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Decision-analysis modelling of effectiveness and cost-effectiveness of pharmacological thromboprophylaxis for surgical inpatients, using variable risk assessment models or other strategies

Short running title: Thromboprophylaxis for surgical patients

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Essentials

- Pharmacological prophylaxis to prevent venous thromboembolism provides an overall health gain
- Health gains are mainly from reduced post-thrombotic complications and not fatal clots prevented
- A risk-based approach is less cost-effective than 'opt-out' prophylaxis for surgical inpatients
- To be cost-effective a risk assessment model would need to have very high sensitivity

Summary

Background: Surgical inpatients are at risk of venous thromboembolism (VTE) which can be life-threatening or result in chronic complications. Thromboprophylaxis reduces VTE risk but incurs costs and may increase bleeding risk. Risk assessment models (RAMs) are currently used to target thromboprophylaxis at high-risk patients.

Objective: To determine the balance of cost, risk, and benefit for different thromboprophylaxis strategies in adult surgical inpatients, excluding major orthopaedic surgery, critical care and pregnant women.

Methods: Decision analytic modelling to estimate the following outcomes for alternative thromboprophylaxis strategies: thromboprophylaxis usage; VTE incidence and treatment; major bleeding; chronic thromboembolic complications; and overall survival. Strategies compared were: no thromboprophylaxis; thromboprophylaxis for all; and thromboprophylaxis given according to RAMs (Caprini and Pannucci). Thromboprophylaxis is assumed to be given for the duration of hospitalisation. The model evaluates life-time costs and quality-adjusted life-years (QALYs) within England's health and social care services.

Results: Thromboprophylaxis for all surgical inpatients had a 70% probability of being the most cost-effective strategy (at a £20,000 per QALY threshold). RAM-based prophylaxis would be the most cost-effective strategy if a RAM with higher sensitivity (99.9%) were available for surgical inpatients. QALY gains were mainly due to reduced post-thrombotic complications. The optimal strategy was sensitive to several other factors including: risk of VTE, bleeding and post thrombotic syndrome; duration of prophylaxis and patient age.

Conclusions: Thromboprophylaxis for all eligible surgical inpatients appeared to be the most cost-effective strategy. Default recommendations for pharmacological thromboprophylaxis, with the potential to 'opt-out', may be superior to a complex risk-based 'opt-in' approach.

Keywords: Anticoagulants; cost-benefit analysis; surgical procedures, operative; risk assessment; venous thromboembolism

Introduction

Surgical inpatients are at increased risk of hospital-associated venous thromboembolism (VTE) during admission and for 90 days post discharge, such as lower limb deep vein thrombosis (DVT) and pulmonary embolism (PE). Whilst most people make a full recovery following VTE, it can be fatal, prolong hospital recovery and increase health resource utilisation. In the long-term VTE can lead to post-thrombotic syndrome (PTS) or chronic thromboembolic pulmonary hypertension (CTEPH).

Pharmacological thromboprophylaxis can be used to prevent VTE in surgical inpatients, but may increase bleeding risk.[1] Complications can include surgical site bleeding, fatal bleeds or non-fatal intracranial haemorrhage (ICH). The widespread use of thromboprophylaxis in surgical inpatients incurs substantial health care costs. It is therefore important to assess the overall balance of costs, benefits and potential harms of thromboprophylaxis. Decision analytic modelling can be used to estimate both the overall clinical effectiveness of thromboprophylaxis in terms of quality-adjusted life years (QALYs) gained (thus weighing the benefits of treatment against the risks), and the cost-effectiveness of thromboprophylaxis in terms of the additional costs required to gain additional QALYs.

Targeting pharmacological thromboprophylaxis at those surgical inpatients with the highest risk of VTE could maximise the benefits in terms of avoiding VTE outcomes, whilst minimising costs and potential harms. Several risk assessment models (RAMs) such as Caprini and Pannucci have been derived and validated in cohorts of surgical inpatients to provide a numerical score that can be used to determine individual patient risk.[2, 3] Certain RAMs originally derived in medical populations (Padua prediction score) have also been validated within mixed cohorts of surgical and medical inpatients. Whether the use of a RAM is superior to clinical gestalt, or which RAM is optimal in the surgical inpatient setting, is currently unclear. Deciding the optimal RAM score at which to offer thromboprophylaxis will necessarily involve a trade-off between sensitivity and specificity, with a corresponding trade-off between preventable VTE and the exposure to increased bleeding risks. In addition, clinical time is needed to administer any RAM and inter-rater reliability is variable.[4, 5] The cost-effectiveness of using alternative RAMs to target thromboprophylaxis has not previously been examined for surgical inpatients. The aim of this analysis was to assess the overall effectiveness and cost-effectiveness of alternative pharmacological thromboprophylaxis strategies in eligible surgical inpatients (i.e. those without contraindications or high bleeding risk). The strategies compared included thromboprophylaxis for all, thromboprophylaxis for none, and thromboprophylaxis targeted at higher risk patients only, using RAMs validated in a surgical population. The analysis assesses whether it is cost-effective to add pharmacological thromboprophylaxis to other preventative

measures, such as early mobilisation or mechanical prophylaxis, rather than assessing pharmacological thromboprophylaxis as an alternative to other measures.

Methods

We developed a decision-analytic model to simulate the management of a cohort of surgical inpatients according to the different thromboprophylaxis strategies and to estimate the short and long-term consequences of each strategy. The model estimates the average QALYs accrued across the cohort and the average health and social care costs incurred to estimate the overall cost-effectiveness (cost-per-QALY gained) of each strategy compared to the next most effective strategy. The costs and QALYs are estimated over the patient's whole lifetime, with costs and benefits incurred in future years being discounted at 3.5% per annum, as per guidance by the UK's National Institute for Health and Care Excellence (NICE).[6]

Model structure

The model structure was developed in collaboration with clinical experts. Existing published models were presented to clinical experts who were asked to provide guidance on the selection of model outcomes based on clinical importance and the appropriateness of data sources and model assumptions.[7-9] The chosen approach drew mainly on previous work to evaluate thromboprophylaxis during lower limb immobilisation.[9] A six-month decision tree model (see Supporting Information Figure 1) was used to estimate the number of patients receiving thromboprophylaxis for each strategy and numbers experiencing symptomatic DVT, asymptomatic DVT, fatal PE, non-fatal PE, and major bleeding. In accordance with national guidance in England, symptomatic DVTs and non-fatal PEs were assumed to result in three months of anticoagulant treatment.[10] A six-month time frame was considered sufficient to capture both the period of risk for hospital-acquired VTE (90 days post admission) and the period of treatment following VTE (three months), during which time patients are also at risk of major bleeding. Diagnosis of PTS and CTEPH was assumed not to occur until the end of the six-month decision-tree phase of the model as it is difficult to distinguish PTS and CTEPH from acute symptoms during the first three months after VTE. Major bleeds were those meeting the International Society on Thrombosis and Haemostasis (ISTH) definition,[11] and were divided into fatal bleeds, non-fatal intracranial haemorrhages (ICHs) and other major bleeds. The latter included any complications related to surgical site bleeding that required patients to return to theatre or that resulted in prolonged hospitalisation. Patients having major bleeds during either thromboprophylaxis or VTE treatment with anticoagulants are assumed to stop their anticoagulant medication at the time of the bleed. The likelihood of VTE and the likelihood

of bleeding during treatment for VTE are assumed to be independent of whether the patient had major bleeding during hospital admission.

A state-transition model (see Supporting Information Figure 2) was then used to extrapolate life-time outcomes including overall survival and ongoing morbidity related to either ICH or VTE. Recurrent VTEs do not appear within the state-transition model as these were not expected to differ according to whether or not patients received thromboprophylaxis during hospital admission. The risk of PTS following VTE is dependent on whether the DVT is symptomatic and treated or asymptomatic and untreated, and also its location (proximal or distal). Patients experiencing CTEPH following PE are divided into medical and surgical management to allow for differential costs and survival between these groups. There is also a post-ICH state to capture ongoing morbidity following ICH. Further adverse outcomes were not modelled in the post-ICH group as lifetime costs and QALYs are assumed to be predominantly determined by morbidity related to ICH. The state-transition model has one six-month cycle to extrapolate the outcomes of the decision tree up to one year with all-cause mortality during the first year applied at six months. Thereafter, the cycle length is one year, and the health state occupancy is half-cycle corrected such that all transitions between states, including mortality, are assumed to occur mid-cycle.

Population

The population was hospitalised surgical inpatients excluding critical care patients, children (under the age of 18 years), and pregnant women. We also excluded patients having elective hip and knee replacement and hip fracture repair from this analysis. These patients are recognised as being at higher risk of VTE and consequently provided with extended spectrum pharmacological thromboprophylaxis (using both LMWH and direct oral anticoagulant [DOAC] agents) as standard in the UK and other countries.[12, 13] We have considered patients having major orthopaedic surgery in a separate analysis reported elsewhere.[14] Patients identified to be at high risk of bleeding, or in whom pharmacological thromboprophylaxis is contraindicated, are considered ineligible for thromboprophylaxis and are therefore excluded from the model under all strategies. One of the more established RAMs (Caprini) has been validated in a cohort covering both elective and emergency surgical patients and includes questions that identify specific groups requiring emergency surgery. Therefore, rather than model separate decision-making processes in elective and emergency surgical patients, we decided to model the surgical population as a whole and to treat the reason for surgery as a risk factor. Trauma patients requiring surgical management fall within the scope of the model, provided they do not require critical care. Although some RAMs exist for use specifically in trauma patients,[15] we have not modelled the use of these RAMs in trauma patients as a specific

subpopulation, as these RAMs have been typically developed and validated in countries where trauma patients are treated in a critical care environment. The population characteristics at baseline (age 54 years and 46% male) were based on an analysis of routine hospital admission data from the UK.[16]

Risk assessment models

The sensitivity and specificity of RAMs for predicting VTE, which determines the number receiving thromboprophylaxis, were derived from a systematic review of the clinical literature.[15] Data from external validation studies in cohorts of surgical in patients were identified for the Caprini and Pannucci RAMs and their performance data are summarised in Figure 1.[2, 3] Performance data are also shown in Figure 1 for the Padua RAM, which was developed for use in medical inpatients but has been validated in a mixed cohort of surgical and medical patients,[17] and for this reason is considered in a scenario analysis. The Department of Health VTE risk assessment tool is commonly used for VTE risk assessment of hospitalised patients in the UK, but no data were available on the performance of this tool. As such, the cost-effectiveness of using this specific RAM could not be modelled.[10, 15]

Thromboprophylaxis and treatment of VTE

Thromboprophylaxis was assumed to be with subcutaneous low molecular weight heparin (LMWH) at the dose licensed for surgical inpatients for the duration of the admission, which is typically five days.[18] This is in line with national UK guidance, licensing recommendations and current clinical practice.[10, 19] We did not incorporate the use of weight-adjusted dosing for LMWH in the analysis, but we do not expect this additional complexity in dosing would significantly alter the results of the analysis because the costs of a single dose of LMWH are essentially identical across weight bands in the UK.[20] It is assumed that each administration requires 2.5 minutes of nursing time and the lowest cost preparation is prescribed. Although national guidance has recommended that LMWH is given for a minimum of seven days,[10] a survey of 25 UK exemplar centres suggest that the majority of hospitals give LMWH for the duration of hospital admission only.[21] However, a scenario analysis was conducted exploring the impact of assuming a further two days of post-discharge administration to achieve a minimum of seven days thromboprophylaxis. As national guidance recommends extending thromboprophylaxis to 28 days in patients having major cancer surgery in the abdomen, this is also explored in scenario analysis.[10] Anticoagulant treatment for subsequent VTEs was assumed to be either DOACs or phased anticoagulation (LMWH followed by warfarin); a 40:60 split was assumed based on registry data,[22] with higher use of DOACs explored in a scenario analysis given contemporaneous international data suggesting wider use with increasing familiarity.[23]

The effectiveness of prophylactic LMWH was taken from a systematic review and network meta-analysis conducted by Wade et al., which reported the odds ratio (OR) for LMWH versus no LMWH (OR=0.26, 95% Confidence Interval [CI] 0.09 to 0.87) for the outcome of hospital acquired VTE in surgical patients.[24] Subsequent research published after completion of our work confirms this estimate of effectiveness; Marcucci et al report the OR for LMWH to range between 0.19 and 0.33 (depending on dose) for the outcome of symptomatic VTE compared to no active treatment, within a cohort of 45,445 patients undergoing non-cardiac surgery.[1] The relative risk (RR) of major bleeding for LMWH compared to either placebo or mechanical prophylaxis was based on a published meta-analysis of studies in patients having abdominal surgery (RR=2.98, 95%CI 0.88 to 14.80).[10]

Epidemiological parameters

Data on the absolute risks of fatal PE, non-fatal PE, DVT, fatal bleeding, non-fatal major bleeding (including ICH), PTS and CTEPH were obtained from the literature.[3, 8, 10, 25-36] Patients were assumed to have an increased risk of mortality compared to the general population in the year after hospital admission, in the first six years following ICH and following CTEPH.[37-42] The clinical parameters incorporated in the model are summarised in Table 1, with further details provided in the Supporting Information (Text 1 and Table 1).

Resource use and costs

Resource use and unit costs were based on standard National Health Service (NHS) sources and published estimates.[20, 43-47] Costs were assessed from an NHS and Social Services in England perspective and are reported in pound sterling based on 2020 prices. Administration of a RAM by a hospital physician was assumed to take five minutes. It is assumed that the duration of discharge delay caused by a hospitalised patient experiencing VTE would be similar to the duration of admission for patients having VTE after discharge. Costs applied in the model are summarised in Table 2 with additional information on resource use provided in the Supporting Information (Text 1 and Tables 2 to 4).

Health-related quality of life

In order to estimate QALYs it is necessary to quantify an individual's health utility, which is a measure of health-related quality of life (HRQoL) on a scale of zero to one, where one represents full health and zero represents a state equivalent to death. Utility values estimated from the general population were applied to those not having any adverse clinical outcomes.[48] Reductions in utility were applied up to six months for those having DVT, for one month after other major bleeds (non-ICH) and for the duration of thromboprophylaxis or anticoagulant treatment. Life-long utility decrements were applied

following ICH, PTS and CTEPH. Utility data applied in the model are summarised in Table 2 with further details in Supporting Information Tables 5 to 7.[49-55]

Probabilistic sensitivity analysis

We assigned probability distributions to reflect the uncertainty around each parameter input and used Monte-Carlo simulation to propagate this uncertainty through the model to quantify the decision uncertainty based on 10,000 sets of parameter samples. We used sensitivity and specificity estimates from a single RAM (Pannucci) in the probabilistic sensitivity analysis (PSA). Details of the distributions assumed for each parameter included in the PSA can be found in the Supporting Information (Tables 1 and 7).

Scenario analyses

We conducted a scenario analysis using performance estimates from the Padua RAM,[17] to explore whether the use of RAMs would be cost-effective, if a more accurate RAM could be identified and what the optimal trade-off between sensitivity and specificity would be. We explored whether the optimal strategy differed when extending the duration of thromboprophylaxis to either seven or 28 days. The disutility for PTS after DVT was not stratified by PTS severity so we conducted a sensitivity analysis to determine whether the conclusions differed when assuming a smaller disutility for PTS (2% versus 10%). This alternative value was estimated by combining registry data on the distribution of PTS severity with utility estimates stratified by PTS severity.[27, 56] In addition, we conducted a sensitivity analysis to see if the conclusions differed when assuming a zero incidence of PTS in patients having asymptomatic distal DVT as previous modelling has identified this as a potentially important outcome with uncertain incidence.[9] Sensitivity analyses were also conducted to explore the impact of assuming a higher or lower average risk for VTE and bleeding, assuming all VTEs are treated with DOACs, and to explore the impact of alternative patient characteristics; examining starting ages of 20 and 80 years and assuming no increased risk of mortality in the year following surgery to reflect lower risk patient cohorts.

Role of the funding source

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Patient and public involvement

The project team included two patient and public involvement (PPI) members who contributed to the study design and ensured that patient and public values were reflected in the decision analytic modelling. Based on their advice we included disutility associated with LMWH injections in the analysis as this was considered important to patients. In addition, the modelling methods and results were presented to a broader PPI group to ensure that the interpretation of the results was comprehensible and relevant to patients and the public.

Results

Short and long-term clinical outcomes per 10,000 patients are presented in Table 3 for the strategies of thromboprophylaxis for all and thromboprophylaxis for none. The risk of serious adverse outcomes (fatal PE, fatal bleeds and non-fatal ICHs) is low in surgical inpatients without thromboprophylaxis (7 per 10,000), but it is increased slightly by thromboprophylaxis (11 per 10,000) due to the increased risk of fatal bleeds and non-fatal ICHs. However, all-cause mortality at five years is similar (352 per 10,000 versus 353 per 10,000). Symptomatic VTE is reduced from 140 per 10,000 to 41 per 10,000, but thromboprophylaxis for all also results in an increase in other major bleeds (238 additional bleeds per 10,000 patients, including 36 additional major surgical site bleeds). RAM-based thromboprophylaxis strategies using either the Caprini or Pannucci RAMs provide a different set of clinical outcomes at each threshold representing different trade-offs points between the benefits of VTE prevention and the increased risks of bleeding.

Figure 2 shows the incremental costs and QALYs compared to no thromboprophylaxis for the Pannucci and Caprini RAMs and the strategy of thromboprophylaxis for all from the base-case deterministic analysis.[2, 3] The incremental costs and QALYs both increase as lower thresholds for the Caprini and Pannucci RAMs are considered, resulting in wider use of thromboprophylaxis. However, thromboprophylaxis for all appears to be more cost-effective than using either of these RAMs when applying the incremental cost-effectiveness ratio (ICER) threshold of £20,000 per QALY (typically applied in the UK).[6] This is partly due to the fact that the costs of administering a RAM are avoided when using a thromboprophylaxis for all strategy. Results are also shown in Figure 2 for a scenario analysis exploring higher estimates of RAM performance, using alternative performance estimates for the Padua RAM.[17] Offering thromboprophylaxis at a Padua score of ≥3 appears to 'dominate' thromboprophylaxis for all in this scenario because it provides greater QALY gains at lower cost. This is because the high RAM performance in this particular study (99.9% sensitivity; 23.7% specificity at a

Padua score of ≥3) means that offering thromboprophylaxis to all would result in additional patients being exposed to bleeding risks, with no additional VTEs prevented.

Base-case results from the PSA are presented in Table 4 for the Pannucci RAM. Thromboprophylaxis for all is estimated to result in 0.035 additional QALYs (95% credible interval [CrI] 0.002 to 0.080) whilst generating additional costs of £48 (95% CrI £-96 to £254). Thromboprophylaxis for all dominates no thromboprophylaxis in 24% of PSA samples and there is a 70% probability that thromboprophylaxis for all is the optimal strategy (when valuing a QALY at 20,000) compared to RAM-based thromboprophylaxis using the Pannucci RAM or thromboprophylaxis for none. Table 4 also presents the results of the PSA for the scenario analysis assuming higher RAM performance using data for the Padua RAM. In this scenario offering thromboprophylaxis at a Padua score of ≥ 3 has a 54% probability of being the most cost-effective strategy when valuing a QALY at £20,000 and a 63% probability when valuing a QALY at £30,000; whilst offering thromboprophylaxis for all had a low probability of being the optimal strategy (<10%) at either threshold.

In the sensitivity analyses, thromboprophylaxis for those with a Pannucci score ≥3 was the optimal strategy (assuming a QALY is valued at £20,000) when applying a lower utility decrement for PTS; halving the risk of VTE; doubling the risk of major bleeding; extending the use of prophylaxis to 28 days; or increasing the starting age to 80 . Thromboprophylaxis for those with a Pannucci score ≥1 was the optimal strategy when assuming no PTS following asymptomatic distal DVT; assuming that LMWH is administered for seven days including two days post-discharge; assuming length of stay increases to 16 days; or assuming no cost for administering a RAM. The optimal strategy remained thromboprophylaxis for all in the scenarios assuming a starting age of 20 years; no increased risk of mortality in the year following surgery or that all VTE events would be treated with DOACs.

Discussion

Offering pharmacological thromboprophylaxis to all eligible surgical inpatients appears to be more cost-effective than using RAMs to target thromboprophylaxis at higher risk patients, due to the weak predictive performance of existing RAMs validated in cohorts of surgical inpatients. However, there is uncertainty regarding the optimal thromboprophylaxis strategy, as using RAM-based prophylaxis became more cost-effective than thromboprophylaxis for all when exploring plausible alternative inputs in sensitivity analyses. Furthermore, a scenario analysis identified that RAM-based prophylaxis

would be the most cost-effective strategy if a RAM with higher sensitivity were available for surgical inpatients.

A cost-effectiveness analysis from a Chinese Health System perspective found that seven days of thromboprophylaxis was cost-effective in non-orthopaedic surgical patients with a Caprini score of 3 to 6 and was cost saving in patients with higher scores.[57] However, it is difficult to make a direct comparison with our analysis because the authors included patients with a Caprini score ≥3 rather than including all surgical patients.

A key strength of this de novo economic analysis is the synthesis of evidence on both benefits and harms to explore the trade-off between preventing VTE and the adverse events profile associated with thromboprophylaxis. The results suggest that the benefits of thromboprophylaxis, in terms of reducing VTE, outweigh the harms of increased bleeding in the surgical inpatient population, as all strategies resulted in QALY gains compared to no thromboprophylaxis.

In the decision analytic model, much of the benefit of thromboprophylaxis was realised in the reduction of long-term complications rather than in the reduction of short-term risks such as fatal PE. The short-term risks were largely offset by the increased risk of fatal bleeding and non-fatal ICH. This is in-line with the findings of a recent systematic review and meta-analysis which concluded that the causal effect of venous thromboembolism prevention on mortality was null.[58]

The scenario analyses suggest that prevention of PTS is an important driver of cost-effectiveness, as RAM-based prophylaxis became more cost-effective than thromboprophylaxis for all when assuming no risk of PTS following asymptomatic distal DVT or assuming that PTS has a smaller impact on health-related quality of life. It is also important to note that a substantial proportion of the PTS cases predicted by the model (40%) occur after asymptomatic distal DVT, but the incidence of PTS after undiagnosed untreated asymptomatic distal DVT is uncertain. A long-term follow-up study of patients having minor orthopaedic surgery found an 8% cumulative incidence of PTS over 3 years following diagnosis of asymptomatic DVT (of which 91% were distal) by screening 3 to 6 weeks after surgery.[59] We applied a PTS risk of 15% for patients following asymptomatic distal DVT in the model. This higher figure was considered reasonable, given that all patients in the study with screening detected DVT were treated with anticoagulants for 3 to 6 months, and those having asymptomatic distal DVT in clinical practice would not be identified and offered anticoagulant treatment. However, if clinicians and policymakers are not convinced that using thromboprophylaxis will reduce the risk of subsequent PTS, they may place more weight on the fact that our overall findings were sensitive to this assumption. Furthermore, any shared decision-making should involve informing patients that the

overall benefit of thromboprophylaxis appears to be based on preventing long-term complications rather than acute events.

There are several limitations to our analysis. Outside of clinical trials, there is uncertainty regarding the incidence of VTE and major bleeding in patients who do not receive thromboprophylaxis. To address this, we conducted sensitivity analyses and identified that a RAM-based thromboprophylaxis strategy would become more cost-effective than thromboprophylaxis for all patients if the VTE risk was halved or the major bleeding risk was doubled. Our economic analysis assumed patients had no high risks for bleeding and our findings therefore do not apply to individual patients at high risk of bleeding, such as severe active bleeding at presentation. We did not factor in concomitant use of single or dual antiplatelet therapy, so we do not know whether use of these medications has a bearing on our findings. Furthermore, the analysis is not expected to be applicable to highly specialised patient groups, such as neurosurgical patients, where a decision whether to use prophylaxis is often based on an individualised and expert consensus approach.

There are limited data on RAM performance in surgical inpatients, with only two RAMs being identified as having been validated in a surgical cohort (Caprini and Pannucci). A scenario analysis was conducted exploring alternative RAM performance estimates using data from the Padua RAM in a mixed cohort of surgical and medical inpatients. In this scenario analysis, the optimal strategy was to use a RAM rather than to offer thromboprophylaxis for all. This is because Elias et al. reported a sensitivity of 99.9% and a specificity of 23.7% for a Padua score of ≥3 resulting in 80% of patients receiving thromboprophylaxis. We do not conclude that the Padua RAM should be adopted in surgical inpatients because it is unknown whether the Padua RAM would have equivalent performance in a cohort of surgical patients. However, these findings suggest that a future RAM validated for use in surgical patients would need to have high sensitivity to be more cost-effective than a strategy of thromboprophylaxis for all and therefore would still likely result in a very high proportion of patients receiving thromboprophylaxis.

One of the key issues with the studies of RAM performance is that the routine use of thromboprophylaxis within observational cohorts may lead to the performance of RAMs being underestimated, as the VTE events that would have occurred in higher risk patients are prevented by thromboprophylaxis. The Elias et al. RAM performance estimates for the Padua RAM were taken from the subset of patients not receiving thromboprophylaxis. Equivalent data on RAM performance in a subset without prophylaxis were not available for the Pannucci or Caprini RAMs.[2, 3] This may partly explain the higher estimate of sensitivity, although Elias et al. report that the performance was similar in the subset of patients receiving thromboprophylaxis.[17] In the cohort used to validate the Pannucci

RAM, two-thirds of patients had received prophylaxis.[3] This illustrates the difficulty of conducting future studies which are likely to involve cohorts with widespread usage of thromboprophylaxis, making estimation of RAM performance problematic. Future research could focus on randomised studies of pharmacological thromboprophylaxis versus no pharmacological thromboprophylaxis in patients identified as low-risk for VTE during hospital admission.

To conclude, we found that thromboprophylaxis for all eligible surgical inpatients is expected to generate additional health benefits for an additional cost that is likely to be considered cost-effective within the NHS in England. In addition, the risk of severe adverse outcomes, such as fatal PEs is low with much of the health benefits of thromboprophylaxis being accrued from avoiding long-term chronic complications following VTE. Scenario analyses suggest that for any RAM to be worth using, it would need to achieve a very high sensitivity. Based on these findings, future research should potentially focus on which surgical inpatients can safely forego thromboprophylaxis to inform a future 'opt-out' strategy. Such a strategy could replace the current 'opt-in' process in which time-consuming RAMs, with limited reliability, are used to determine which surgical inpatients should be offered thromboprophylaxis.

Addendum

S. Davis developed the decision analytic model and conducted the cost-effectiveness analysis. A. Pandor and D. Horner conducted the systematic reviews that informed the modelling. S. Goodacre, D. Horner, K. de Wit, M. Holland, X.L. Griffin and B.J. Hunt were members of the expert clinical group that informed development of the decision analytic model. All named authors contributed to management of the project and interpretation of the analysis. All named authors contributed to redrafting and approved the final draft of the paper. S. Davis is the lead author and guarantor for the paper.

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Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: the research described was conducted as part of a wider project funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) programme (project number NIHR127454); S Goodacre is chair of the NIHR Clinical Trials Unit Standing Advisory Committee; K de Wit reports a grant from Bayer, outside the submitted work; M Holland has lectured for Pfizer and lectured for and attended a symposium sponsored by Bristol-Myers Squibb Pharmaceuticals Ltd; D Horner is a topic expert for National Institute of Health and Care Excellence (NICE) VTE guidelines in England; no other relationships or activities that could appear to have influenced the submitted work.

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Tables and Figures for main text

Figure Legends

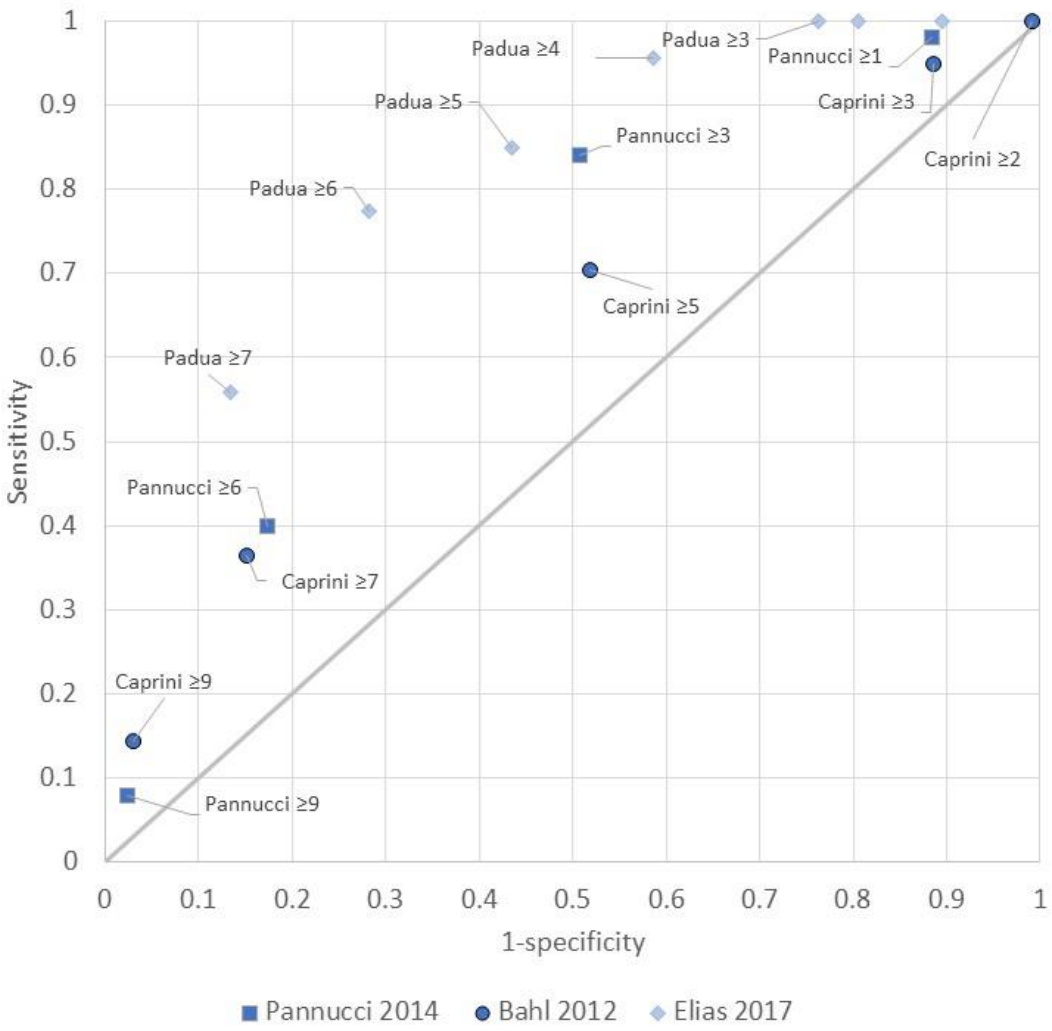

Figure 1 Receiver operator characteristics (ROC) curve for Caprini and Pannucci risk assessment models (RAMs) to predict VTE in surgical inpatients[2, 3] (also shows data for Padua RAM from an alternative study, Elias 2017,[17] that recruited a mixed cohort of medical and surgical inpatients)

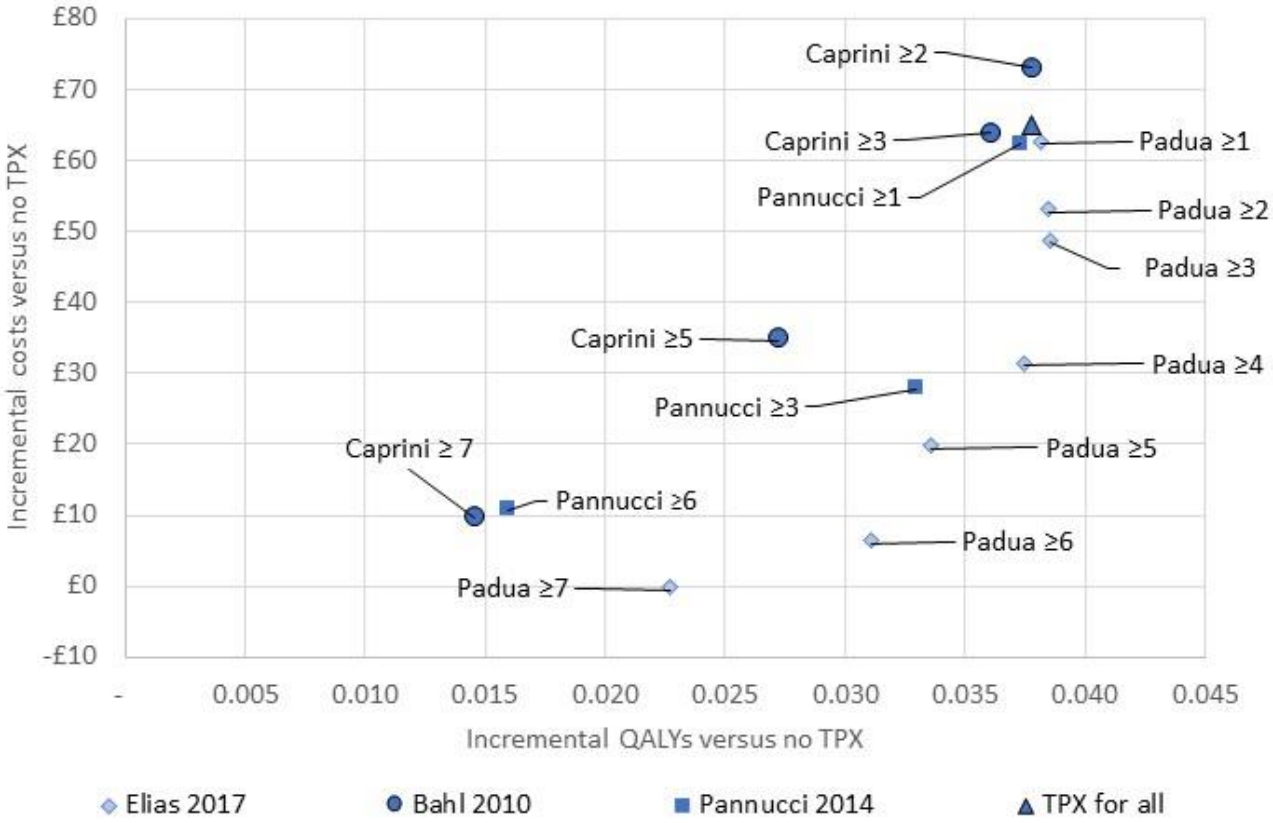

Figure 2 Cost-effectiveness plane for two RAMs validated in cohorts of surgical inpatients (Caprini and Pannucci) [2, 3] and for the Padua RAM from an alternative study (mixed cohort of medical and surgical patients)[17]

Table 1 Summary of key clinical parameters *

Parameter description	**Value**
Absolute risks in six months after admission without thromboprophylaxis;	
- PE	0.62%
- Symptomatic DVT	0.78%
- Asymptomatic DVT	12.61%
Absolute risks in six months after admission with thromboprophylaxis (LMWH);	
- PE	0.18%
- Symptomatic DVT	0.23%
- Asymptomatic DVT	3.65%
Major bleed risk by type for surgical inpatients without thromboprophylaxis;	
- fatal major bleeding	0.01%
- ICH	0.02%
- Surgical site bleeding requiring return to theatre	0.16%
- Other major bleeding	1.05%
Any major bleeding	1.24%
Major bleed risk by type for surgical inpatients having thromboprophylaxis;	
- fatal major bleeding	0.03%
- ICH	0.07%
- Surgical site bleeding requiring return to theatre	0.48%
- Other major bleeding	3.12%
Any major bleeding	3.70%

Major bleed risk by type for patients having anticoagulant treatment after VTE;	
- fatal major bleeding	0.21%
- ICH	0.08%
- Other major bleeding	0.56%
Any major bleeding	0.85%
Case-fatality rate for PE	6.0%
SMR versus general population;	
- in the year following surgical admission	5.0
- in years two to six following ICH†	2.2
Cumulative three-year risk of PTS for DVT	
- Symptomatic proximal (treated)	32.4%
- Asymptomatic proximal (untreated)	56.5%
- Distal (symptomatic and treated or asymptomatic and untreated)	15.6%
Cumulative two-year incidence of CTEPH	3.2%
Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; LMWH, low molecular weight heparin; PE, pulmonary embolism; PTS, post-thrombotic syndrome; SMR, standardised mortality ratio; VTE, venous thromboembolism	
* Sources described in full in Supporting Information Table 1	
† SMR for non-fatal ICH in year after ICH was 4.5 so SMR for surgical inpatients was applied in first year after ICH	

Table 2 Cost and utility parameter summary *

Parameter description	**Cost**	**Utility**
Application of RAM to patient	£9.08	Not applicable
Thromboprophylaxis - five days of inpatient LMWH (Dalteparin) administered by a hospital nurse (band 6)	£23.91	Decrement of 0.007 applied during thromboprophylaxis
Well patient without symptomatic VTE or major bleeding	NA	0.849 in year one with age adjustment thereafter
Symptomatic proximal DVT	£763.12	0.817 up to six months Decrement of 0.011 during anticoagulant treatment Beyond six months, multiplier applied only to those having PTS
Symptomatic distal DVT	£642.95	
Non-fatal PE	£1,848.75	0.815 up to six months Decrement of 0.011 during anticoagulant treatment Beyond six months, multiplier applied only to those having CTEPH
Fatal PE	£1,517.13	0
Fatal bleed	£1,865.51	0
Non-fatal non-ICH bleed	£1,209.75	0.727 for one month after bleed
Non-fatal ICH	£21,987.80 in first 90 days £8,292.83 per annum thereafter	0.629 in first six months Multiplier of 0.894 thereafter
PTS	£293.16 in year one	Multiplier of 0.895

	£78.00 in each subsequent year	
CTEPH medically managed	£18,569.53 each year	Multiplier of 0.629
CTEPH surgically managed	£10,236.60 in year one and zero in year two onwards	Multiplier of 0.629 in the first year only

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; LMWH, low molecular weight heparin; PE, pulmonary embolism; PTS, post-thrombotic syndrome; RAM, risk assessment model; VTE, venous thromboembolism

* Sources described in full in Supporting Information Tables 2 to 6

Table 3 Predicted clinical outcomes per 10,000 surgical inpatients for each thromboprophylaxis strategy

TPX strategy	% TPX	Outcomes at six months per 10,000 patients							Outcomes at five years per 10,000 patients				
		Fatal PE	Fatal bleed	Non-fatal ICH	Other major bleed*	Non-fatal PE	Symptomatic DVT	Asymptomatic DVT	PTS	PE survivor with CTEPH	PE survivor without CTEPH	ICH survivor	Dead (any cause)
TPX for none	0	4	1	2	122	58	78	1260	367	1	54	2	353
TPX for Caprini ≥ 7‡	18	3	2	3	165	43	58	934	272	1	40	3	352
TPX for Pannucci ≥6†	20	3	2	3	170	42	56	902	263	1	39	3	352
TPX for Caprini ≥ 5‡	54	2	3	5	251	29	39	631	184	1	27	5	352
TPX for Pannucci ≥ 3†	55	1	3	5	254	23	32	509	148	1	22	5	351
TPX for Caprini ≥ 3‡	89	1	3	6	327	19	25	411	120	0	18	6	352
TPX for Pannucci ≥1†	90	1	3	6	336	18	24	383	112	0	17	6	352
TPX for Caprini ≥ 2‡	99	1	3	7	335	17	23	365	107	0	16	6	352
TPX for all	100	1	3	7	360	17	23	365	107	0	16	6	352

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension, DVT, deep vein thrombosis; ICH, intracranial haemorrhage; PE, pulmonary embolism, TPX, thromboprophylaxis; PTS, post-thrombotic syndrome.

* Patients having other major bleeds could also have a DVT or non-fatal PE, † sensitivity and specificity data from Pannucci et al.[3] ‡ sensitivity and specificity from Bahl et al.[2]

Table 4 Base-case results for the Pannucci RAM and scenario analysis using data from the Padua RAM (mean from 10,000 PSA samples)

	% TPX	Sensitivity	Specificity	Absolute costs, £	Absolute QALYs	Cost vs no TPX, £	QALYs vs no TPX	ICER vs TPX for none, £	ICER versus previous non-dominated strategy, £
Base-case results using performance data from a cohort of surgical inpatients (Pannucci 2014)[3]									
TPX for none	0%	0%	100%	159.13	13.9214	-	NA	NA	NA
TPX for Pannucci ≥6	20%	40%	83%	165.89	13.9362	6.76	0.0148	457.59	457.59
TPX for Pannucci ≥3	55%	84%	49%	176.99	13.9519	17.86	0.0306	584.51	703.28
TPX for Pannucci ≥1	90%	98%	12%	206.09	13.9561	46.96	0.0347	1,353.16	Extendedly dominated
TPX for all	100%	100%	0%	207.01	13.9565	47.88	0.0351	1,363.99	6,600.12
Scenario analysis using performance data from an alternative study * (Elias 2017)[17]									
TPX for none	0%	0%	100%	160.35	13.9208	-	-	-	Dominated
TPX for Padua ≥7	19%	56%	87%	155.99	13.9419	-4.37	0.0211	-206.59	-
TPX for Padua ≥6	35%	77%	72%	159.88	13.9497	-0.48	0.0290	-16.44	496.38
TPX for Padua ≥5	49%	85%	57%	170.79	13.9522	10.44	0.0314	332.46	4,509.71
TPX for Padua ≥4	64%	96%	41%	180.10	13.9557	19.75	0.0350	564.59	2,593.41
TPX for Padua ≥3	80%	100%	24%	194.78	13.9569	34.42	0.0361	953.42	13,066.60
TPX for Padua ≥2	83%	100%	20%	198.73	13.9568	38.38	0.0360	1,066.03	Dominated
TPX for Padua ≥1	91%	100%	11%	207.22	13.9565	46.86	0.0357	1,312.01	Dominated
TPX for all	100%	100%	0%	208.11	13.9561	47.76	0.0354	1,349.75	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; NA, not applicable; TPX, thromboprophylaxis; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life-years. An intervention is said to dominate another if it has lower costs and higher QALYs. An intervention is extendedly dominated when an intervention with greater QALY gain has a lower ICER when compared to a previous non-dominated strategy

* Elias et al. recruited a mixed cohort of medical and surgical patients rather than an exclusive surgical cohort[17]