
Article:
Davis, S. orcid.org/0000-0002-6609-4287, Goodacre, S., Horner, D. et al. (5 more authors) (2023) Decision-analysis modelling of effectiveness and cost-effectiveness of pharmacological thromboprophylaxis for surgical inpatients, using variable risk assessment models or other strategies. Journal of Thrombosis and Haemostasis, 21 (6). pp. 1580-1591. ISSN 1538-7836

https://doi.org/10.1016/j.jtha.2023.02.018

Received: 17 October 2022 | Revised: 4 February 2023 | Accepted: 23 February 2023

https://doi.org/10.1016/j.jtha.2023.02.018

ORIGINAL ARTICLE

Decision-analysis modeling of effectiveness and cost-effectiveness of pharmacologic thromboprophylaxis for surgical inpatients using variable risk assessment models or other strategies

Sarah Davis[1] | Steve Goodacre[1] | Daniel Horner[1,2,3] | Abdullah Pandor[1] | Xavier L. Griffin[4] | Kerstin de Wit[5] | Beverley J. Hunt[6] | Mark Holland[7]

[1]School of Health and Related Research, Faculty of Medicine, Dentistry and Health, University of Sheffield, Sheffield, United Kingdom

[2]Department of Emergency and Intensive Care Medicine, Northern Care Alliance Foundation Trust, Stott Lane, Salford, United Kingdom

[3]Division of Immunology, Infection, Immunity and Respiratory Medicine, University of Manchester, Manchester, United Kingdom

[4]Barts Bone and Joint Health, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom

[5]Department of Emergency Medicine, Queen's University, Kingston, Ontario, Canada

[6]Department of Thrombosis and Haemostasis, Kings Healthcare Partners, London, United Kingdom

[7]School of Clinical and Biomedical Sciences, Faculty of Health and Wellbeing, University of Bolton, Bolton, United Kingdom

Correspondence
Sarah Davis, School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA, United Kingdom.
Email: s.davis@sheffield.ac.uk

Funding information
UK National Institute for Health Research

Abstract

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

Objectives: To determine the balance of cost, risk, and benefit for different thromboprophylaxis strategies in adult surgical inpatients, excluding patients who underwent major orthopedic surgery or were under critical care and pregnant women.

Methods: Decision analytic modeling was performed 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 as follows: no thromboprophylaxis; thromboprophylaxis for all; and thromboprophylaxis given according to RAMs (Caprini and Pannucci). Thromboprophylaxis is assumed to be given for the duration of hospitalization. The model evaluates lifetime 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 a higher sensitivity (99.9%) were available for surgical inpatients. QALY gains were mainly due to reduced postthrombotic complications. The optimal strategy was sensitive to several other factors such as the risk of VTE, bleeding and postthrombotic syndrome, duration of prophylaxis, and patient age.

Conclusion: Thromboprophylaxis for all eligible surgical inpatients seemed to be the most cost-effective strategy. Default recommendations for pharmacologic

Manuscript handled by: Sabine Eichinger

Final decision: Sabine Eichinger, 23 February 2023

Health Technology Assessment programme (project reference NIHR127454).

The views expressed are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health, who had no role in the design, execution, analyses, interpretation and reporting of results.

thromboprophylaxis, with the potential to opt-out, may be superior to a complex risk-based opt-in approach.

KEYWORDS
anticoagulants, cost-benefit analysis, operative, risk assessment, surgical procedures, venous thromboembolism

1 | INTRODUCTION

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

Pharmacologic thromboprophylaxis can be used to prevent VTE in surgical inpatients but may increase bleeding risk [1]. Complications can include surgical site bleeding, fatal bleeding, or nonfatal intracranial hemorrhage (ICH). The widespread use of thromboprophylaxis in surgical inpatients incurs substantial health care costs. Therefore, it is important to assess the overall balance of costs, benefits, and potential harms of thromboprophylaxis. Decision analytic modeling can be used to estimate both the overall clinical effectiveness of thromboprophylaxis in 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 pharmacologic thromboprophylaxis at surgical inpatients with the highest risk of VTE could maximize the benefits of avoiding VTE outcomes while minimizing 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 an individual patient's 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 interrater reliability is variable [4,5]. The cost-effectiveness of using alternative RAMs to target thromboprophylaxis has not been examined previously for surgical inpatients. The aim of this analysis was to assess the overall effectiveness and cost-effectiveness of alternative pharmacologic thromboprophylaxis strategies in eligible surgical inpatients (ie, 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 assessed whether it is cost effective to add pharmacologic thromboprophylaxis to other preventative measures, such as early mobilization or mechanical prophylaxis, rather than assessing pharmacologic thromboprophylaxis as an alternative to other measures.

Essentials

- Pharmacologic prophylaxis to prevent venous thromboembolism provides an overall health gain.
- Health gains are mainly from reduced postthrombotic 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 a very high sensitivity.

2 | 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-term 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 with those of the next most effective strategy. The costs and QALYs are estimated over a 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 National Institute for Health and Care Excellence [6].

2.1 | 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 immobilization [9]. A 6-month decision tree model (Supplementary Figure S1) was used to estimate the number of patients receiving thromboprophylaxis for each strategy and numbers experiencing symptomatic DVT, asymptomatic DVT, fatal PE, nonfatal PE, and major bleeding. In accordance with national guidance in England, symptomatic DVTs and nonfatal PEs were assumed to result in 3 months of anticoagulant treatment [10]. A 6-month time frame was considered sufficient to capture both the period of risk for hospital-acquired VTE (90 days after the admission) and the period of treatment after VTE (3 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 6-month decision tree phase of the model because it is difficult to distinguish PTS and CTEPH from acute symptoms during the first 3 months after VTE. Major bleeds were those meeting the International Society on Thrombosis and Haemostasis definition [11] and were divided into fatal bleeds, nonfatal ICHs, and other major bleeds. The latter included any complications related to surgical site bleeding that required patients to return to theater or that resulted in prolonged hospitalization. Patients with major bleeds during either thromboprophylaxis or VTE treatment with anticoagulants were assumed to stop their anticoagulant medication at the time of the bleed. The likelihood of VTE and of bleeding during the treatment of VTE are assumed to be independent of whether the patient experienced major bleeding during hospital admission.

A state-transition model (Supplementary Figure S2) was then used to extrapolate lifetime outcomes such as overall survival and ongoing morbidity related to either ICH or VTE. Recurrent VTEs do not appear within the state-transition model because these were not expected to differ according to whether patients received thromboprophylaxis during hospital admission. The risk of PTS after VTE was dependent on whether the DVT was symptomatic and treated or asymptomatic and untreated and its location (proximal or distal). Patients experiencing CTEPH after PE were divided into medical and surgical management to allow for differential costs and survival between these groups. There was also a post-ICH state to capture ongoing morbidity after ICH. Further adverse outcomes were not modeled in the post-ICH group because lifetime costs and QALYs were assumed to be predominantly determined by morbidity related to ICH. The state-transition model had one 6-month cycle to extrapolate the outcomes of the decision tree up to 1 year with all-cause mortality during the first year applied at 6 months. Thereafter, the cycle length was 1 year, and the health state occupancy was half-cycle corrected such that all transitions between the states, including mortality, were assumed to occur midcycle.

2.2 | Population

The population was hospitalized surgical inpatients excluding patients under critical care, children (younger than 18 years), and pregnant women. We also excluded patients having elective hip or knee replacement or hip fracture repair from this analysis. These patients were recognized as being at a higher risk of VTE and consequently provided with extended spectrum pharmacologic thromboprophylaxis (using both low-molecular-weight heparin [LMWH] and direct-oral anticoagulant [DOAC] agents) as standard in the United Kingdom and other countries [12,13]. We considered patients having major orthopedic surgery in a separate analysis reported elsewhere [14]. Patients identified to be at a high risk of bleeding or in whom pharmacologic thromboprophylaxis was contraindicated were considered ineligible for thromboprophylaxis and were, therefore, excluded from the model under all strategies. One of the most 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 this model, provided they do not require critical care. Although some RAMs exist for use particularly in trauma patients [15], we did not model the use of these RAMs in trauma patients as a specific subpopulation because these RAMs have been typically developed and validated in countries where trauma patients are treated in a critical care environment. The population characteristics at the baseline (age 54 years and 46% men) were based on an analysis of routine hospital admission data from the United Kingdom [16].

2.3 | Risk assessment models

The sensitivity and specificity of RAMs for predicting VTE, which determine the number receiving thromboprophylaxis, were derived from a systematic review of the clinical literature [15]. Data from external validation studies in cohorts of surgical inpatients were identified for the Caprini and Pannucci RAMs. Their performance data are summarized in Figure 1 [2,3]. Also shown in Figure 1, are performance data 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, was considered in a scenario analysis. The Department of Health VTE risk assessment tool is commonly used for the VTE risk assessment of hospitalized patients in the United Kingdom, but no data were available on the performance of this tool. Hence, the cost-effectiveness of using this specific RAM could not be modeled [10,15].

2.4 | Thromboprophylaxis and treatment of VTE

Thromboprophylaxis was assumed to be with subcutaneous LMWH at a dose licensed for surgical inpatients for the duration of the admission, which is typically 5 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, because we did not expect this additional complexity in dosing would significantly alter the results of the

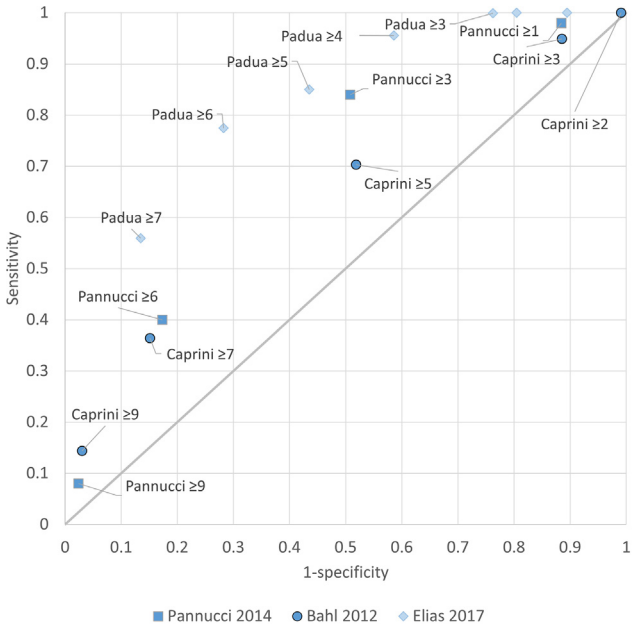

FIGURE 1 Receiver operator characteristics (ROC) curve for the Caprini and Pannucci risk assessment models (RAMs) to predict VTE in surgical inpatients [2,3]. In addition, the figure shows data for Padua RAM from an alternative study [17] that recruited a mixed cohort of medical and surgical inpatients. VTE, venous thromboembolism.

analysis with the costs of a single dose of LMWH being essentially identical across weight bands in the United Kingdom [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 7 days [10], a survey of 25 United Kingdom exemplar centers suggest that most hospitals give LMWH for the duration of hospital admission only [21]. However, a scenario analysis was conducted exploring the effect of assuming a further 2 days of postdischarge administration to achieve a minimum of 7 days of thromboprophylaxis. To comply with the national guidance recommendation of extending thromboprophylaxis to 28 days in patients with major cancer surgery in the abdomen, this was also explored in a scenario analysis [10]. The anticoagulant treatment of 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 a higher use of DOACs explored in the 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. [24], which reported the odds ratio (OR) for LMWH vs no LMWH (OR: 0.26; 95% CI: 0.09-0.87) for the outcome of hospital-acquired VTE in surgical patients. A subsequent meta-analysis published after the completion of our work confirmed this estimate of effectiveness: Marcucci et al. [1] reported the OR for LMWH compared with no active treatment to range between 0.19 and 0.33 (depending on the dose) for the outcome of symptomatic VTE, within a cohort of 45 445 patients who underwent noncardiac surgery. The relative risk of major bleeding for LMWH compared with that of either placebo or mechanical prophylaxis was based on a published meta-analysis of studies in patients who underwent abdominal surgery (relative risk: 2.98, 95% CI: 0.88-14.80) [10].

2.5 | Epidemiologic parameters

Data on the absolute risks of fatal PE, nonfatal PE, DVT, fatal bleeding, nonfatal major bleeding (including ICH), PTS, and CTEPH were obtained from the literature [3,8,10,25–36]. Patients were assumed to experience an increased risk of mortality compared with the general population in the year after hospital admission, in the first 6 years after ICH and after CTEPH [37–42]. The clinical parameters incorporated into the model are summarized in Table 1, with further details provided in Supplementary Text S1 and Supplementary Table S1.

2.6 | 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. The administration of a RAM by a hospital physician was assumed to take 5 minutes. It was assumed that the duration of discharge delay caused by a hospitalized patient experiencing VTE would be similar to the duration of admission for patients with VTE after discharge. Costs applied in the model are summarized in Table 2, with additional information on the resource use provided in Supplementary Text S1 and Supplementary Tables S2–S4.

2.7 | Health-related quality of life

To estimate QALYs, it is necessary to quantify an individual's health utility, which is a measure of health-related quality of life on a scale of zero to 1, where 1 represents full health and 0 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 6 months for those with DVT, for 1 month after other major bleeds (non-ICH), and for the duration of thromboprophylaxis or anticoagulant treatment. Life-long utility decrements were applied after ICH, PTS, and CTEPH. Utility data applied in the model are summarized in Table 2, with further details in Supplementary Tables S5–S7 [49–55].

2.8 | 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

TABLE 1 A summary of key clinical parameters[a].

Parameter description	Value
Absolute risks in 6 mo after admission without thromboprophylaxis	
PE	0.62%
Symptomatic DVT	0.78%
Asymptomatic DVT	12.61%
Absolute risks in 6 mo 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 theater	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 theater	0.48%
Other major bleeding	3.12%
Any major bleeding	3.70%
Major bleed risk by type for patients taking 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 vs general population	
In the year after surgical admission	5.0
In years 2-6 after ICH[b]	2.2
Cumulative 3-y 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 2-y incidence of CTEPH	3.2%

CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial hemorrhage; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; PTS, postthrombotic syndrome; SMR, standardized mortality ratio; VTE, venous thromboembolism.

[a]Sources described in full in Supplementary Table S1.
[b]SMR for nonfatal ICH in year after ICH was 4.5, so SMR for surgical inpatients was applied in first year after ICH.

the probabilistic sensitivity analysis (PSA). The details of the distributions assumed for each parameter included in the PSA can be found in Supplementary Tables S1 and S7.

2.9 | 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 7 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% vs 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 whether the conclusions differed when assuming a zero incidence of PTS in patients with asymptomatic distal DVT because of previous modeling identifying this as a potentially important outcome with uncertain incidence [9]. Moreover, sensitivity analyses were conducted to explore the effect of assuming a higher or lower average risk for VTE and bleeding, assuming all VTEs are treated with DOACs, and to explore the effect of alternative patient characteristics, examining starting ages of 20 and 80 years and assuming no increased risk of mortality in the year after surgery to reflect lower risk patient cohorts.

2.10 | Patient and public involvement

The project team included 2 patient and public involvement members who contributed to the study design and ensured that patient and public values were reflected in the decision analytic modeling. On the basis of their advice, we included disutility associated with LMWH injections in the analysis because this was considered important to patients. In addition, the modeling methods and results were presented to a broader patient and public involvement group to ensure that the interpretation of the results was comprehensible and relevant to patients and the public.

3 | RESULTS

Short-term 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 nonfatal ICHs) was low in surgical

TABLE 2 Cost and utility parameter summary[a].

Parameter description	Cost (£)	Utility
Application of RAM to a patient	9.08	Not applicable
Thromboprophylaxis: 5 d of inpatient LMWH (Dalteparin), administered by a hospital nurse (band 6)	23.91	Decrement of 0.007 applied during thromboprophylaxis
Patient without symptomatic VTE or major bleeding	NA	0.849 in year 1 with age adjustment thereafter
Symptomatic proximal DVT Symptomatic distal DVT	763.12 642.95	0.817 up to 6 mo Decrement of 0.011 during anticoagulant treatment Beyond 6 mo, multiplier applied only to those having PTS
Nonfatal PE	1848.75	0.815 up to 6 mo Decrement of 0.011 during anticoagulant treatment Beyond 6 mo, multipliers applied only to those having CTEPH
Fatal PE	1517.13	0
Fatal bleed	1865.51	0
Nonfatal non-ICH bleed	1209.75	0.727 for 1 mo after bleeding
Nonfatal ICH	21 987.80 in first 90 d 8292.83 per annum thereafter	0.629 in the first 6 mo Multiplier of 0.894 thereafter
PTS	293.16 in year 1 78.00 in each subsequent year	Multiplier of 0.895
CTEPH medically managed	18 569.53 each year	Multiplier of 0.629
CTEPH surgically managed	10 236.60 in year 1 and zero in year 2 onward	Multiplier of 0.629 in the first year only

CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial hemorrhage; LMWH, low-molecular-weight heparin; NA, not applicable; PE, pulmonary embolism; PTS, postthrombotic syndrome; RAM, risk assessment model; VTE, venous thromboembolism.
[a]Sources described in full in Supplementary Tables S2–S6.

inpatients without thromboprophylaxis (7/10 000), but was increased slightly by thromboprophylaxis (11/10 000) owing to the increased risk of fatal bleeds and nonfatal ICHs. However, all-cause mortality at 5 years was similar (352/10 000 vs 353/10 000). Symptomatic VTE reduced from 140 per 10 000 to 41 per 10 000, but thromboprophylaxis for all resulted 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 provided 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 with those for 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 increased when lower thresholds for the Caprini and Pannucci RAMs were considered, resulting in a wider use of thromboprophylaxis. However, thromboprophylaxis for all seemed to be more cost effective than using either of these RAMs when applying the incremental cost-effectiveness ratio threshold of £20 000 per QALY (typically applied in the United Kingdom) [6]. This was partly because the costs of administering a RAM were avoided when using a thromboprophylaxis for all strategy. The 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 seemed to dominate thromboprophylaxis for all in this scenario because it provided greater QALY gains at a lower cost. This was because the high RAM performance in this particular study (99.9% sensitivity; 23.7% specificity at a Padua score of ≥3) meant 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 was estimated to result in 0.035 additional QALYs (95% credible interval: 0.002-0.080) while generating additional costs of £48 (95% credible interval: £−96 to £254). Thromboprophylaxis for all dominated no thromboprophylaxis in 24% of the PSA samples, and there was a 70% probability that thromboprophylaxis for all was the optimal strategy (when valuing a QALY at 20 000) compared with RAM-based thromboprophylaxis using the Pannucci RAM or thromboprophylaxis for none. Table 4 also

TABLE 3 Predicted clinical outcomes per 10 000 surgical inpatients for each thromboprophylaxis strategy.

		Outcomes at 6 mo per 10 000 patients							Outcomes at 5 y per 10 000 patients				
TPX strategy	% TPX	Fatal PE	Fatal bleed	Nonfatal ICH	Other major bleed[a]	Nonfatal 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[b]	18	3	2	3	165	43	58	934	272	1	40	3	352
TPX for Pannucci ≥6[c]	20	3	2	3	170	42	56	902	263	1	39	3	352
TPX for Caprini ≥5[b]	54	2	3	5	251	29	39	631	184	1	27	5	352
TPX for Pannucci ≥3[c]	55	1	3	5	254	23	32	509	148	1	22	5	351
TPX for Caprini ≥3[b]	89	1	3	6	327	19	25	411	120	0	18	6	352
TPX for Pannucci ≥1[c]	90	1	3	6	336	18	24	383	112	0	17	6	352
TPX for Caprini ≥2[b]	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

CTEPH, chronic thromboembolic pulmonary hypertension, DVT, deep vein thrombosis; ICH, intracranial hemorrhage; PE, pulmonary embolism, PTS, postthrombotic syndrome; TPX, thromboprophylaxis.

[a]Patients with other major bleeds could also present with a DVT or nonfatal PE.

[b] Sensitivity and specificity data from Bahl et al. [2].

[c] Sensitivity and specificity data from Pannucci et al. [3].

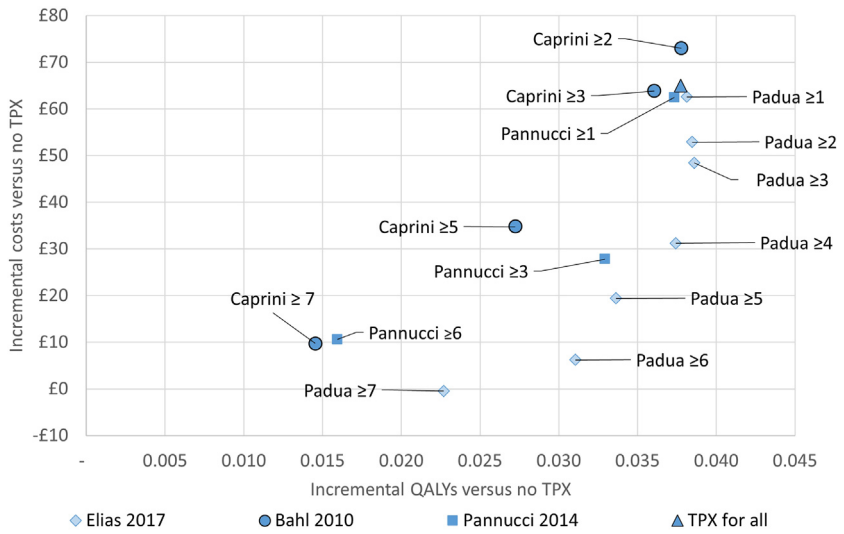

FIGURE 2 Cost-effectiveness plane for 2 RAMs validated in cohorts of surgical inpatients (Caprini and Pannucci) [2,3] and for the Padua RAM from an alternative study (mixed cohort of medical and surgical patients) [17]. QALY, quality-adjusted life-year; RAM, risk assessment model; TPX, thromboprophylaxis.

presents the results of the PSA for the scenario analysis, assuming a higher RAM performance using data for the Padua RAM. In this scenario, offering thromboprophylaxis at a Padua score of ≥ 3 showed 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, whereas 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 years. Thromboprophylaxis for those with a Pannucci score ≥1 was the optimal strategy when assuming no PTS after asymptomatic distal DVT; assuming that LMWH was administered for 7 days including 2 days after discharge; assuming the length of stay increased 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 after surgery; or all VTE events would be treated with DOACs.

4 | DISCUSSION

Offering pharmacologic thromboprophylaxis to all eligible surgical inpatients seems to be more cost effective than using RAMs to target thromboprophylaxis at higher risk patients, owing to the weak predictive performance of existing RAMs validated in cohorts of surgical inpatients. However, there is uncertainty regarding the optimal thromboprophylaxis strategy because using RAM-based prophylaxis became more cost effective than thromboprophylaxis for all when exploring plausible alternative inputs in the 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 to become available for surgical inpatients.

A cost-effectiveness analysis from a Chinese Health System perspective found that 7 days of thromboprophylaxis was cost effective in nonorthopedic surgical patients with a Caprini score of 3 to 6 and was cost saving in patients with higher scores [57]. However, it was 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 event profile associated with thromboprophylaxis. The results suggest that the benefits of thromboprophylaxis in reducing VTE outweigh the harms of increased bleeding in the surgical inpatient population because all strategies resulted in QALY gains compared with no thromboprophylaxis.

In the decision analytic model, much of the benefit of thromboprophylaxis was realized 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 nonfatal ICH. This is in line with the findings of a recent systematic review and meta-analysis that concluded that the causal effect of VTE prevention on mortality was null [58].

The scenario analyses suggest that prevention of PTS is an important driver of cost-effectiveness because RAM-based prophylaxis became more cost effective than thromboprophylaxis for all when assuming no risk of PTS after asymptomatic distal DVT or assuming that PTS affects the patient's health-related quality of life less. 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 with minor orthopedic surgery found an 8% cumulative incidence of PTS over 3 years after the 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 after asymptomatic distal DVT in the model. This higher figure was

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 strategy	% TPX	Sensitivity (%)	Specificity (%)	Absolute costs (£)	Absolute QALYs	Cost vs no TPX (£)	QALYs vs no TPX	ICER vs TPX for none (£)	ICER vs previous nondominated strategy (£)
Base-case results using performance data from a cohort of surgical inpatients (Pannucci et al. [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	1353.16	Extendedly dominated
TPX for all	100	100	0	207.01	13.9565	47.88	0.0351	1363.99	6600.12
Scenario analysis using performance data from an alternative study[a] (Elias et al. [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	4509.71
TPX for Padua ≥4	64	96	41	180.10	13.9557	19.75	0.0350	564.59	2593.41
TPX for Padua ≥3	80	100	24	194.78	13.9569	34.42	0.0361	953.42	13066.60
TPX for Padua ≥2	83	100	20	198.73	13.9568	38.38	0.0360	1066.03	Dominated
TPX for Padua ≥1	91	100	11	207.22	13.9565	46.86	0.0357	1312.01	Dominated
TPX for all	100	100	0	208.11	13.9561	47.76	0.0354	1349.75	Dominated

An intervention is said to dominate another if it has lower costs and higher QALYs. An intervention is extendedly dominated when an intervention with a greater QALY gain has a lower ICER than a previous nondominated strategy.

ICER, incremental cost-effectiveness ratio; NA, not applicable; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years; RAM, risk assessment model; TPX, thromboprophylaxis.

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

considered reasonable, given that all patients in the study with screening detected DVT were treated with anticoagulants for 3 to 6 months and those with 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 are sensitive to this assumption. Furthermore, any shared decision-making should involve informing patients that the overall benefit of thromboprophylaxis seems 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 experienced no high risks for bleeding and our findings, therefore are not applicable 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 specialized patient groups, such as neurosurgical patients, where a decision whether to use prophylaxis is often based on an individualized and expert consensus approach.

There are limited data on RAM performance in surgical inpatients, with only 2 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. [17] 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 because the VTE events that would have occurred in higher risk patients are prevented by thromboprophylaxis. The RAM performance estimates for the Padual RAM from Elias et al. [17] 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 might partly explain the higher estimate of sensitivity, although Elias et al. [17] reported that the performance was similar in the subset of patients receiving thromboprophylaxis. In the cohort used to validate the Pannucci RAM, two-thirds of patients received prophylaxis [3]. This illustrates the difficulty of conducting future studies that are likely to involve cohorts with a widespread usage of thromboprophylaxis, making estimation of RAM performance problematic. Future research could focus on randomized studies of pharmacologic thromboprophylaxis vs no pharmacologic thromboprophylaxis in patients identified as being at 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 after VTE. Scenario analyses suggest that for any RAM to be worth using, it would need to achieve a very high sensitivity. On the basis of 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.

ACKNOWLEDGMENTS

The authors thank all members of the Patient and Public Involvement Group and the Study Steering Group for their advice and comments throughout the project.

AUTHOR CONTRIBUTIONS

S.D. developed the decision analytic model and conducted the cost-effectiveness analysis. A.P. and D.H. conducted the systematic reviews that informed the modeling. S.G., D.H., K.d.W., M.H., X.L.G., and B.J.H. were the members of the expert clinical group that informed development of the decision analytic model. All authors contributed to the management of the project and interpretation of the analysis, contributed to redrafting, and approved the final draft of the paper. S.D. is the lead author and guarantor for the paper.

DECLARATION OF COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare that 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.G. is the chair of the NIHR Clinical Trials Unit Standing Advisory Committee; K.d.W. reports a grant from Bayer, outside the submitted work; M.H. has lectured for Pfizer and lectured for and attended a symposium sponsored by Bristol-Myers Squibb Pharmaceuticals; D.H. is a topic expert for the National Institute of Health and Care Excellence (NICE) VTE guidelines in England; no other relationships or activities that could seem to have influenced the submitted work.

REFERENCES

[1] Marcucci M, Etxeandia-Ikobaltzeta I, Yang S, Germini F, Gupta S, Agarwal A, Ventresca M, Tang S, Morgano GP, Wang M, Ahmed MM, Neumann I, Izcovich A, Criniti J, Popoff F, Devereaux PJ, Dahm P, Anderson D, Lavikainen LI, Tikkinen KAO, et al. Benefits and harms of direct oral anticoagulation and low molecular weight heparin for thromboprophylaxis in patients undergoing non-cardiac surgery: systematic review and network meta-analysis of randomised trials. *BMJ*. 2022;376:e066785.

[2] Bahl V, Hu HM, Henke PK, Wakefield TW, Campbell DA Jr, Caprini JA. A validation study of a retrospective venous thromboembolism risk scoring method. *Ann Surg*. 2010;251:344–50.

[3] Pannucci CJ, Laird S, Dimick JB, Campbell DA, Henke PK. A validated risk model to predict 90-day VTE events in postsurgical patients. *Chest*. 2014;145:567–73.

[4] Vyas D. Variations in risk assessment models may contribute to the existing gap between venous thromboembolism prophylaxis guidelines and adherence. *Springerplus*. 2012;1:60.

[5] Beck MJ, Haidet P, Todoric K, Lehman E, Sciamanna C. Reliability of a point-based VTE risk assessment tool in the hands of medical residents. *J Hosp Med*. 2011;6:195–201.

[6] Guide to the methods of technology appraisal. NICE process and methods guides. London: The National Institute for Health and Care Excellence; 2013.

[7] Le P, Martinez KA, Pappas MA, Rothberg MB. A decision model to estimate a risk threshold for venous thromboembolism prophylaxis in hospitalized medical patients. *J Thromb Haemost*. 2017;15:1132–41.

[8] National Clinical Guideline Centre—Acute and Chronic Conditions (UK). Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital (NICE clinical guidelines, no. 92.). London: Royal College of Physicians; 2010.

[9] Pandor A, Horner D, Davis S, Goodacre S, Stevens JW, Clowes M, Hunt BJ, Nokes T, Keenan J, de Wit K. Different strategies for pharmacological thromboprophylaxis for lower-limb immobilisation after injury: systematic review and economic evaluation. *Health Technol Assess*. 2019;23:1–190.

[10] National Guideline Centre. *Venous thromboembolism in over 16s—reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism: NICE guideline NG89*. London: National Institute for Health and Care Excellence; 2018.

[11] Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Subcommittee on Control of Anticoagulation of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost*. 2010;8:202–4.

[12] Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, Kahn SR, Rahman M, Rajasekhar A, Rogers FB, Smythe MA, Tikkinen KAO, Yates AJ, Baldeh T, Balduzzi S, Brożek JL, Ikobaltzeta IE, Johal H, Neumann I, Wiercioch W, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. *Blood Adv*. 2019;3:3898–944.

[13] Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, Samama CM. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e227S–7.

[14] NIHR 127454: the cost-effectiveness of venous thromboembolism risk assessment tools for hospital inpatients. https://fundingawards.nihr.ac.uk/award/NIHR127454; 2019 [accessed January 9, 2023].

[15] Pandor A, Tonkins M, Goodacre S, Sworn K, Clowes M, Griffin XL, Holland M, Hunt BJ, de Wit K, Horner D. Risk assessment models for venous thromboembolism in hospitalised adult patients: a systematic review. *BMJ Open*. 2021;11:e045672.

[16] Fowler AJ, Abbott TEF, Prowle J, Pearse RM. Age of patients undergoing surgery. *Br J Surg*. 2019;106:1012–8.

[17] Elias P, Khanna R, Dudley A, Davies J, Jacolbia R, McArthur K, Auerbach AD. Automating venous thromboembolism risk calculation using electronic health record data upon hospital admission: the automated Padua prediction score. *J Hosp Med*. 2017;12:231–7.

[18] NHS Digital. Hospital admitted patient care activity 2018-2019. https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19; 2019 [accessed December 6, 2020].

[19] Thrombosis UK. National thrombosis survey. https://thrombosisuk.org/downloads/TUK-GIRFT-REPORT.pdf; 2021 [accessed January 11, 2023].

[20] Joint Formulary Committee. British National Formulary (online) [Drug Tariff]. http://www.medicinescomplete.com; [accessed April 6, 2020].

[21] Gee E. The National VTE Exemplar Centres Network response to implementation of updated NICE guidance: venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism (NG89). *Br J Haematol*. 2019;186:792–3.

[22] Cohen AT, Gitt AK, Bauersachs R, Fronk EM, Laeis P, Mismetti P, Monreal M, Willich SN, Bramlage P, Agnelli G. Prefer In Vte Scientific Steering Committee And The Prefer In Vte Investigators OBOT. The management of acute venous thromboembolism in clinical practice. Results from the European PREFER in VTE registry. *Thromb Haemost*. 2017;117:1326–37.

[23] Ghanima W, Schultze A, Donaldson R, Brodin E, Halvorsen S, Graham S, Carroll R, Ulvestad M, Lambrelli D. Oral anticoagulation therapy for venous thromboembolism in Norway: time trends and treatment patterns. *Clin Ther*. 2021;43:1179–90.e3.

[24] Wade R, Sideris E, Paton F, Rice S, Palmer S, Fox D, Woolacott N, Spackman E. Graduated compression stockings for the prevention of deep-vein thrombosis in postoperative surgical patients: a systematic review and economic model with a value of information analysis. *Health Technol Assess*. 2015;19:1–220.

[25] Bergqvist D, Flordal PA, Friberg B, Frisell J, Hedberg M, Ljungström KG, Mätzsch T, Törngren S. Thromboprophylaxis with a low molecular weight heparin (tinzaparin) in emergency abdominal surgery. A double-blind multicenter trial. *Vasa*. 1996;25:156–60.

[26] Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, Delcroix M, Pruszczyk P, Mairuhu AT, Huisman MV, Klok FA. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur Respir J*. 2017;49.

[27] Hach-Wunderle V, Bauersachs R, Gerlach HE, Eberle S, Schellong S, Riess H, Carnarius H, Rabe E. Post-thrombotic syndrome 3 years after deep venous thrombosis in the Thrombosis and Pulmonary Embolism in Out-Patients (TULIPA) PLUS Registry. *J Vasc Surg Venous Lymphat Disord*. 2013;1:5–12.

[28] Kooiman J, van Hagen N, Iglesias Del Sol A, Planken EV, Lip GY, van der Meer FJ, Cannegieter SC, Klok FA, Huisman MV. The HAS-BLED score identifies patients with acute venous thromboembolism at high risk of major bleeding complications during the first six months of anticoagulant treatment. *PLOS ONE*. 2015;10:e0122520.

[29] Nagata C, Tanabe H, Takakura S, Narui C, Saito M, Yanaihara N, Okamoto A. Randomized controlled trial of enoxaparin versus intermittent pneumatic compression for venous thromboembolism prevention in Japanese surgical patients with gynecologic malignancy. *J Obstet Gynaecol Res*. 2015;41:1440–8.

[30] Nieto JA, Solano R, Ruiz-Ribó MD, Ruiz-Gimenez N, Prandoni P, Kearon C, Monreal M. Riete Investigators. Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: findings from the RIETE registry. *J Thromb Haemost*. 2010;8:1216–22.

[31] Osman Y, Kamal M, Soliman S, Sheashaa H, Shokeir A, Shehab el-Dein AB. Necessity of routine postoperative heparinization in non-risky live-donor renal transplantation: results of a prospective randomized trial. *Urology*. 2007;69:647–51.

[32] Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, Albanese P, Biasiolo A, Pegoraro C, Iliceto S, Prandoni P, Thromboembolic Pulmonary Hypertension Study Group. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med*. 2004;350:2257–64.

[33] Sakon M, Kobayashi T, Shimazui T. Efficacy and safety of enoxaparin in Japanese patients undergoing curative abdominal or pelvic cancer surgery: results from a multicenter, randomized, open-label study. *Thromb Res*. 2010;125:e65–70.

[34] Song KY, Yoo HM, Kim EY, Kim JI, Yim HW, Jeon HM, Park CH. Optimal prophylactic method of venous thromboembolism for gastrectomy in Korean patients: an interim analysis of prospective randomized trial. *Ann Surg Oncol*. 2014;21:4232–8.

[35] Turpie AG, Haas S, Kreutz R, Mantovani LG, Pattanayak CW, Holberg G, Jamal W, Schmidt A, van Eickels M, Lassen MR. A non-interventional comparison of rivaroxaban with standard of care for thromboprophylaxis after major orthopaedic surgery in 17,701 patients with propensity score adjustment. *Thromb Haemost*. 2014;111:94–102.

[36] van Dongen CJ, Prandoni P, Frulla M, Marchiori A, Prins MH, Hutten BA. Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome. *J Thromb Haemost*. 2005;3:939–42.

[37] Clark D, Schofield L, Graham FM, Isles C, Gott M, Jarlbaek L. Likelihood of death within one year among a national cohort of hospital inpatients in Scotland. *J Pain Symptom Manage*. 2016;52:e2–4.

[38] Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, Bresser P, Torbicki A, Mellemkjaer S, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Jaïs X, Ambroz D, et al. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *Circulation*. 2016;133:859–71.

[39] Fogelholm R, Murros K, Rissanen A, Avikainen S. Long term survival after primary intracerebral haemorrhage: a retrospective population based study. *J Neurol Neurosurg Psychiatry*. 2005;76:1534–8.

[40] Goodacre S, Horspool K, Shephard N, Pollard D, Hunt BJ, Fuller G, Nelson-Piercy C, Knight M, Thomas S, Lecky F, Cohen J. Selecting pregnant or postpartum women with suspected pulmonary

embolism for diagnostic imaging: the DiPEP diagnostic study with decision-analysis modelling. *Health Technol Assess*. 2018;22:1–230.

[41] Moore E, Munoz-Arroyo R, Schofield L, Radley A, Clark D, Isles C. Death within 1 year among emergency medical admissions to Scottish hospitals: incident cohort study. *BMJ Open*. 2018;8:e021432.

[42] Office of National Statistics. National Life Tables, England, 1980-82 to 2016-18. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2016to2018; 2019 [accessed April 1, 2020].

[43] Curtis L, Burns A. Unit costs of health and social care 2019, Personal Social Services Research Unit. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/; 2019 [accessed April 15, 2020].

[44] Curtis L, Burns A. Unit costs of health and social care 2017. Personal Social Services Research Unit. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/; 2017 [accessed April 15, 2020].

[45] Luengo-Fernandez R, Yiin GSC, Gray AM, Rothwell PM. Population-based study of acute- and long-term care costs after stroke in patients with AF. *Int J Stroke*. 2013;8:308–14.

[46] Menakaya CU, Pennington N, Muthukumar N, Joel J, Ramirez Jimenez AJ, Shaw CJ, Mohsen A. The cost of outpatient venous thromboembolism prophylaxis following lower limb injuries. *Bone Joint J*. 2013;95-B:673–7.

[47] NHS Improvement. National cost collection: national schedule of NHS costs—year 2018-19. https://www.england.nhs.uk/publication/2018-19-national-cost-collection-data-publication/; 2020 [accessed March 2, 2020].

[48] Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. *Value Health*. 2011;14:539–45.

[49] Chuang LH, Gumbs P, van Hout B, Agnelli G, Kroep S, Monreal M, Bauersachs R, Willich SN, Gitt A, Mismetti P, Cohen A, Jimenez D. Health-related quality of life and mortality in patients with pulmonary embolism: a prospective cohort study in seven European countries. *Qual Life Res*. 2019;28:2111–24.

[50] Enden T, Wik HS, Kvam AK, Haig Y, Kløw NE, Sandset PM. Health-related quality of life after catheter-directed thrombolysis for deep vein thrombosis: secondary outcomes of the randomised, non-blinded, parallel-group CaVenT study. *BMJ Open*. 2013;3:e002984.

[51] Lubberts B, Paulino Pereira NR, Kabrhel C, Kuter DJ, DiGiovanni CW. What is the effect of venous thromboembolism and related complications on patient reported health-related quality of life? A meta-analysis. *Thromb Haemost*. 2016;116:417–31.

[52] Luengo-Fernandez R, Gray AM, Bull L, Welch S, Cuthbertson F, Rothwell PM, Oxford Vascular Study. Quality of life after TIA and stroke: ten-year results of the Oxford Vascular Study. *Neurology*. 2013;81:1588–95.

[53] Marchetti M, Pistorio A, Barone M, Serafini S, Barosi G. Low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous thromboembolism: a cost-effectiveness analysis. *Am J Med*. 2001;111:130–9.

[54] Meads DM, McKenna SP, Doughty N, Das C, Gin-Sing W, Langley J, Pepke-Zaba J. The responsiveness and validity of the CAMPHOR Utility Index. *Eur Respir J*. 2008;32:1513–9. https://doi.org/10.1183/09031936.00069708

[55] Monreal M, Agnelli G, Chuang LH, Cohen AT, Gumbs PD, Bauersachs R, Mismetti P, Gitt AK, Kroep S, Willich SN, Van Hout B. Deep vein thrombosis in Europe—health-related quality of life and mortality. *Clin Appl Thromb Hemost*. 2019;25:1076029619883946.

[56] Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. *J Am Med Inform Assoc*. 1997;4:49–56.

[57] Bao Y, Zhao G, Qu S, Xiong T, Yao X, Wu B. A Caprini risk score-based cost-effectiveness analysis of enoxaparin for the thromboprophylaxis of patients after nonorthopedic surgery in a Chinese healthcare setting. *Clin Drug Investig*. 2020;40:161–71.

[58] Klemen ND, Feingold PL, Hashimoto B, Wang M, Kleyman S, Brackett A, Gross CP, Pei KY. Mortality risk associated with venous thromboembolism: a systematic review and Bayesian meta-analysis. *Lancet Haematol*. 2020;7:e583–93.

[59] Persson LM, Lapidus LJ, Lärfars G, Rosfors S. Deep venous thrombosis after surgery for Achilles tendon rupture: a provoked transient event with minor long-term sequelae. *J Thromb Haemost*. 2011;9:1493–9.

SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.jtha.2023.02.018