each patient episode to determine the accuracy of these methods in identifying relevant clinical outcomes, compared to a gold standard of case note review. The primary outcome measures for workstream two were contingency tables with sensitivity, specificity and predictive values. Feasibility criteria for any future study using efficient data methods were set a priori. We also estimated the potential variation in prescribing recommendations using multiple validated RAMs and estimated key parameters for any future implementation study.

The Venous ThromboEmbolism Assessment Methods study received a favourable opinion from the Proportionate Review Sub-committee of the London – West London & Gene Therapy Advisory Committee (GTAC) Research Ethics Committee and approval from the Health Research Authority (HRA) and Care Research Wales (HCRW) on 18 September 2019 (reference 19/LO/1303, IRAS project ID 262220).

Results

Workstream 1

Our updated systematic review included 51 studies, comprising 24 unique validated RAMs. The vast majority of studies evaluated VTE RAMs in medical (n = 21), surgical (n = 15) or mixed (n = 4) cohorts of hospital inpatients. The most widely evaluated models were the Caprini RAM (22 studies), the Padua prediction score (16 studies), the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) models (8 studies), the Geneva Risk Score (4 studies) and the Kucher Score (4 studies). All studies had a high or unclear risk of bias, with the main issues related to patient selection, outcome and analysis factors. *C*-statistics varied markedly between these studies and between models, with no RAM performing obviously better than other models. Similarly, estimates for sensitivity and specificity were highly variable.

In the decision analytic modelling, we estimate that in medical inpatients, prophylaxis reduces serious adverse outcomes [fatal PEs, fatal bleeding and non-fatal intracranial haemorrhage (ICH)] from 53 per 10,000 to 42 per 10,000, with a reduction in symptomatic DVTs and non-fatal PEs that is higher than the increase in other bleeds. In the long-term outcomes at 5 years, there is a large reduction in the number of patients experiencing post-thrombotic syndrome (PTS) following prophylaxis from 787 per 10,000 to 385 per 10,000, but minimal difference in overall survival. Modelling showed that thromboprophylaxis for all has a high probability (> 99%) of being the most cost-effective strategy (£20,000 per QALY threshold) based on the performance of existing RAMs in cohorts of medical inpatients. This finding was generally robust under the scenario and sensitivity analyses with one exception; targeting thromboprophylaxis using a Padua score ≥ 3 (84% of cohort) had a 76.6% probability of being the most cost-effective strategy when assuming higher RAM performance (sensitivity 99.9%; specificity 23.7%).

The overall expected value of perfect information (EVPI) associated with all parameters included in the probabilistic sensitivity analysis (PSA) when valuing a QALY at £20,000 was £0.06 per patient per year due to the high probability that prophylaxis for all is the optimal strategy. However, the EVPI would be £2.42 per person per year if a more accurate RAM could be developed for medical inpatients.

In surgical inpatients, the risk of a serious adverse outcome (as above) is low at 7 per 10,000 but it is increased slightly by prophylaxis to 11 per 10,000 due to the additional risk of fatal bleeding or non-fatal ICH. Although the risk of any symptomatic VTE is reduced form 140 per 10,000 to 41 per 10,000, the risk of any major bleeding is increased from 125 per 10,000 to 370 per 10,000. Prophylaxis still reduces the risk of PTS in surgical inpatients, from 367 per 10,000 to 107 per 10,000, but PTS is less common in the surgical cohort than in the medical cohort. Modelling showed that giving prophylaxis to all surgical inpatients has the highest probability of being cost-effective at £20,000 per QALY, with a 70% likelihood of being optimal, but there is also a 17% likelihood that using a Pannucci score of ≥ 3 would be optimal and a 9% likelihood that using a Pannucci score of ≥ 1 would be optimal. These findings were sensitive to some uncertainties explored in the scenario and sensitivity analyses. In particular, prophylaxis for all may no longer be the optimal strategy for surgical inpatients when the risk of PTS is lower, when using an extended duration of prophylaxis or where a RAM is assumed to have a very high sensitivity.

The overall EVPI associated with all parameters included in the PSA when valuing a QALY at £20,000 was £16.35 per person. This does not include the uncertainty of considering which RAM to use as the EVPI and does not include any uncertainty not captured in the PSA, such as uncertainty around the model assumptions or the choice of data sources, or uncertainty around the estimates of sensitivity and specificity. In the analysis of parameter EVPI [expected value of partial perfect information (EVPPI)], the relative risk of VTE for patients having thromboprophylaxis compared to patients not having thromboprophylaxis was the parameter with the largest EVPPI.

In specific surgical populations requiring longer durations of prophylaxis, we found that pharmacological prophylaxis for all eligible patients remained optimal in those having elective knee replacement. Offering prophylaxis at a Pannucci score of ≥ 3 (sensitivity of 84% and specificity of 49%) was optimal when prescribing 28 days of low-molecular-weight heparin (LMWH) to patients having elective hip replacement. These conclusions were sensitive to prophylaxis strategy; using direct oral anticoagulants (DOACs) rather than LMWH resulted in prophylaxis for all as the optimal strategy for both hip and knee patients.

Workstream 2

The observational cohort study was conducted across all four sites, enrolling 2115 patient hospitalisation episodes, with 2008 eligible for analysis. Medical and surgical cases were evenly balanced, but with more emergency (73.7%) than elective (25.8%) admissions. The sensitivity of routine coding data for detection of HAT and major bleeding events was 62% [95% confidence interval (CI) 54 to 69] and 38% (95% CI 27 to 50), respectively. Local VTE data sets performed better, with sensitivity of 81% (95% CI 75 to 87). The specificity of routine coding data for VTE and bleeding was 98% (95% CI 97 to 99) and 95% (95% CI 94 to 96), respectively, and the specificity of local VTE data sets was 100% (95% CI 99 to 100). We were unable to demonstrate overall feasibility of using efficient outcome measures and did not meet several prespecified criteria.

In a smaller subgroup of patients with prospectively collected data, we evaluated potential variation in pharmacological prophylaxis using different RAMs. We identified 543 hospital episodes with VTE risk assessment performed during 2019, with 254 episodes suitable for inclusion, data extraction and comparative analysis. Overall recommendations for pharmacological prophylaxis varied substantially between seven RAMs, ranging from 13% of admitted patients for the IMPROVE associative score (95% CI 9.4 to 17.7) to 91% (95% CI 86.3 to 93.6) for the Department of Health (now Department of Health and Social Care) VTE risk assessment tool. The latter tool resulted in an absolute increase of 28% for prophylaxis recommendation, compared to other RAMs.

Within this multicentre cohort of hospitalised inpatients, the HAT event rate was 1.6% (95% CI 1.0 to 2.2) and the major bleeding event rate was 2.5% (95% CI 1.8 to 3.2).

Conclusions

We updated prior systematic reviews to conclude that that the available evidence has significant methodological limitations and demonstrates current RAMs to have weak predictive accuracy.

Decision-analytic modelling showed that the balance of VTE or major bleeding risks, combined with the RAM performance in medical cohorts, means that thromboprophylaxis for all is the optimal strategy within our model for medical inpatients. These findings were robust to multiple scenarios and sensitivity analyses. The optimal strategy for surgical inpatients is to offer thromboprophylaxis to all. However, the scenario analyses for surgical inpatients found that the optimal strategy was sensitive to many of the individual model inputs and assumptions tested. In addition, the optimal strategy for surgical patients receiving extended duration thromboprophylaxis appeared dependent on duration of therapy and prophylaxis strategy.

The findings from our cohort study suggest that efficient methods for identifying VTE or major bleeding events during hospital admission or within 90 days of discharge, are not sufficiently sensitive for use in a large data-enabled study. We did not reach several predefined feasibility metrics. We also found limitations in the ability of efficient methods to identify individual risk variables and facilitate RAM comparison in future work. The majority of our sites did not collect contemporaneous data on risk assessment in a digital, or easily accessible format.

Implications for policy-makers

If, despite drug costs and potential harms, pharmacological prophylaxis for all is the most cost-effective strategy, use of unvalidated RAMs may be suboptimal. Based on our findings, it may be preferable for policy-makers to consider evaluating a new paradigm of 'opt-out' VTE prevention, in which all eligible patients are routinely offered pharmacological prophylaxis on hospital admission without complex risk assessment. In this circumstance, patients who are ineligible for pharmacological prophylaxis due to high bleeding risk, specific contraindications or personal choice could opt out, but still utilise evidence-based mechanical thromboprophylaxis strategies.

The findings from our cohort study have implications for funders looking to support further work in this area. These data suggest large studies entirely reliant on routine data collection methods for complex time-dependent outcome measures (such as HAT or major bleeding) are likely to be inaccurate.

Recommendations for future research

Further research should evaluate the following themes in this area of clinical care:

1. Evaluation of routine pharmacological prophylaxis for all eligible medical and surgical patients on hospital admission, compared to current practice of risk assessment using a RAM. Such work would need to be conducted at scale and could not rely on efficient methods for outcome measurement in isolation.
2. Development and validation of RAMs to identify individuals receiving prophylaxis at very low risk of blood clots, who could therefore potentially discontinue pharmacological prophylaxis early during hospital stay.

3. Our analysis was inevitably limited in scope and did not examine the use of RAMs to identify accurate prediction of bleeding risk, the use of mechanical prophylaxis in medical patients with increased bleeding risk (or contraindications to pharmacological prophylaxis) or patients at risk of thromboprophylaxis failure. These issues could be priorities for future research.

Study registration

This study is registered as Research Registry 5216, PROSPERO CRD42020165778.

Funding

This award was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme (NIHR award ref: NIHR127454) and is published in full in *Health Technology Assessment*; Vol. 28, No. 20. See the NIHR Funding and Awards website for further award information.

Health Technology Assessment

ISSN 2046-4924 (Online)

Impact factor: 3.6

A list of Journals Library editors can be found on the NIHR Journals Library website

Launched in 1997, *Health Technology Assessment* (HTA) has an impact factor of 3.6 and is ranked 32nd (out of 105 titles) in the 'Health Care Sciences & Services' category of the Clarivate 2022 Journal Citation Reports (Science Edition). It is also indexed by MEDLINE, CINAHL (EBSCO Information Services, Ipswich, MA, USA), EMBASE (Elsevier, Amsterdam, the Netherlands), NCBI Bookshelf, DOAJ, Europe PMC, the Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ, USA), INAHTA, the British Nursing Index (ProQuest LLC, Ann Arbor, MI, USA), Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and the Science Citation Index Expanded™ (Clarivate™, Philadelphia, PA, USA).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta.

Criteria for inclusion in the *Health Technology Assessment* journal
Manuscripts are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This manuscript

The research reported in this issue of the journal was funded by the HTA programme as award number NIHR127454. The contractual start date was in July 2019. The draft report began editorial review in January 2022 and was accepted for publication in September 2022. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this manuscript.

This manuscript presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).