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Effectiveness and cost effectiveness of pharmacological thromboprophylaxis for medical inpatients: decision analysis modelling study

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ABSTRACT

OBJECTIVE To determine the balance of costs, risks, and benefits for different thromboprophylaxis strategies for medical patients during hospital admission.

DESIGN Decision analysis modelling study.

SETTING NHS hospitals in England.

POPULATION Eligible adult medical inpatients, excluding patients in critical care and pregnant women.

INTERVENTIONS Pharmacological thromboprophylaxis (low molecular weight heparin) for all medical inpatients, thromboprophylaxis for none, and thromboprophylaxis given to higher risk inpatients according to risk assessment models (Padua, Caprini, IMPROVE, Intermountain, Kucher, Geneva, and Rothberg) previously validated in medical cohorts.

MAIN OUTCOME MEASURES Lifetime costs and quality adjusted life years (QALYs). Costs were assessed from the perspective of the NHS and Personal Social Services in England. Other outcomes assessed were incidence and treatment of venous thromboembolism, major bleeds including intracranial haemorrhage, chronic thromboembolic complications, and overall survival.

RESULTS Offering thromboprophylaxis to all medical inpatients had a high probability (>99%) of being the most cost effective strategy (at a threshold of £20 000 (€23 440; $25 270) per QALY) in the probabilistic sensitivity analysis, when applying performance data from the Padua risk assessment model, which was typical of that observed across several risk assessment models in a medical inpatient cohort. Thromboprophylaxis for all medical inpatients was estimated to result in 0.0552 additional QALYs (95% credible interval 0.0209 to 0.1111) while generating cost savings of £28.44 (−£47 to £105) compared with thromboprophylaxis for none. No other risk assessment model was more cost effective than thromboprophylaxis for all medical inpatients when assessed in deterministic analysis. Risk based thromboprophylaxis was found to have a high (76.6%) probability of being the most cost effective strategy only when assuming a risk assessment model with very high sensitivity is available (sensitivity 99.9% and specificity 23.7% *v* base case sensitivity 49.3% and specificity 73.0%).

CONCLUSIONS Offering pharmacological thromboprophylaxis to all eligible medical inpatients appears to be the most cost effective strategy. To be cost effective, any risk assessment model would need to have a very high sensitivity resulting in widespread thromboprophylaxis in all patients except those at the very lowest risk, who could potentially avoid prophylactic anticoagulation during their hospital stay.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Medical inpatients are at risk of venous thromboembolism, which can be life threatening or result in long term complications; but this condition can be reduced by offering thromboprophylaxis (low molecular weight heparin) to eligible patients (ie, those without contraindications or high bleeding risk)

⇒ It is widely presumed that not all patients benefit from thromboprophylaxis; risk assessment models help clinicians further select medical inpatients who are at increased risk of venous thromboembolism to receive thromboprophylaxis

⇒ Uncertainty exists over which risk assessment models are optimal, and whether using these models is more cost effective than offering thromboprophylaxis to all eligible medical inpatients

WHAT THIS STUDY ADDS

⇒ Offering thromboprophylaxis to all eligible medical inpatients is expected to have lower costs and greater health benefits than using risk assessment models to select higher risk groups for tailored prescribing

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Future research should focus on identifying patients with a low risk of venous thromboembolism who could forego the default option of thromboprophylaxis for all eligible patients

⇒ These results support a shift towards using an opt-out system for thromboprophylaxis based on simple critera, rather than the current opt-in system

Introduction

Medical inpatients are at increased risk of venous thromboembolism (VTE), such as lower limb deep vein thrombosis (DVT) and pulmonary embolism, during initial hospital admission and for 90 days after discharge.[1] While most people make a full recovery following VTE, it can complicate hospital recovery and lead to post-thrombotic syndrome or chronic thromboembolic pulmonary

hypertension. It can also increase health resource use and occasionally result in death.

Pharmacological thromboprophylaxis can be used to prevent VTE, but is also associated with a potentially increased risk of bleeding,[2] including fatal bleeds or non-fatal intracranial haemorrhage, which can result in clinically significant morbidity. The widespread use of thromboprophylaxis in medical patients in hospital incurs substantial healthcare costs. Therefore, the overall balance of costs, benefits, and potential harms of thromboprophylaxis should be assessed. This assessment involves estimating 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 patients with the highest risk of VTE could maximise the benefits in terms of avoiding VTE outcomes, while minimising costs and potential harms. Many risk assessment models (RAMs) derived from internally valid study designs have undergone external validation in cohorts of medical inpatients, with the most commonly assessed being the Padua, Geneva, IMPROVE, and Kucher models.[3] Such models do not perfectly predict those individuals who will go on to have a VTE, so a trade-off between sensitivity and specificity is required to determine the optimal threshold for providing thromboprophylaxis. In addition, clinical time is needed to administer any risk assessment model and inter-rater reliability is variable.[4 5] The cost effectiveness of using these models to target thromboprophylaxis has not previously been examined for medical inpatients. The aim of this analysis was to assess the overall effectiveness, cost, and cost effectiveness of alternative strategies for pharmacological thromboprophylaxis in medical inpatients. The strategies included thromboprophylaxis for all eligible inpatients, thromboprophylaxis for none, and thromboprophylaxis targeted at higher risk patients using seven RAMs previously validated in medical cohorts.

Methods

We developed a decision analytical model to simulate the management of a cohort of medical inpatients according to the different thromboprophylaxis strategies and to estimate the short and long term consequences of each strategy. The model estimates the average health and social care costs incurred and the average QALYs accrued across the cohort to estimate the overall cost effectiveness (cost per QALY gained) of each strategy compared with the next most effective strategy. The costs and QALYs are estimated over the patient's whole lifetime, but a discounting rate was applied (3.5% per annum) because benefits and costs occurring early are valued more than those occurring later.[6]

Model structure

The model has been developed in collaboration with clinical experts who provided guidance on the selection of model outcomes based on clinical importance and assessed the appropriateness of data sources and model assumptions. Existing published models were presented to the clinical experts to inform this discussion.[7–9] The chosen approach drew mainly on previous work to evaluate thromboprophylaxis during lower limb immobilisation.[9] A decision tree model (online supplemental figure 1) was used to estimate the number of patients receiving thromboprophylaxis for each strategy and numbers experiencing fatal pulmonary embolism, non-fatal pulmonary embolism, symptomatic DVT, asymptomatic DVT, and major bleeding over a six month time frame. Symptomatic DVTs and non-fatal pulmonary embolisms are assumed to require three months of anticoagulant treatment in accordance with national guidance in England.[10] The six month time frame was considered sufficient to capture both the period of risk for hospital acquired VTE (90 days after admission) and the period of treatment following VTE (three months), during which time patients are also at risk of major bleeding.

Major bleeds were divided into fatal bleeds, non-fatal intracranial haemorrhages, and other major bleeds. Patients with major bleeds during either thromboprophylaxis or VTE treatment with anticoagulants are assumed to stop their anticoagulant treatment at the time of the bleed. The likelihood of VTE was assumed to be independent of whether the patient had major bleeding during hospital admission. Major bleeding during hospital stay and with VTE treatment were assumed to be independent events, given the differing doses (between prophylaxis and treatment anticoagulation) and the fact that the model is attempting to estimate average outcomes across the population. Post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension can be difficult to distinguish from acute symptoms during the first three months after VTE, so diagnosis of these chronic complications was assumed not to occur until the end of the decision tree phase of the model. Heparin induced thrombocytopenia was not included in the model because the most important consequence of this condition is an increased risk of VTE. However, any increased VTE risk in patients with heparin induced thrombocytopenia would have contributed to the VTE risk in the prophylaxis arm of the clinical trials and is therefore already accounted for in the model.

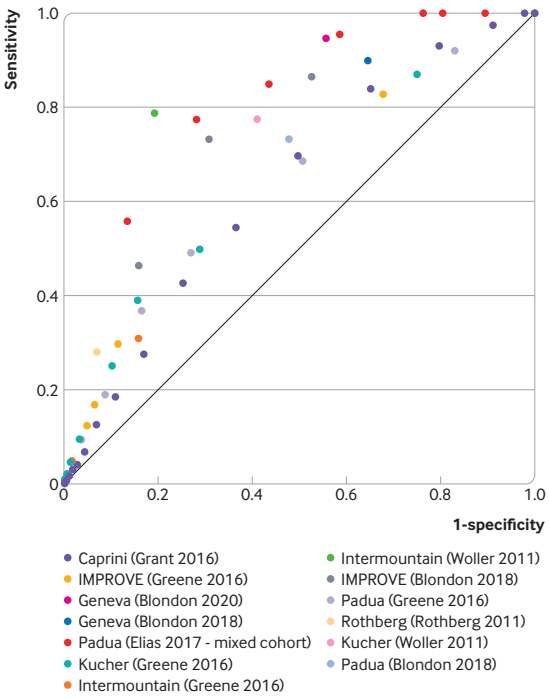

Figure 1 | Receiver operator characteristics curve for risk assessment models to predict venous thromboembolism in eligible medical inpatients.[15–20] Coloured dots refer to model name (and evaluation study). Data from an alternative study[54] that recruited a mixed cohort of medical and surgical inpatients are also included

A Markov model (online supplemental figure 2) was then used to extrapolate lifetime outcomes including overall survival and ongoing morbidity related to either intracranial haemorrhage or VTE. The Markov model captures the risk of post-thrombotic syndrome following VTE and the risk of chronic thromboembolic pulmonary hypertension following pulmonary embolism. The risk of post-thrombotic syndrome depends on whether the DVT is symptomatic and treated, or is asymptomatic and untreated, and depends also on its location (proximal or distal). Patients experiencing chronic thromboembolic pulmonary hypertension are divided into medical and surgical management to allow for differential costs and survival between these groups. There is also a health state to capture ongoing morbidity following intracranial haemorrhage. Further adverse outcomes (post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension) are not modelled after intracranial haemorrhage, because lifetime costs and QALYs are assumed to be predominantly determined by morbidity related to intracranial haemorrhage. Recurrent VTEs do not appear within the Markov model because these were not expected to differ according to whether patients received thromboprophylaxis during their hospital stay. The Markov model has a six month cycle to extrapolate the outcomes of the decision tree up to one year, followed by annual cycles thereafter. All cause mortality during the first year is applied at six months. Thereafter, 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 acutely ill medical patients in hospital excluding critical care patients, children (under age 18 years), and pregnant women. The patient groups excluded are known to have VTE risk profiles that differ substantially from the general inpatient population; any risk or effectiveness estimates provided through data evaluating the use of generic RAMs in medical inpatients will not be valid within such populations. Patients identified to be at increased risk of active bleeding, or in whom thromboprophylaxis is contraindicated for other reasons, were excluded from studies used to estimate risks of VTE and bleeding.[11–14] Such patients are also ineligible for pharmacological thromboprophylaxis in real world populations and were therefore excluded from the model under all strategies. The population characteristics at baseline (age 65.8 years and 44.5% male sex) were based on average characteristics in a cohort of medical inpatients.[15]

Risk assessment models

The sensitivity and specificity of RAMs for predicting VTE risk, which determines the number receiving thromboprophylaxis, were derived from our previous systematic review of the clinical literature.[3] This review had identical population inclusion criteria and was intended to directly inform this cost effectiveness work. Available data (summarised in figure 1) suggest that published RAMs generally have weak predictive performance for VTE in medical inpatients, although the studies evaluated were at high risk of bias and were heterogenous in population, design, and ascertainment of VTE cases.[3] Also, there are clear examples of heterogeneity in estimates of RAM performance when the same RAM is evaluated in different cohorts (eg, Intermountain in Woller 2011, and IMPROVE in Blondon 2018 when compared with their respective performances in Greene 2016).[15–17] However, more consistency is seen among the performance of five different RAMs (Padua, Caprini, Intermountain, Kucher, IMPROVE) when evaluated in the same cohort,[15 18] which suggests that any apparent differences in RAM performance are likely to be explained by differences in study design rather than differences between RAMs. Therefore, rather than try to identify the most cost effective RAM, we used regression to explore the trade-off between sensitivity and specificity for a typical RAM. The regression was informed by data from the five RAMs evaluated in a single cohort.[15 18] Additional details on the regression are provided in the appendix (online supplemental text 2 and figure 3). The performance of the five individual RAMs has been evaluated in

the deterministic base case in addition to using the sensitivity and specificity values obtained from the regression. A secondary analysis has also been conducted examining individual estimates of RAM performance for these five RAMs and two additional RAMs (Geneva and Rothberg) externally validated in four other cohorts of medical inpatients.[16 17 19 20] National UK guidance currently recommends VTE risk assessment for medical inpatients, and the most commonly used tool is the Department of Health's VTE risk assessment tool.[10 21] However, no data were available on the performance of this tool, so the cost effectiveness of using this specific RAM could not be modelled.[3]

Thromboprophylaxis and treatment of venous thromboembolism

Pharmacological thromboprophylaxis was assumed to be with subcutaneous, low molecular weight heparin (LMWH) at the dose licensed for medical inpatients for the duration of the hospital admission. Although national guidance has recommended that LMWH is given for a minimum of seven days,[10] a survey of 25 UK exemplar centres suggests that the majority of hospitals give this treatment for the duration of hospital admission only,[22] which is typically five days.[23] It is assumed that the lowest cost preparation is prescribed and that 2.5 minutes of nursing time is required per dose administered. A scenario analysis was conducted to explore the impact of assuming a further two days of LMWH treatment after hospital discharge to achieve a minimum of seven days of thromboprophylaxis. Anticoagulant treatment for subsequent VTEs was assumed to be either phased anticoagulation (LMWH followed by warfarin) or direct oral anticoagulants; a 60:40 split was assumed, based on registry data,[24] with more widespread use of direct oral anticoagulants explored in a scenario analysis.

LMWH effectiveness was estimated by conducting a random effects meta-analysis of VTE outcomes from three studies giving a relative risk of VTE of 0.49 (95% confidence interval 0.37 to 0.67; online supplemental figure 4).[12–14] These studies were identified from a published review as being relevant, because they compared standard dose LMWH with placebo in medical inpatients and reported both pulmonary embolism and DVT outcomes, allowing the relative risk of VTE to be estimated.[10] The relative risk of major bleeding from these three studies was taken directly from a published review (relative risk 1.53, 95% confidence interval 0.8 to 2.92).[10]

Epidemiological parameters

Data on the absolute risks of DVT, fatal pulmonary embolism, non-fatal pulmonary embolism, fatal bleeding, non-fatal major bleeding (including intracranial haemorrhage), post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension were obtained from the literature.[8 11–14 25–34] Patients were assumed to have an increased risk of mortality compared with the general population in the year after hospital admission, in the first six years following intracranial haemorrhage and when experiencing chronic thromboembolic pulmonary hypertension.[35–39] The clinical parameters incorporated in the model are summarised in table 1, with further details provided in the appendix (online supplemental text 1 and table 1).

Resource use and costs

Costs were assessed from an NHS and Social Services in England perspective and are reported in pound sterling based on 2020 prices. Resource use and unit costs were based on standard NHS sources and published estimates, with historical estimates uplifted using standard healthcare specific inflation indices.[40–45] We assumed that any patient with VTE during their original medical admission would have their length of stay extended by a duration similar to the duration of admission for patients having VTE after discharge. Use of a RAM by a hospital physician was assumed to take 5 minutes. Costs applied in the model are summarised in table 2 with additional information on resource use in the appendix (online supplemental text 1 and tables 2–4).

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 on a scale of 0-1, where 1 represents full health and 0 represents a state equivalent to death. General population utility values were applied to those individuals not having any adverse clinical outcomes.[46] Lifelong utility decrements were applied following intracranial haemorrhage, pulmonary embolism, post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension. Reductions in utility were applied up to six months for those patients with DVT, for one month after other major bleeds (non-intracranial bleeds), and for the duration of thromboprophylaxis or anticoagulant treatment. Utility data applied in the model are summarised in table 2 with further details in online supplemental tables 5–7.[47–53]

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. As RAM performance was similar across the five models when evaluated in a single cohort, we used sensitivity and specificity estimates from one RAM (Padua) in the probabilistic sensitivity analysis. Rather than including the uncertainty in the sensitivity and specificity

Table 1 | Key clinical parameters incorporated in the decision analytical model to predict clinical outcomes for alternative thromboprophylaxis strategies in eligible medical inpatients*

Parameter description	Value (95% CI)
Absolute risk of VTE in 90 days after hospital admission, without thromboprophylaxis (%)	
Pulmonary embolism	1.38 (0.72 to 2.24)
Symptomatic DVT	2.02 (1.21 to 2.97)
Asymptomatic DVT	30.46 (16.90 to 50.87)
Absolute risk of VTE in 90 days after hospital admission, with thromboprophylaxis (low molecular weight heparin) (%)	
Pulmonary embolism	0.68 (0.34 to 1.18)
Symptomatic DVT	0.99 (0.54 to 1.63)
Asymptomatic DVT	14.93 (7.72 to 27.79)
Major bleed risk by type for medical inpatients without thromboprophylaxis (up to 90 days after admission) (%)	
Fatal major bleeding	0.10 (0.03 to 0.23)
Intracranial haemorrhage	0.06 (0.02 to 0.14)
Other major bleeding	0.51 (0.23 to 1.07)
Any major bleeding	0.67 (0.30 to 1.40)
Major bleed risk by type, for medical inpatients having thromboprophylaxis (up to 90 days after admission) (%)	
Fatal major bleeding	0.15 (0.07 to 0.26)
Intracranial haemorrhage	0.09 (0.03 to 0.16)
Other major bleeding	0.79 (0.50 to 1.14)
Any major bleeding	1.02 (0.65 to 1.47)
Major bleed risk by type, for patients having three months of anticoagulant treatment after VTE (%)	
Fatal major bleeding	0.21 (0.03 to 0.49)
Intracranial haemorrhage	0.08 (0.01 to 0.19)
Other major bleeding	0.56 (0.09 to 1.32)
Any major bleeding	0.85 (0.15 to 1.99)
Case fatality rate for pulmonary embolism (%)	26.8 (11.3 to 33.1)
Standardised mortality ratio *v* general population	
1 year following hospital admission	9.4 (8.9 to 10.0)
2-6 years following intracranial haemorrhage†	2.2 (1.8 to 2.7)
Cumulative 3 year risk of post-thrombotic syndrome for DVT (%)	
Symptomatic proximal location (treated)	32.4 (22.1 to 43.6)
Asymptomatic proximal location (untreated)	56.5 (36.5 to 73.8)
Distal location (symptomatic and treated, or asymptomatic and untreated)	15.6 (7.9 to 25.3)
Cumulative 2 year incidence of chronic thromboembolic pulmonary hypertension (%)	3.2 (2.0 to 4.4)

*Sources described in full in online supplemental table 1.

†Standardised mortality ratio for non-fatal intracranial haemorrhage in year after intracranial haemorrhage was 4.5, so the ratio for medical inpatients was applied in first year after intracranial haemorrhage.

CI, confidence interval; DVT, deep vein thrombosis; VTE, venous thromboembolism.

of this single model within the probabilistic sensitivity analysis, which is likely to under-represent the uncertainty related to RAM performance, the sensitivity and specificity values from the Padua RAM were fixed in the probabilistic sensitivity analysis and the uncertainty related to the sensitivity and specificity of RAMs was explored through scenario analysis. Details of the distributions assumed for each parameter included in the probabilistic sensitivity analysis can be found in online supplemental tables 1 and 7.

Scenario analyses

We explored the optimal balance between sensitivity and specificity by fitting a linear regression on the logit scale to the receiver operating characteristic curve for all RAMs evaluated in the cohort reported by Greene et al,[15] to identify the point on the curve that maximised cost effectiveness when valuing a QALY at either £20 000 (€23 440; $25 270) or £30,000; this range represents the threshold for cost effectiveness generally applied in England.[6]

To explore the impact of uncertainty in several key model estimates, we completed multiple specific scenario analyses. Given the heterogeneity in RAM performance (eg, sensitivity and specificity) across the studies (figure 1), we conducted a scenario analysis to explore whether the use of RAMs would be cost effective, if RAM performance was better than the typical performance reported by Greene et al.[15] For this analysis, we used estimates of RAM performance for the Padua RAM reported by Elias et al, in a study that recruited a mixed cohort of surgical and medical patients.[54] Post-thrombotic syndrome following asymptomatic distal DVT is also a potentially important outcome with uncertain incidence. We conducted a sensitivity analysis to determine whether the conclusions differed when assuming a zero incidence of post-thrombotic syndrome in patients with asymptomatic distal DVT. In addition, the utility decrement for post-thrombotic syndrome after DVT was not stratified by post-thrombotic syndrome severity, so we conducted a sensitivity analysis to determine whether the conclusions differed when assuming a smaller utility decrement for post-thrombotic syndrome (2% *v* 10%) estimated by combining registry data on the distribution of post-thrombotic syndrome severity with utility estimates stratified by post-thrombotic syndrome severity.[27 55] Considerable heterogeneity in the case fatality rate for pulmonary embolism was reported in the literature,[13 14 28–30] so a range of values (13-67%) were explored in sensitivity analyses. Sensitivity analyses were also conducted to explore the impact of assuming a higher or lower average risk for VTE and bleeding.

Patient and public involvement

The project team included four patient and public involvement members who contributed to the study design and ensured that patient and public values were reflected in the decision analytical modelling. This work included advice about the importance of capturing the utility decrement associated with

Table 2 | Summary of cost and utility parameters used in the decision analytical model comparing alternative thromboprophylaxis strategies in eligible medical inpatients*

Parameter description	Cost	Utility‡
Application of risk assessment model to patient	£9.08	Not applicable
Thromboprophylaxis†	£23.91	Decrement of 0.007 applied during thromboprophylaxis
Well patient without symptomatic VTE or major bleeding	NA	0.800 in year 1, with age adjustment thereafter
Symptomatic proximal DVT	£763.12	0.769 up to six months; decrement of 0.011 during anticoagulant treatment; beyond six months, multiplier applied only to those individuals with post-thrombotic syndrome
Symptomatic distal DVT	£642.95	
Non-fatal pulmonary embolism	£1848.75	0.768 up to six months; decrement of 0.011 during anticoagulant treatment; beyond 6 months, multiplier applied only to those individuals with chronic thromboembolic pulmonary hypertension
Fatal pulmonary embolism	£1517.13	0
Fatal bleed	£1865.51	0
Non-fatal, non-intracranial bleed	£1209.75	0.685 for one month after bleed
Non-fatal intracranial haemorrhage	£21 987.80 in first 90 days; £8292.83 per year thereafter	0.580 in first six months; multiplier of 0.888 thereafter
Post-thrombotic syndrome	£293.16 in year 1; £78.00 in each subsequent year	Multiplier of 0.895
Medically managed chronic thromboembolic pulmonary hypertension	£18 569.53 each year	Multiplier of 0.629
Surgically managed chronic thromboembolic pulmonary hypertension	£10 236.60 in year 1; £0 in year 2 onwards	Multiplier of 0.629

Costs are based on 2020 prices. £1 (€1.17; $1.26).

*Sources described in full in online supplemental tables 2–6.

†Five days of low molecular weight heparin (dalteparin) for medical inpatients, administered by a hospital nurse (band six).

‡An individual's health utility is a measure of health related quality of life on a scale of 0-1, where 1 represents full health and 0 represents a state equivalent to death.

DVT, deep vein thrombosis; NA, not applicable; VTE, venous thromboembolism.

LMWH injections and the suitability of RAMs. In addition, the modelling 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.

Results

Table 3 shows short and long term clinical outcomes per 10 000 patients when using sensitivity and specificity data for the Padua RAM from medical inpatients. Offering thromboprophylaxis to all medical inpatients results in a lower incidence of serious adverse outcomes (fatal pulmonary embolism, fatal bleeds, and non-fatal intracranial haemorrhages) than thromboprophylaxis for none (42 *v* 53 per 10

Table 3 | Predicted number of clinical outcomes per 10 000 eligible medical inpatients for each thromboprophylaxis strategy

	Outcomes at 6 months per 10 000 patients							Outcomes at 5 years per 10 000 patients				
Patient group offered thromboprophylaxis	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	Death (from any cause)
None	37	10	6	53	101	201	3041	787	2	83	5	1498
Padua ≥7†	36	10	6	54	98	196	2965	767	2	81	5	1497
Padua ≥6†	35	11	6	54	96	191	2893	749	2	79	5	1497
Padua ≥5†	33	11	6	56	91	181	2747	711	2	75	5	1495
Padua ≥4†	30	11	6	59	82	163	2469	639	2	68	5	1493
Padua ≥3†	28	12	7	62	75	150	2277	589	2	62	5	1491
Padua ≥2†	24	13	7	68	65	130	1975	511	1	54	6	1489
Padua ≥1†	20	14	8	75	53	106	1612	417	1	44	7	1487
All	18	15	9	79	49	98	1489	385	1	41	7	1486

*Patients having other major bleeds could also have deep vein thrombosis or non-fatal pulmonary embolism.

†Numbers denote Padua scores at which thromboprophylaxis is offered to patients; sensitivity and specificity data for each Padua score taken from Greene et al.[15]

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

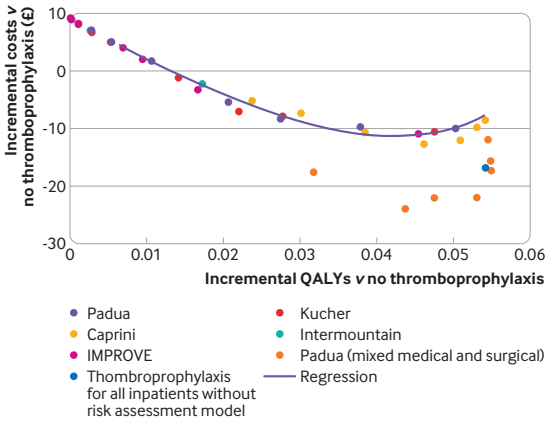

Figure 2 | Cost effectiveness plane for offering thromboprophylaxis in eligible medical inpatients according to five risk assessment models. All five models are validated in one cohort of medical inpatients,[15 18] and the Padua risk assessment model is also validated in another study with mixed cohort of medical and surgical patients.[54] £1=€1.17; $1.26. Costs are based on 2020 prices. QALY=quality adjusted life years

000). However, thromboprophylaxis for all medical inpatients also results in an increase in other major bleeds (79 *v* 53 per 10 000). The most common adverse outcome for patients in the long term was post-thrombotic syndrome.

Figure 2 shows the incremental costs and QALYs, compared with no thromboprophylaxis, that are expected to be achieved for the five RAMs evaluated in the cohort reported by Greene et al.[15] The multiple points presented for each study reflect the different cut-off scores available, each of which represents a different sensitivity and specificity profile. In addition, the line in figure 2 shows expected costs and QALYs for a typical RAM, based on the linear regression for RAM performance across these five RAMs. In general, a strategy of thromboprophylaxis for all medical inpatients dominates the alternative of using a RAM to determine thromboprophylaxis (ie, has both higher QALYs and lower costs) because QALY gains and cost savings from preventing VTE increase as the proportion of people receiving thromboprophylaxis increases and these gains/savings largely outweigh the additional costs of LMWH. Therefore, the point on the receiver operating characteristic curve that maximises QALY gains and cost savings would have a sensitivity of 100% and a specificity of 0%; this performance is the same as that for thromboprophylaxis for all medical inpatients, but with the added clinical cost of applying a RAM. In the secondary analysis, none of the estimates of model performance in other medical cohorts was sufficient to alter the conclusion that thromboprophylaxis for all medical inpatients is more cost effective than using RAMs (online supplemental figure 5). However, in the scenario analysis exploring higher estimates of model performance, using estimates from Elias et al[54] offering thromboprophylaxis to only patients with a Padua score of ≥3 was more cost effective than offering it to all patients—the high performance of the RAM in this particular study (99.9% sensitivity) meant that offering thromboprophylaxis to all medical inpatients resulted in additional patients being exposed to bleeding risks with no additional VTEs prevented.

Table 4 presents base case results from the probabilistic sensitivity analysis for the Padua RAM as an example of a typical RAM developed and validated in medical inpatients, although similar results are expected for the alternative models based on figure 2. The regression was not used for the probabilistic sensitivity analysis because it would have been necessary to have arbitrarily selected specific points on the curve to compare. Thromboprophylaxis for all medical inpatients was estimated to result in 0.0552 additional QALYs (95% credible interval 0.0209 to 0.1111) while generating cost savings of £28.44 (−£47 to £105). Thromboprophylaxis for all medical inpatients dominates no thromboprophylaxis in 79.1% of samples from the probabilistic sensitivity analysis, and we estimated a 99.8% probability that the incremental cost effectiveness ratio is under £20 000 per QALY. Table 4 also presents the results of the probabilistic sensitivity analysis for the scenario assuming higher RAM performance based on Elias et al.[54] In this scenario, offering thromboprophylaxis to only patients with a Padua score of ≥3 has a 76.6% probability of being the most cost effective strategy when valuing a QALY at £20 000, and a corresponding 79.8% probability when valuing a QALY at £30 000.

In sensitivity analyses (online supplemental table 8), thromboprophylaxis for all medical inpatients continued to dominate thromboprophylaxis for none when applying a lower utility decrement for post-thrombotic syndrome and when applying either a lower or higher case fatality rate for pulmonary embolism. The scenario analysis assuming all VTE events could be treated with direct oral anticoagulants had minimal impact on the results. When assuming no risk of post-thrombotic syndrome from asymptomatic DVT, thromboprophylaxis for all medical inpatients remained the most cost effective strategy (when valuing a QALY at £20 000), but it no longer resulted in lower costs, giving a cost per QALY of £2089 versus no thromboprophylaxis. Similarly, in the scenario analysis assuming that LMWH is administered for seven days, including two days after discharge, thromboprophylaxis for all medical inpatients remained the optimal strategy but had a cost per QALY of £1200 compared with no thromboprophylaxis.

Table 4 | Base case results and scenario analysis results for offering thromboprophylaxis in eligible medical inpatients according to the Padua risk assessment model (mean of 10 000 samples from probabilistic sensitivity analysis)

Patient group offered TPX‡	TPX (%)	Sensitivity (%)	Specificity (%)	Costs (£)	No of QALY	Incremental cost effectiveness ratio *v* previous non-dominated* strategy (£)
Base case results using performance data from a cohort of medical inpatients (Greene 2016)[15]						
None	0	0	100	244.93	9.0033	Dominated by TPX for all
Padua ≥7	3	5	98	251.40	9.0061	Dominated by TPX for all
Padua ≥6	6	10	96	249.09	9.0087	Dominated by TPX for all
Padua ≥5	12	19	91	244.81	9.0141	Dominated by TPX for all
Padua ≥4	23	37	84	235.91	9.0243	Dominated by TPX for all
Padua ≥3	35	49	73	231.70	9.0311	Dominated by TPX for all
Padua ≥2	57	69	49	227.79	9.0417	Dominated by TPX for all
Padua ≥1	86	92	17	224.43	9.0544	Dominated by TPX for all
All inpatients	100	100	0	216.49	9.0585	Dominates all other strategies
Scenario analysis using performance data from alternative study (Elias 2017)[54†]						
None	0	0	100	242.95	9.0031	Dominated by Padua ≥4
Padua ≥7	28	56	87	220.57	9.0351	Dominated by Padua ≥4
Padua ≥6	45	77	72	212.07	9.0471	Dominated by Padua ≥4
Padua ≥5	58	85	57	212.90	9.0510	Dominated by Padua ≥4
Padua ≥4	71	96	41	211.68	9.0567	Dominates TPX for none
Padua ≥3	84	100	24	215.49	9.0586	1918 *v* Padua ≥4
Padua ≥2	87	100	20	217.03	9.0586	Dominated by Padua ≥3
Padua ≥1	93	100	11	220.41	9.0583	Dominated by Padua ≥3
All inpatients	100	100	0	215.31	9.0580	Extendedly dominated

*An intervention is said to dominate another if it has lower costs and higher QALYs.
†Elias et al recruited a mixed cohort of medical and surgical patients rather than an exclusive medical cohort.[54]
‡Numbers denote Padua scores at which thromboprophylaxis is offered to patient
QALYs, quality adjusted life years; TPX, thromboprophylaxis.

The optimal strategy was relatively robust to changes in the baseline risks of symptomatic VTE and major bleeding, with thromboprophylaxis for all medical inpatients remaining optimal until the risk of VTE was reduced sixfold (from 3.4% to 0.6%) or the risk of bleeding was increased sixfold (from 0.67% to 4.00%). However, thromboprophylaxis for all medical inpatients was no longer a cost saving strategy when the VTE risk halved or the bleeding risk doubled, giving incremental cost effectiveness ratios of £915 per QALY and £426 per QALY, respectively. Two-way sensitivity analysis identified that the optimal strategy was no longer thromboprophylaxis for all medical inpatients when a threefold increase in bleeding risk (2.00%) was combined with a halving of VTE risk (1.7%). If considering only the balance of benefits and harms, thromboprophylaxis for all medical inpatients would result in QALY losses compared with no thromboprophylaxis, in a cohort with a 1.7% risk of symptomatic VTE and a 4% risk of major bleeding without thromboprophylaxis.

Discussion

Principal findings

Offering pharmacological thromboprophylaxis to all eligible medical inpatients appears to be more cost effective than using existing RAMs to target thromboprophylaxis at higher risk patients, owing to the weak predictive performance of existing RAMs. However, scenario analysis suggested that using a high sensitivity RAM to select low risk patients who could avoid thromboprophylaxis might be cost effective, if such a RAM could be developed and validated.

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 risk in the medical inpatient population. The conclusion that thromboprophylaxis for all medical inpatients is optimal is fairly robust to the changes explored in the scenario and sensitivity analyses. Furthermore, our findings that thromboprophylaxis for all eligible medical inpatients appears dominant renders moot further complex discussions on the appropriate threshold for prescribing.

The inherent value for any clinical decision rule guiding treatment is based entirely on whether it can outperform generic prescribing; given that thromboprophylaxis for all medical inpatients dominated a variety of threshold values with differing sensitivity and specificity characteristics, the discussion on who selects appropriate thresholds for prescribing becomes obsolete. Overall, our findings suggest that it might be better to move towards a default strategy of offering thromboprophylaxis to all eligible medical

inpatients. This strategy would be a change from the current system of using RAMs to select higher risk groups for thromboprophylaxis (opt-in).

A cost effectiveness analysis from a US health system perspective found that LMWH is cost effective for medical inpatients when the risk of VTE is over 1%.[7] Le et al discussed the use of RAMs to identify patients with a risk lower than 1%, but did not explicitly model the cost effectiveness of this strategy by taking into account the performance of specific RAMs.[7] Furthermore, the US analysis only included patients with pulmonary embolism and symptomatic proximal DVTs in the model; therefore, the results would not be expected to be comparable with our model, which includes both distal DVT and asymptomatic proximal DVT.

Limitations of the study

A key limitation of our analysis is the heterogeneity in the estimates of RAM performance across the various cohorts. Owing to this heterogeneity, the uncertainty in the performance of RAMs was explored through scenario analysis, rather than incorporating the precision for a single RAM within the probabilistic sensitivity analysis. In the scenario analysis exploring estimates of model performance from an alternative study, the optimal strategy was to use a RAM rather than to offer thromboprophylaxis for all medical inpatients. This change in the optimal strategy was because Elias et al reported a sensitivity of 99.9% and a specificity of 23.7% for a Padua score of ≥3, resulting in 84% of patients receiving thromboprophylaxis.[54] These findings likely overestimate sensitivity and are in contrast to the sensitivity and specificity values reported by Greene et al for a Padua score of ≥3 in an exclusively medical cohort, which were 49.3% and 73.0%, respectively.[15] This heterogeneity could reflect differences in the calibration performance of the RAM, whereby patients with a Padua score <3 have a much lower absolute VTE risk in the Elias et al cohort, owing to the mix of medical and surgical patients.

Using a poorly calibrated model might be more harmful than adopting an approach of thromboprophylaxis for all medical inpatients, if it underpredicts VTE risk in patients who are then advised to forgo thromboprophylaxis.[56] These findings suggest that a RAM would need to be well calibrated and have a high sensitivity to be more cost effective than a strategy of thromboprophylaxis for all and even then, would still likely result in a very high proportion of patients receiving thromboprophylaxis. The Department of Health's model for assessing VTE risk, which has not been validated but has been widely used in the NHS since 2010, results in over 70% of medical inpatients in the UK receiving thromboprophylaxis, with some trusts offering thromboprophylaxis to over 90% of medical inpatients.[10] This high usage of thromboprophylaxis could be one of the reasons for the reported national improvement in outcome, regarding reduction in post-admission mortality attributable to VTE.[57]

Other limitations include the potential regular use of antiplatelet treatment in a proportion of this cohort and the increasing use of weight adjusted dosing for LMWH agents.[21] Our key RAM validation studies did not report on single or dual antiplatelet use at baseline, or on weight adjusted dosing of LMWH. As such, we are unable to comment on whether these treatments have any specific incremental impact on VTE and bleeding risk, and our findings should be applied with caution to these groups. In addition, our findings do not evaluate the use of RAMs in patients on any kind of baseline anticoagulant drug treatment and should not be applied to these groups; furthermore, patients receiving anticoagulation treatment are already established on pharmacological thromboprophylaxis, so do not require additional risk assessment. Of note, the costs of one dose of LMWH are essentially identical across weight bands[42]; we therefore do not believe that use of weight adjusted LMWH thromboprophylaxis would substantially affect the results of the model, unless this strategy can be proven to reduce VTE event rates compared with a standard dosing regimen.

One key issue with studies of RAM performance is that the routine use of thromboprophylaxis within observational cohorts could lead to the performance of these models being underestimated, because the VTE events that would have occurred in higher risk patients are prevented by thromboprophylaxis. The estimates of performance from the study by Elias et al were taken from the subset of patients not receiving thromboprophylaxis, which might partly explain the higher estimate of sensitivity and specificity, although Elias and colleagues reported that the performance was similar in the subset of patients receiving thromboprophylaxis.[54] Given that the available data suggest that widespread use of pharmacological thromboprophylaxis is both beneficial to patients and is cost effective, future studies are likely to involve cohorts with widespread use of thromboprophylaxis, thus 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.

Conclusion

We found that pharmacological thromboprophylaxis for all eligible medical inpatients is expected to have lower costs and greater health benefits compared with

selective thromboprophylaxis based on currently available models assessing the risk of venous thromboembolism. 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 medical inpatients can safely forego thromboprophylaxis, rather than who should commence it.

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Contributors SD developed the decision analytical model and conducted the cost effectiveness analysis. AP and DH conducted the systematic reviews that informed the modelling. SG, DH, KdW, MH, XLG, and BH were members of the expert clinical group that informed development of the decision analytical 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. SD is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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REFERENCES

1 Jordan Bruno X, Koh I, Lutsey PL, *et al*. Venous thrombosis risk during and after medical and surgical hospitalizations: the medical inpatient thrombosis and hemostasis (MITH) study. J Thromb Haemost 2022;20:1645–52. 10.1111/jth.15729
2 Dentali F, Douketis JD, Gianni M, *et al*. Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. Ann Intern Med 2007;146:278–88. 10.7326/0003-4819-146-4-200702200-00007
3 Pandor A, Tonkins M, Goodacre S, *et al*. Risk assessment models for venous thromboembolism in hospitalised adult patients: a systematic review. BMJ Open 2021;11:e045672. 10.1136/bmjopen-2020-045672
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. 10.1186/2193-1801-1-60
5 Beck MJ, Haidet P, Todoric K, *et al*. Reliability of a point-based VTE risk assessment tool in the hands of medical residents. J Hosp Med 2011;6:195–201. 10.1002/jhm.860
6 The National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. NICE process and methods guides. London, UK The National Institute for Health and Care Excellence; 2013.
7 Le P, Martinez KA, Pappas MA, *et al*. A decision model to estimate a risk threshold for venous thromboembolism prophylaxis in hospitalized medical patients. J Thromb Haemost 2017;15:1132–41. 10.1111/jth.13687
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 (UK); 2010.
9 Pandor A, Horner D, Davis S, *et al*. Different strategies for pharmacological thromboprophylaxis for lower-limb Immobilisation after injury: systematic review and economic evaluation. Health Technol Assess 2019;23:1–190. 10.3310/hta23630
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, UK: National Institute for Health and Care Excellence, 2018.
11 Barbar S, Noventa F, Rossetto V, *et al*. A risk assessment model for the identification of hospitalized medical patients at risk for venous

thromboembolism: the padua prediction score. J Thromb Haemost 2010;8:2450–7. 10.1111/j.1538-7836.2010.04044.x
12 Lederle FA, Sacks JM, Fiore L, *et al*. The prophylaxis of medical patients for thromboembolism pilot study. Am J Med 2006;119:54–9. 10.1016/j.amjmed.2005.03.049
13 Leizorovicz A, Cohen AT, Turpie AGG, *et al*. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 2004;110:874–9. 10.1161/01.CIR.0000138928.83266.24
14 Samama MM, Cohen AT, Darmon JY, *et al*. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med 1999;341:793–800. 10.1056/NEJM199909093411103
15 Greene MT, Spyropoulos AC, Chopra V, *et al*. Validation of risk assessment models of venous thromboembolism in hospitalized medical patients. Am J Med 2016;129:1001. 10.1016/j.amjmed.2016.03.031
16 Blondon M, Spirk D, Kucher N, *et al*. Comparative performance of clinical risk assessment models for hospital-acquired venous thromboembolism in medical patients. Thromb Haemost 2018;118:82–9. 10.1160/TH17-06-0403
17 Woller SC, Stevens SM, Jones JP, *et al*. Derivation and validation of a simple model to identify venous thromboembolism risk in medical patients. Am J Med 2011;124:947–954. 10.1016/j.amjmed.2011.06.004
18 Grant PJ, Greene MT, Chopra V, *et al*. Assessing the caprini score for risk assessment of venous thromboembolism in hospitalized medical patients. Am J Med 2016;129:528–35. 10.1016/j.amjmed.2015.10.027
19 Blondon M, Righini M, Nendaz M, *et al*. External validation of the simplified Geneva risk assessment model for hospital-associated venous thromboembolism in the padua cohort. J Thromb Haemost 2020;18:676–80. 10.1111/jth.14688
20 Rothberg MB, Lindenauer PK, Lahti M, *et al*. Risk factor model to predict venous thromboembolism in hospitalized medical patients. J Hosp Med 2011;6:202–9. 10.1002/jhm.888
21 Thrombosis UK. National thrombosis survey. London, UK, 2021.
22 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. 10.1111/bjh.16010
23 NHS Digital. Hospital admitted patient care activity 2018-2019. Leeds, UK: NHS Digital, 2019.
24 Cohen AT, Gitt AK, Bauersachs R, *et al*. The management of acute venous thromboembolism in clinical practice. results from the European PREFER in VTE registry. Thromb Haemost 2017;117:1326–37. 10.1160/TH16-10-0793
25 Decousus H, Tapson VF, Bergmann J-F, *et al*. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. Chest 2011;139:69–79. 10.1378/chest.09-3081
26 Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, *et al*. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. Eur Respir J 2017;49:1601792. 10.1183/13993003.01792-2016
27 Hach-Wunderle V, Bauersachs R, Gerlach HE, *et al*. 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. 10.1016/j.jvsv.2012.07.003
28 Harenberg J, Roebruck P, Heene DL. Subcutaneous low-molecular-weight heparin versus standard heparin and the prevention of thromboembolism in medical inpatients. Haemostasis 1996;26:127–39. 10.1159/000217198
29 Hull RD. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. Ann Intern Med 2010;153:8. 10.7326/0003-4819-153-1-201007060-00004
30 Kleber FX, Witt C, Vogel G, *et al*. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. Am Heart J 2003;145:614–21. 10.1067/mhj.2003.189
31 Kooiman J, van Hagen N, Iglesias Del Sol A, *et al*. 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. 10.1371/journal.pone.0122520
32 Nieto JA, Solano R, Ruiz-Ribó MD, *et al*. Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: findings from the RIETE registry. J Thromb Haemost 2010;8:1216–22. 10.1111/j.1538-7836.2010.03852.x
33 Pengo V, Lensing AWA, Prins MH, *et al*. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004;350:2257–64. 10.1056/NEJMoa032274
34 van Dongen CJJ, Prandoni P, Frulla M, *et al*. Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome. J Thromb Haemost 2005;3:939–42. 10.1111/j.1538-7836.2005.01333.x
35 Delcroix M, Lang I, Pepke-Zaba J, *et al*. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. Circulation 2016;133:859–71. 10.1161/CIRCULATIONAHA.115.016522
36 Fogelholm R, Murros K, Rissanen A, *et al*. Long term survival after primary intracerebral haemorrhage: a retrospective population based study. J Neurol Neurosurg Psychiatry 2005;76:1534–8. 10.1136/jnnp.2004.055145
37 Goodacre S, Horspool K, Shephard N, *et al*. 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. 10.3310/hta22470
38 Moore E, Munoz-Arroyo R, Schofield L, *et al*. Death within 1 year among emergency medical admissions to Scottish hospitals: incident cohort study. BMJ Open 2018;8:e021432. 10.1136/bmjopen-2017-021432
39 Office of National Statistics. National life tables, England 1980-82 to 2016-18. London, UK: Office for National Statistics, 2019.
40 Curtis LA, Amanda B. Unit costs of health and social care 2019. Canterbury, UK: Personal Social Services Research Unit, 2019.
41 Curtis LA, Burns A. Unit costs of health and social care 2017. Canterbury, UK: Personal Social Services Research Unit, 2017.
42 Joint Formulary Committee. British national formulary. [Drug Tariff]. London, UK;
43 Luengo-Fernandez R, Yiin GSC, Gray AM, *et al*. Population-based study of acute- and long-term care costs after stroke in patients with AF. Int J Stroke 2013;8:308–14. 10.1111/j.1747-4949.2012.00812.x
44 Menakaya CU, Pennington N, Muthukumar N, *et al*. The cost of outpatient venous thromboembolism prophylaxis following lower limb injuries. Bone Joint J 2013;95-B:673–7. 10.1302/0301-620X.95B5.30555
45 NHS Improvement. National cost collection: national schedule of NHS costs - year 2018-19 - NHS trust and NHS foundation trusts. London, UK; 2020.
46 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. 10.1016/j.jval.2010.10.029
47 Chuang L-H, Gumbs P, van Hout B, *et al*. 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. 10.1007/s11136-019-02175-z
48 Enden T, Wik HS, Kvam AK, *et al*. 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. 10.1136/bmjopen-2013-002984
49 Lubberts B, Paulino Pereira NR, Kabrhel C, *et al*. 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. 10.1160/TH16-02-0152
50 Luengo-Fernandez R, Gray AM, Bull L, *et al*. Quality of life after TIA and stroke: ten-year results of the oxford vascular study. Neurology 2013;81:1588–95. 10.1212/WNL.0b013e3182a9f45f
51 Marchetti M, Pistorio A, Barone M, *et al*. Low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous thromboembolism: a cost-effectiveness analysis. Am J Med 2001;111:130–9. 10.1016/s0002-9343(01)00793-8
52 Meads DM, McKenna SP, Doughty N, *et al*. The responsiveness and validity of the CAMPHOR utility index. Eur Respir J 2008;32:1513–9. 10.1183/09031936.00069708
53 Monreal M, Agnelli G, Chuang LH, *et al*. Deep vein thrombosis in Europe-health-related quality of life and mortality. Clin Appl Thromb Hemost 2019;25:1076029619883946. 10.1177/1076029619883946
54 Elias P, Khanna R, Dudley A, *et al*. 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. 10.12788/jhm.2714
55 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. 10.1136/jamia.1997.0040049
56 Van Calster B, Vickers AJ. Calibration of risk prediction models: impact on decision-analytic performance. Med Decis Making 2015;35:162–9. 10.1177/0272989X14547233
57 Hunt BJ. Preventing hospital associated venous thromboembolism. BMJ 2019;365:l4239. 10.1136/bmj.l4239

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Decision-analysis modelling of effectiveness and cost-effectiveness of thromboprophylaxis for medical inpatients – Supplementary materials

Appendix

Text 1: Additional details on epidemiological parameters, resource use and utilities

The absolute risk of symptomatic VTE in patients not receiving thromboprophylaxis was taken from the risk reported in a prospective observational study by Barbar et al., which was the derivation study for the Padua RAM, using data from the subset not receiving thromboprophylaxis (80% of the cohort). [1] This was considered preferable to using data from the placebo arms of RCTs due to the selective nature of recruitment for RCTs and the age of the studies. The ratio of asymptomatic to symptomatic

DVTs (604:40) and proportion of DVTs that are proximal (31%) were taken from a published model used to inform previous NICE guidance on VTE prevention in hospitalised patients.[2] VTEs are assumed to occur at 42 days post-admission based on data from Barbar et al.[1] The absolute risk of major bleeding during thromboprophylaxis was estimated across the thromboprophylaxis arms of the three RCTs used to estimate the RR of bleeding.[3-5] Bleeds during prophylaxis are assumed to occur half-way through prophylaxis (i.e. 2.5 days). Data from the IMPROVE registry was used to determine the proportions of major bleeds occurring in medical inpatients that are fatal, non-fatal ICH and other major bleeds.[6] The absolute risk of bleeding during anticoagulant treatment, and the proportion of bleeds that are fatal, non-fatal ICH and other major bleeds was based on registry studies in patients having treatment for VTE.[7, 8] The cumulative risk of PTS was also based on a registry study.[9] A study which examined the relationship between PTS and adequate anticoagulation following DVT was used to adjust the risk of PTS in patients with asymptomatic proximal DVT, which is assumed to remain undiagnosed and untreated.[10] The two-year risk of CTEPH in patients surviving three to six months after PE was taken from a systematic review.[11] Based on a prospective study with 10-year follow-up, we assumed that no new case of CTEPH would be diagnosed more than two years after PE.[12] The proportion of patients having medical or surgical management of CTEPH and the long-term survival in each group was taken from a registry study.[13] Patients not having CTEPH, ICH, fatal PEs or fatal bleeds were assumed to have mortality risks equivalent to the general population,[14] except in the first year after hopsital admission where a standardised mortality ratio (SMR) is applied (SMR = 9.4) to reflect the increased mortality risk in the year following a hospital admission.[15] An increased risk of mortality was applied in the first six years following haemorrhagic stroke based on estimates from a retrospective study.[16] The case-fatality rate following PE in medical inpatients (26.8%) was estimated using data from five RCTs,[4, 5, 17-19] identified from a published review, which reported both fatal and non-fatal PE incidence for any thromboprophylaxis or placebo arm.[2]

During the decision tree phase of the model, absolute utility values are applied, with patients who are well having general population utility values and all other patients having values applied according to the adverse consequences experienced (DVT, PE, ICH and non-ICH major bleeds). For PE and DVT, these are applied from the time these are experienced until the end of the decision tree model (i.e. up to six months) whereas non-ICH major bleeds are assumed only to have an adverse impact on utility for one month. In addition, absolute utility decrements are applied during thromboprophylaxis to reflect patients' wishes to avoid daily injections and during anticoagulant treatment to reflect patients' wishes to avoid long-term anticoagulation with warfarin. Patients having ICH were assumed to have reduced HRQoL life-long with separate utility values in the short and long-term models. During the

Markov model phase (i.e beyond six months), patients without long-term sequelae or ongoing symptoms (ICH, PTS, PE with CTEPH, or PE without CTEPH) have general population levels of utility which vary with age, based on UK population norms,[20] and those with sequelae or ongoing symptoms have utility multipliers applied which reduce their utility by a fixed proportion relative to the general population level for their age (e.g. multiplier of 0.888 for ICH reduces age-adjusted utility by 11.2%). DVT without PTS was assumed not to result in any HRQoL reduction beyond six months. Patients having successful surgical treatment of CTEPH were assumed to have the same HRQoL as those with PE without CTEPH after one year.

The previous model on thromboprophylaxis in lower limb immobilisation used utility estimates for PE and DVT from the PREFER-VTE registry study.[21] Updated utility values from the PREFER-VTE registry study were identified in the published literature and these were used to calculate utility multipliers for PE and DVT relative to age /gender matched general population estimates.[22, 23] These were used in preference to the previous values as the updated utility estimates were provided separately for patients with and without cancer allowing the impact of VTE independent of cancer to be estimated. For PE, the utility values compared favourably to general population utility values between six and 12 months, therefore the midpoint utility values applied was 1 with a sampled range of 0.998 to 1.000 applied in the PSA. The assumption applied previously, that utility in the month following a non-fatal non-intracranial major bleed would be similar to utility in the first month after PE, was maintained but the multiplier was updated to use utility in the month after PE from the newly the published estimates from PREFER-VTE. The utility estimates applied for other health states (ICH, CTEPH, PTS) were the same as used in the previous published model for thromboprophylaxis following lower limb injury including the disutility applied for thromboprophylaxis and anticoagulant treatment of VTE.[24-27]

Drug costs were based on the NHS Drug Tariff.[28] In the scenario analysis on giving seven days of thromboprophylaxis, resource use associated with post-discharge administration was based on a published estimate by Menakaya *et al.* [29] This study was also used to estimate the cost of LMWH during phased anticoagulant treatment. Monitoring costs were also included for those receiving either warfarin or DOACs. For DOACs these consisted of one nurse led telephone follow-up at 10 days and one consultant led follow-up at three months to assess need for ongoing treatment. For warfarin, follow-up was assumed to consisted of nine face-to-face visit at non-consultant led anticoagulation service over three months plus a consultant led follow-up at three months to assess need for ongoing treatment.

Resource use in patients experiencing a VTE, including GP and Emergency Department (ED) attendance, diagnostics tests and emergency admission, was based on clinical expert opinion using assumptions applied in a previous model for patients having outpatient thromboprophylaxis during lower limb immobilisation.[21] Unit costs for these and for fatal bleeds, non-fatal ICH, non-ICH bleeds, PTS and CTEPH were based on 2018/19 NHS reference costs,[30] or national estimates of unit costs for staff time.[31] Exceptions to this were that the costs of fatal bleeds, non-fatal ICHs and the cost of medical treatment for CTEPH were based directly on published sources.[2, 32] Historical prices used as model inputs were uplifted using the hospital and community health services (HCHS) pay and prices index up to 2016 prices[33] and the NHS cost Inflation Index (NHSCII) thereafter.[31]

Text 2: Additional details on the regression to estimate typical RAM performance

Appendix Figure 3 shows the regression of logit(sensitivity) against logit(1-sensitivity) which was used to estimate the performance of a typical RAM in a cohort of medical inpatients. The data points were taken from five RAMs evaluated in a single cohort of medical inpatients,[34, 35] using a range of thresholds to determine the trade-off between sensitivity and specificity. The model was run deterministically for pairs of sensitivity / specificity estimates taken from multiple points along this curve to generate the estimates of costs and QALYs plotted as the dashed line denoted as 'Regression' on Figure 2 and Appendix Figure 5.

Appendix Table 1: Clinical parameters (including probabilistic distributions)

Parameter description	Midpoint value	Uncertainty measure	Distribution	Source
Probability of PE in medical inpatients	1.38%	95% CI 0.7% to 2.2%	Beta(13,929)	Barbar 2010[1]
Probability of symptomatic DVT in medical inpatients	2.02%	95% CI 1.2% to 3.0%	Beta(19,923)	Barbar 2010[1]
Proportion of all DVTs that are symptomatic	6.21%	95% CI 4.4% to 8.2%	Beta(40,604)	CG92[2]
Proportion of DVTs that are distal (same proportion applied for symptomatic and asymptomatic DVTs)	69%	95%CI 67% to 71%	=1-Beta(1991,32713)/Beta(6467,28789)	CG92[2] reports that 31% of all DVTs were proximal as estimated from the RCTs in their review that reported the incidence of both: (1,991/34,704)/(6,467/35,256)=(6%/18%)=31%
Effectiveness of prophylaxis in acutely ill medical inpatients – Risk ratio (RR) for VTE	0.49	95% CI 0.37 to 0.67	Lognormal (-0.40,0.15)	Meta-analysis of VTE events in the three RCTs[3-5] included in NG89[36] for LMWH (standard dose / standard duration) versus placebo in acutely ill medical patients (see Appendix Figure 4)
Risk of major bleeding for PPX in medical inpatients	1.02%	95CI 0.65% to 1.47%	Beta(23,2236)	Incidence of bleeding across the LMWH arms of three RCTs which reported bleeding risk in the systematic review of LMWH versus placebo for acutely ill medical inpatients reported in NG89[36]
Proportion of major bleeding during PPX that is fatal for medical inpatients	14%	95% CI 8% to 23%	Beta(12,71)	Bleeds occurring within 14 days of hospitalisation for medical inpatient (minimum length of stay of three days) from IMPROVE registry – average across cohort regardless of use of PPX or not[6]

Proportion of non-fatal major bleeding during PPX that is ICH for medical inpatients	10%	95% CI 4% to 18%	Beta(7,64)	Bleeds occurring within 14 days of hospitalisation for medical inpatient (minimum length of stay of three days) from IMPROVE registry – average across cohort regardless of use of PPX or not[6]
Relative risk of bleeding for prophylaxis versus none in medical inpatients – HR	1.53	95% CI 0.90 to 2.53	Lognormal (0.43,0.33)	Meta-analysis of VTE events in the three RCTs included in NG89 for LMWH (standard dose / standard duration) versus placebo in acutely ill medical patients[36]
Risk of bleeding during three month anticoagulant treatment for VTE	0.8%	95% CI 0.2% to 2.0%	Beta(3,352)	Six-month incidence pooled across patients with HAS-BLED score of zero or one from Kooiman et al.[7]
Proportion of major bleeds during VTE treatment that are fatal	25%	95% CI 21% to 28%	Beta(135,411)	Based on case-fatality rates for major bleeds within the RIETE registry[8]
Proportion of non-fatal major bleeds during VTE treatment that are ICH	9%	95% CI 6.5% to 11.9%	Beta(37,374)	Based on proportion of major non-fatal bleeds within RIETE registry that were ICH (Nieto *et al.*) [8]
All-cause (non VTE related) mortality for general population not in hospital	Varies by age	Assumed fixed	Not applicable	ONS lifetables[14] Risk applied each year is based on current age and is not adjusted to account for contribution of VTE to population mortality.
SMR for deaths in emergency medical inpatients in year after admission compared with deaths in age and sex matched general population	9.43	Ratio of two sampled death rates 11.7 (95%CI 11.6 to 11.8) in general population	Norm(11.7,0.05)	Moore 2018[15]

		108 (95%CI 104.4 to 116.5) in hospitalised medical patients	Norm(108,3.09)	
SMR for patients surviving ICH compared with general population				SMR from Fogelholm *et al* (2005)[16] applied for years two to six and then assumed no increased mortality risk
– year one after ICH	NA	Same as for all hospitalised patients		Increased risk in year after ICH is assumed to be the same as for all hospital inpatients as the SMR for ICH is lower than for the SMR for all medical inpatients
- years two to six after ICH	- 2.2	95% CI 1.8 to 2.7	Log(SMR) = norm(0.8,0.1)	Confidence intervals around SMR not reported so have assumed ±20% on the log scale
Probability of PE being fatal in general medical inpatients	26.8%	95% CI 11.3% to 33.1%	Beta(11,30)	Average case-fatality rate across five RCTs[4, 5, 17-19] reporting both PE and fatal PE incidence in NG89[36]
Cumulative risk of PTS for treated symptomatic DVT at three years				Cumulative incidence at three years based on the TULIPA PLUS registry.[9] Distribution of risk across years one to three based on van Dongen 2005 *et al.*[10] Zero risk assumed from year four onwards
- proximal	- 32.4%	- 95% CI 22.1% to 43.6%	Beta(23,48)	
- distal	- 15.6%	- 95% CI 7.9% to 25.3%	Beta(10,54)	
OR for PTS in asymptomatic untreated proximal DVT versus treated proximal DVT	2.71	95% CI 1.44 to 5.1	Log(OR) = norm(0.99, 0.32)	OR from van Dongen *et al.* [10] OR applied to risk for treated asymptomatic DVT to get incidence at three years of 56.6% for proximal

				[this gives a PTS risk of 56.5% (95%CI 29.0% to 79.8%) in asymptomatic untreated proximal DVT]
OR for PTS in asymptomatic distal DVT	1	Fixed	Not applicable	Assumed no increased risk for asymptomatic in distal DVT.
Incidence of CTEPH at two years (converted to annual risk of 1.6%)	3.2%	95% CI 2.0 % to 4.4%	Beta(32,967)	Ende-Verhaar *et al.* [11]based on incidence in those surviving the initial treatment period of three to six months Assumed no risk beyond two years based on Pengo *et al.* [12]
Proportion of CTEPH treated surgically	59.5%	95% CI 55.8% to 63.2%	Beta(404,275)	Delcroix *et al.* [13]
Proportion of CTEPH that are surgically treated who also received bridging medical care	30.0%	95% CI 24.6% to 33.5%	Beta(117, 287)	Delcroix *et al.* [13]
Mean hazard for exponential survival curve in medically treated patients with CTEPH	0.1168	SE = 0.0123	Norm(0.1168, 0.0123)	Original data from Delcroix *et al.* but curves taken from Goodacre *et al.* [13, 37] (If the death hazard falls below general population values then general population values apply)
Mean and SD for lognormal survival curve in surgically treated patients with CTEPH	Mean = 5.08 SD = 3.34	SE of mean = 0.574 SE of SD = 0.399	Multivariate normal	Original data from Delcroix *et al.* but curves taken from Goodacre *et al.* [13, 37] (If the death hazard falls below general population values then general population values apply) Variance – covariance matrix Mean log SD log

				Mean log	0.017708	-0.05572
				SD log	-0.05572	0.230935
Age Age x Age Constant	-0.000172 -0.000034 0.9584588	SE=0.0003737 SE=3.96 x 10^{-6} SE = 0.0077431	Multivariate normal			

Abbreviations: CI, confidence interval; CG, clinical guideline; CTEPH, chronic thromboembolic pulmonary hypertension; CODA, convergence diagnostics and output analysis; DVT, deep vein thrombosis; GI, gastrointestinal; ICH, intracranial haemorrhage; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; ONS, Office for National Statistics; OR, odds ratio; PSA, probabilistic sensitivity analysis; PE, pulmonary embolism; PTS, post-thrombotic syndrome; RAM, risk assessment model; RIETE, Computerized Registry of Patients with Venous Thromboembolism;RCT, randomised controlled trial; SD, standard deviation; SE, standard error; SMR, standardised mortality ratio; TULIPA PLUS, Thrombosis and Pulmonary Embolism in Out-Patients – plus; VTE, venous thromboembolism.

Appendix Table 2: Summary of cost parameters

Parameter description	Mean value	95% CI *	Source	Notes
Application of RAM to patient	£9.08	Fixed	Curtis *et al.* [31]	Cost for five minute of hospital consultant time
Prophylaxis for medical – five days of LMWH (Dalteparin) administered by hospital nurse	£23.91	NA	Admin costs from Curtis *et al.* [31] Drug costs based on Drug Tariff [28]	Dalteparin is lowest cost formulation of LMWH based on current Drug Tariff prices. [28]
Treatment of symptomatic proximal DVT	£763.12	£748.04 to £795.10	NHS reference costs[30] Drug Tariff[28]	Clinical expert discussion regarding likelihood resource use, combined with NHS reference cost data for healthcare contacts and drug tariff costs for treatments (see Appendix Table 4 for more detailed costing breakdown).
Treatment of symptomatic distal DVT	£642.95	£621.76 to £668.61	NHS reference costs[30] Drug Tariff [28]	Clinical expert discussion regarding likelihood resource use, combined with NHS reference cost data for healthcare contacts and drug tariff costs for treatments (see Appendix Table 4 for more detailed costing breakdown)
Treatment of non-fatal PE	£1,848.75	£1,816.98 to £1,884.53	NHS reference costs[30] Drug Tariff [28]	Clinical expert discussion regarding likelihood resource use, combined with NHS reference cost data for healthcare contacts and drug tariff costs for treatments

				(see Appendix Table 4 for more detailed costing breakdown)
Fatal PE	£1,517.13	£1,491.37 to £1,542.99	NHS reference costs[30]	As per non-fatal minus drug therapy for PE
Fatal bleed	£1,865.51	£678.86 to £3698.12	Luengo-Fernandez *et al.* [32]	Costs of fatal haemorrhagic stroke from OXVASC subgroup with atrial fibrillation. Uplifted to current prices using inflation indices
Non-fatal non-ICH bleed	£1,209.75	£1199.79 to £1220.07	NHS reference costs [30]	Weighted average of reference costs for gastrointestinal bleed (HRG codes FZ38G – FZ38P)
Post non-fatal ICH - first 90 days	£21,987.80	£17,413.48 to £27,302.45	Luengo-Fernandez *et al.*[32]	Weighted average of costs for non-fatal haemorrhagic strokes Uplifted to current prices using inflation indices
Post non-fatal ICH - post acute (beyond 90 days) costs per annum	£8,292.83	£5,57.42 to £11,613.69	Luengo-Fernandez *et al.* [32]	Average costs across all stroke types (haemorrhagic not reported separately). Includes GP and ED costs and long-term care cost Uplifted to current prices using inflation indices
PTS cost per annum – year one -Mild/moderate	£293.16 in year one	£279.90 to £306.40	NHS reference costs [30]	One first and one follow-up vascular surgery outpatient appointments

-severe				Weighted average of consultant led and non-consultant led outpatient appointments for non-admitted face-to-face first attendance (WF01B) and follow-up (WF01A) for vascular surgery (service code 107)
PTS cost per annum – year two -Mild/moderate -severe	£78.00 in each subsequent year	Fixed	Curtis *et al.* [31]	2 x GP surgery consultations with qualification costs including direct care staff costs at £37 per appointment
CTEPH cost per annum - Medically managed	£18,569.53 each year	Fixed	NICE CG92[2]	Cost in CG92 was £1,219 per four weeks in 2008/09 prices. This was uplifted to 2018/19 prices using inflation indices. Assume treatment lifelong
CTEPH cost per annum - Surgically managed	£10,236.60 in year one and zero in year two onwards	£9,932.52 to £10,557.20	NHS reference costs [30]	Average of DZ02H, DZ02J and DZ02K "Complex thoracic procedures" relating to procedure code L041 "Pulmonary thromboendodartectomy" for elective inpatients including excess bed days In addition, 29% of surgically treated patients require medical bridging therapy for 4.6 months (average cost £1992)

CI, confidence interval; CG, clinical guideline; CTEPH, chronic thromboembolic pulmonary hypertension; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ED, emergency department; GI, gastrointestinal; GP, general practitioner; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; HR, hazard ratio; HRG, healthcare resource group; ICH, intracranial haemorrhage; LMWH, low molecular weight heparin; LTRiP(cast), Leiden–Thrombosis Risk Prediction for patients with cast immobilisation score; NHS, national health service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; ONS, Office for National Statistics; OR, odds ratio; OXVASC, Oxford Vascular Study; PE, pulmonary embolism; PTS, post-thrombotic syndrome; RCT, randomised controlled trial; RIETE, The Computerized Registry of Patients with Venous Thromboembolism; SMR, standardised mortality ratio; TULIPA, Thrombosis and Pulmonary Embolism in Out-Patients; SD, standard deviation; SE, standard error; VKA, vitamin K antagonist; VTE, venous thromboembolism;

* except where stated otherwise e.g. SD or SE

Appendix Table 3: Drug costs for treating DVT and PE

Drug	**Dosing and delivery**	**Product and cost**[28]	**Drug cost per course**	**Monitoring / administration cost**[30]	**Proportion using treatment**[21]
Apixaban	Initially 10 mg twice daily for seven days, orally. Followed by 5 mg twice daily, orally for the remainder of the three month (91 days) treatment period	Apixaban 5 mg = £53.20 for 56 tablets (cost per tablet is same for 28 tablet pack size)	£186.20	£73 *	20% (half of the 40% using DOACs)
Rivaroxaban	Initially 15 mg twice daily for 21 days, to be taken orally with food. Followed by 20 mg once daily, to be taken orally with food for the remainder of the three month (91 days) treatment period	Rivaroxaban 20 mg = £50.40 for 28 tablets (cost per tablet is same for 15mg and larger and smaller pack sizes)	£201.60	£73 *	20% (half of the 40% using DOACs)
Enoxaparin	1.5 mg/kg every 24 hours by subcutaneous injection until adequate oral anticoagulation established (seven days) i.e. 120 mg if assuming weight of 80kg	Clexane Forte 120mg/0.8ml solution (Sanofi) - £87.93 for 10 pre-filled syringes Prescription only medicine assumed for other drugs	£61.55	£72.71†	30% (45% of heparin use)

Dalteparin	15 000 units (assuming body weight of 80kg) once daily until adequate oral anticoagulation established (seven days)	Dalteparin sodium 15,000 units / 0.6ml solution (Pfizer Ltd / Ennogen Healthcare Ltd / JM McGill Ltd) - £42.34 for five pre-filled syinges	£59.28	£72.71†	18% (35% of heparin use)
Tinzaparin	175 units / kg once daily until adequate oral anticoagulation established (seven days) i.e. 14,000 units if assuming 80kg	Innohep 14,000 units / 0.7ml solution (LEO Pharma) - £83.30 for 10 pre-filled syringes	£58.31	£72.71†	6% (20% of heparin use)
Warfarin	5mg once daily orally for three months (91 days)	Warfarin sodium 5mg (various suppliers) = £0.70 for 28 tablets	£3.22	£238.84‡	60%
Average across those using DOACs and those using LMWH /VKA			£115.55	£216.07	**Total: £331.63**

Abbreviations: DVT, deep vein thrombosis; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; PE, pulmonary embolism; VKA, vitamin K antagonist

Note: Costing assumes that packs of syringes and packets of tablets can be split between patients by dispensing pharmacy

* Based on one nurse led telephone follow-up (WF01C) at 10 days and one consultant led follow-up (WF01A) at three months to assess need for ongoing treatment[30]

† Based on the costs estimated by Menakaya *et al[29]* with the number of district nurse administrations reduced to reflect shorter duration of treatment (seven days versus six weeks)

‡ based on HRG costs[30] for nine face-to-face visit at non-consultant led anticoagulation service over three months (WF01B for first attendance and WF01A for follow-up) plus a consultant led follow-up at three months to assess need for ongoing treatment

Appendix Table 4: Resource use and costs for patients presenting with PE and symptomatic DVT

	Proportion using resource[21]				
	Non-fatal PE	**Symptomatic proximal DVT**	**Symptomatic distal DVT**	**Unit cost per patient using this resource**	**Description**
Healthcare contacts / admission					
GP visit	20%	50%	50%	£39	GP cost per surgery consultation with qualification costs including direct care staff costs [31]
Ambulance transfer to Emergency Department	60%	10%	0%	£257	NHS Schedule for Reference Costs 2018-2019 "See and treat and convey", code ASS02. [30]
Emergency department visit leading to admission	60%	10%	0%	£279	NHS Schedule for Reference Costs 2018-2019 VB05Z Type 01 Admitted (Category two investigation with Category three treatment). [30]
Emergency department without admission	40%	90%	100%	£239	NHS Schedule for Reference Costs 2018-2019 VB05Z Type 01 Non-admitted (Category two investigation with Category three treatment) [30]
Short stay admission for PE	60%	0%	0%	£1,410	NHS Schedule for Reference Costs 2018-2019 Weighted average cost of non-elective inpatient (short and long-stay with excess bed days) for "Pulmonary Embolus with Interventions", codes DZ09J to DZ09N & DZ09P and DZ09Q. [30]

Short stay admission for DVT	0%	10%	0%	£904	NHS Schedule for Reference Costs 2018-2019 Weighted average cost of non-elective inpatient (short and long-stay with excess bed days) for "Deep Vein Thrombosis" CC score 0 to 12+, codes YQ51A to YQ51E. [30]
Critical care unit stay	10%	0%	0%	£1,028	NHS Schedule for Reference Costs 2018-2019[30] Weighted average cost of adult Critical Care, zero to six or more organs Supported, codes XC01Z to XC01Z. [30]
Subtotal for healthcare contacts.	**£1,374**	**£379**	**£259**		
Diagnostic costs					
Risk assessment tool (Wells score)	Included in Emergency Department episode so not costed separately				
D-Dimer					
ECG					
Chest x-ray					
Proximal leg vein Ultrasound	0%	100%	100%	£53	NHS Schedule for Reference Costs 2018-2019. RD40Z Outpatient Ultrasound Scan with duration of less than 20 minutes, without contrast £55[30]
CTPA	90%	0%	0%	£108	NHS Schedule for Reference Costs 2018-2019. RD21A Outpatient Computerised Tomography Scan of one area, with post contrast only, 19 years and over[30]

V/Q SPECT	5%	0%	0%	£287	NHS Schedule for Reference Costs 2018-2019. RN08A Outpatient Single Photon Emission Computed Tomography (SPECT), 19 years and over[30]
V/Q planar	5%	0%	0%	£321	NHS Schedule for Reference Costs 2018-2019. RN18A Outpatient Lung Ventilation or Perfusion Scan, 19 years and over[30]
Echocardiogram	20%	0%	0%	£76	NHS Schedule for Reference Costs 2018-2019. RD51A Outpatient simple echocardiogram[30]
Subtotal for unbundled diagnostics	£143	£53	£53		
Subtotal for drug treatment	£332	£332	£332		See Appendix Table 3 above.
Total	£1,849*	£763	£643		

CC, complication or comorbidity; CTPA, computerised tomography pulmonary angiography; DVT, deep vein thrombosis; ECG, electrocardiogram; PE, pulmonary embolism; GP, general practitioner; SPECT, single photon emission tomography; V/Q, ventilation/perfusion

* Fatal PEs are assumed to incur diagnostic and inpatient costs but not VTE treatment costs i.e. total cost of £1,517

Appendix Table 5: Utility values applied in short-term decision tree

Absolute utility value	**Absolute utility value**	**Range**	**Source**	**Notes**
Well / asymptomatic DVT without prophylaxis	0.800	0.799 to 0.801	Ara and Brazier 2010[20]	Population mean utility values based on average age and sex mix at base-line
Symptomatic proximal or distal DVT	0.769	0.756 to 0.779	Monreal 2019[23]	3.8% reduction relative to well patients based on comparison of average utility over six months for DVT (0.820) versus PE versus utility of matched population norms (0.852)
non-fatal PE	0.768	0.756 to 0.779	Chuang 2019[22]	4.0% reduction relative to well patients based on comparison of average utility over six months (0.804) for PE versus utility of matched population norms (0.838)
non-fatal ICH	0.580	0.540 to 0.619	Luengo-Fernandez 2013[25]	Absolute decrement of 0.22 measured at one month
non-fatal non-ICH bleed	0.685	0.684 to 0.686	Chuang 2019[22]	Assumed same utility decrement for PE and GI bleeds at one month. 14% reduction based on utility for PE at one month (0.718) versus utility of matched population norms (0.838) from Chuang 2019[22]
Prophylaxis – absolute decrement applied to utility values of well / asymptomatic DVT	0.007	0.000 to 0.050	Marchetti 2000[26]	Patients willing to trade average of 2.7 days per year to avoid treatment with LMWH
Treatment - absolute decrement applied to utility	0.011	0.000 to 0.083	Marchetti 2000[26]	Patients willing to trade average of four days per year to avoid treatment with warfarin

values for non-fatal PE or symptomatic DVT				
Fatal PE / fatal bleed	0	NA	Assumption	

DVT, deep vein thrombosis; ICH, intracranial haemorrhage; LMWH, low molecular weight heparin; PE, pulmonary embolism

Appendix Table 6 Utility multipliers for state-transition phase of the model

Health state (s)	Utility multiplier relative to well	Range	Source	Notes
PE survivor without CTEPH and PE survivor more than one year after surgery for CTEPH	1.000	0.998 to 1.000	Chuang 2019[22]	Average over six to 12 months following PE compared to matched general population norms[22]
Any DVT without PTS	1	NA	Assumption	Supported by Lubberts *et al*[38] systematic review finding no significant HRQoL decrement in nine long-term studies based on SF-36 outcomes
non-fatal ICH	0.888	0.837 to 0.937	Luengo-Fernandez 2013[25]	Multiplier calculated based on absolute decrement of 0.09 at five years (utility values stable from six months to five years) relative to absolute utility for well state
PTS	0.895	0.816 to 0.952	Enden 2013 [24]	Multiplier calculated based on absolute decrement of 0.09 relative to absolute utility for well state of 0.86
CTEPH –first year for surgically managed and every year for medically managed	0.629	0.579 to 0.690	Meads 2008[27]	Multiplier calculated based on comparison of utility for CTEPH (0.56) versus utility for NYHA class I (0.89)

CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; HRQoL, Health-related quality of life ;ICH, intracranial haemorrhage; LMWH, low molecular weight heparin; NYHA, New York Heart Association; PE, pulmonary embolism; PTS, post-thrombotic syndrome

Appendix Table 7: Probabilistic distributions for cost and utility inputs

Parameter description	Midpoint value	Uncertainty measure	Distribution	Source
Ambulance transfer to ED	£257	SE = £11	Gamma(551,0.47)	NHS Schedule for Reference Costs 2018-2019. HRG code, ASS02 See and treat and convey[30]
ED visit leading to admission	£279	SE = £6	Gamma(2210, 0.15)	NHS Schedule for Reference Costs 2018-2019. HRG code: Type 01, leading to admission, VB05Z Emergency Medicine, Category two Investigation with Category three Treatment[30]
ED visit not leading to admission	£239	SE=£4	Gamma(3204, 0.07)	NHS Schedule for Reference Costs 2018-2019. HRG code: Type 01, not leading to admission, VB05Z Emergency Medicine, Category two Investigation with Category three Treatment[30]
DVT admission - weighted average of following HRG costs;				NHS Schedule for Reference Costs 2018-2019. Non-elective inpatient (NEI) and non-elective short stay (NESS) costs for HRG codes covering Deep vein thrombosis with CC scores ranging from 0 to 12+[30]
YQ51A – NEI (N=1,377)	£4,017	SE=£198	Gamma(412, 9.7)	
YQ51A – NESS (N=492)	£564	SE=£33	Gamma(288, 2.0)	
YQ51B – NEI (N=1,183)	£2,873	SE=£129	Gamma(495, 5.8)	
YQ51B – NESS (N=895)	£470	SE=£13	Gamma(1237,0.4)	
YQ51C – NEI (N=1,665)	£2,433	SE=£78	Gamma(973, 2.5)	
YQ51C – NESS (N=2,391)	£418	SE=£11	Gamma(1433,0.3)	
YQ51D – NEI (N=1,686)	£2,020	SE=£46	Gamma(1903,1.1)	

YQ51D – NESS (N=6,249)	£384	SE=£9	Gamma(1822,0.2)	
YQ51E – NEI (N=908)	£1,772	SE=£42	Gamma(1814,1.0)	
YQ51E- NESS (N=11,731)	£320	SE=9	Gamma(1330,0.2)	
PE admission- weighted average of following HRG costs;				NHS Schedule for Reference Costs 2018-2019. Non-elective inpatient (NEI) costs and non-elective short stay (NESS) costs for HRG codes covering Pulmonary embolus with and without interventions with CC score from 0 to 12+ [30]
DZ09J – NEI (N=888)	£5,450	SE=£277	Gamma(338,14)	
DZ09J – NESS (N=62)	£1,280	SE=£168	Gamma(58, 22)	
DZ09K – NEI (N=585)	£3,384	SE=£130	Gamma(676, 5.0)	
DZ09K – NESS (N=65)	£790	SE=£56	Gamma(199, 4.0)	
DZ09L – NEI (N=3,160)	£3,522	SE=£140	Gamma(663, 5.5)	
DZ09L – NESS (N=1,181)	£667	SE=£21	Gamma(1026, 0.7)	
DZ09M – NEI (N=3,716)	£2,671	SE=£75	Gamma(1255,2.1)	
DZ09M – NESS (N=2,197)	£577	SE=18	Gamma(1054,0.6)	
DZ09N – NEI (N=5,105)	£2,201	SE=£45	Gamma(2358,0.9)	
DZ09N – NESS (N=4,374)	£533	SE=12	Gamma(2091, 0.3)	
DZ09P – NEI (N=6,126)	£1,845	SE=£38	Gamma(2417,0.8)	
DZ09P – NESS (N=8,768)	£488	SE=£12	Gamma(1595, 0.3)	
DZ09Q – NEI (N=3,226)	£1,584	SE=£29	Gamma(2989, 0.5)	
DZ09Q – NESS (N=9,048)	£448	SE=9	Gamma(2376, 0.2)	
Critical care – weighted average of HRG costs for codes;				NHS Schedule for Reference Costs 2018-2019.

XC01Z XC02Z XC03Z XC04Z XC05Z XC06Z XC07Z	£1,673 £1,574 £1,655 £1,640 £1,450 £792 £516	N=1 SE=£152 SE=£114 SE=£67 SE=£49 SE=£78 SE=£129	Fixed Gamma(107, 14.7) Gamma(211, 7.9) Gamma(605, 2.7) Gamma(884, 1.7) Gamma(104, 7.6) Gamma(16.0, 32.2)	HRG codes for Adult Critical Care for zero to six organs supported[30]
Proximal leg vein ultrasound	£53	SE=£1	Gamma(2135,0.03)	NHS Schedule for Reference Costs 2018-2019[30]
CTPA	£108	SE=£4	Gamma(635,0.17)	NHS Schedule for Reference Costs 2018-2019 RD21A Outpatient Computerised Tomography Scan of one area, with post contrast only, 19 years and over[30]
V/Q SPECT	£287	SE=£20	Gamma(202,1.42)	NHS Schedule for Reference Costs 2018-2019 RN08A, Outpatient Single Photon Emission Computed Tomography (SPECT), 19 years and over[30]
V/Q planar	£321	SE=£10	Gamma(1045,0.31)	NHS Schedule for Reference Costs 2018-2019 RN18A Outpatient Lung Ventilation or Perfusion Scan, 19 years and over[30]
Echocardiogram	£76	SE=£6	Gamma(146,0.52)	NHS Schedule for Reference Costs 2018-2019

				RD51A Outpatient Simple Echocardiogram, 19 years and over[30]
Proportion receiving LMWH who need district nurse administration	4%	95% CI 1.3% to 7.8%	Beta(5,123)	Menakaya *et al [29]*
Fatal bleed	£1,592	SD=1886, N=8	Gamma(5.70, 279)	Luengo-Fernandez *et al* (cost before inflation)[32]
Acute costs for non-fatal ICH (first 90 days) - Weighted average of;				Luengo-Fernandez *et al* [32] (cost before inflation)
Non-disabling non-fatal stroke	£9,903	SD = 4510, N=5	Gamma(24, 411)	
Moderately-disabling non-fatal stroke	£25,442	SD = 9635, N=3	Gamma(21, 1216)	
Totally-disabling non-fatal stroke	£43,036	SD = NA, N=1	Fixed	
Residential costs for non-fatal ICH (first 90 days)	£6,880	SD=£15,600, N=136	Gamma(26,260)	Luengo-Fernandez *et al [32]*
GP costs for non-fatal ICH (first 90 days)	£98	95% CI £27 to £169	Norm(98,36)	Luengo-Fernandez *et al [32]*
Emergency care costs for non-fatal ICH (first 90 days)	£99	95% CI £56 to £141	Norm (99, 22)	Luengo-Fernandez *et al [32]* (cost before inflation (cost before inflation)
Non-fatal non-ICH bleed (weighted average of HRG costs);				NHS Schedule for Reference Costs 2018-2019

FD03A – NEI (N=1,110)	£5,377	SE=£201	Gamma(714, 7.5)	HRG codes for GI bleed without interventions, with single interventions and with multiple interventions. [30]
FD03A – NESS (N=30)	£2,360	SE=£310	Gamma(58, 41)	
FD03B– NEI (N=885)	£3,510	SE=£131	Gamma(722, 4.9)	
FD03B– NSS (N=16)	£2,088	SE=£1,109	Gamma(3.6, 590)	
FD03C – NEI (N=1,642)	£3,866	SE=£171	Gamma(514, 7.5)	
FD03C– NSS (N=41)	£1,345	SE=£105	Gamma(166, 8.1)	
FD03D – NEI (N=2,329)	£2,796	SE=£92	Gamma(913, 3.0)	
FD03D– NSS (N=46)	££2,360	SE=£156	Gamma(229, 10)	
FD03E – NEI (N=5,481)	£2,247	SE=£47	Gamma(2331, 1.0)	
FD03E – NEI (N=108)	£1,089	SE=£82	Gamma(£178, 6.1)	
FD03F – NEI (N=2,891)	£2,818	SE=£100	Gamma(792, 3.6)	
FD03F – NEI (N=2,213)	£591	SE=£19	Gamma(1000, 0.6)	
FD03G – NEI (N=7,278)	£2,198	SE=£41	Gamma(2931, 0.8)	
FD03G – NEI (N=8,830)	£541	SE=£15	Gamma(1221,0.4)	
FD03H – NEI (N=16,290)	£1,575	SE=£27	Gamma(3523, 0.8)	
FD03H – NEI (N=40,167)	£438	SE=11	Gamma(1640, 0.3)	
Anticoagulant service face to face follow-up consultant led	£53	SE=£5	Norm(53,5.3) with minimum of zero	NHS Schedule for Reference Costs 2018-2019 Service code 324 - WF01A non-admitted[30]
Anticoagulant service face to face follow-up non-consultant led	£20	SE=£2	Norm(20,2.0) with minimum of zero	NHS Schedule for Reference Costs 2018-2019 Service code 324- WF01A non-admitted[30]

Anticogulant service first face to face attendance non-consultant led	£26	SE=£3	Norm(26,2.6) with minimum of zero	NHS Schedule for Reference Costs 2018-2019 Service code 324- WF01B non-admitted[30]
Anticoagulant service non face to face follow-up non-consultant led	£20	SE=£20	Norm(20,2.0) with minimum of zero	NHS Schedule for Reference Costs 2018-2019 Service code 324– WF01C non-admitted [30]
Vascular surgery first appointment face to face consultant led	£165	SE=£6	Gamma(759,0.22)	NHS Schedule for Reference Costs 2018-2019 Service code 107 – WF01B non-admitted[30]
Vascular surgery follow-up appointment face to face, consultant led	£134	SE=£4	Gamma(942, 0.14)	NHS Schedule for Reference Costs 2018-2019 Service code 107 – WF01A non-admitted[30]
Vascular surgery first appointment face to face non consultant led	£132	SE=£11	Gamma(132,1.0)	NHS Schedule for Reference Costs 2018-2019 Service code 107 – WF01B non-admitted[30]
Vascular surgery follow-up appointment face to face, non consultant led	£121	SE=£14	Gamma(79, 1.53)	NHS Schedule for Reference Costs 2018-2019 Service code 107 – WF01A non-admitted[30]
Surgical management of CTEPH – average of following HRG costs; DZ02H DZ02J DZ02K	 £9,782 £7,500 £6,506	 SE=£363 SE=£300 SE=£270	 Gamma(723, 13.5) Gamma(627, 12.0) Gamma(579,11.2)	NHS Schedule for Reference Costs 2018-2019 HRG codes for Complex Thoracic Procedures, 19 years and over, with CC Score ranging from 0 to 6+[30]
Disutility for stroke up to six months	-0.22	95% CI -0.26 to -0.18	Norm(-0.22, 0.02)	Luengo-Fernandez *et al* (2013)[25]

Disutility for stroke from six months	-0.09	95% CI -0.13 to -0.05	Norm(-0.09, 0.02)	Luengo-Fernandez *et al* (2013)[25]
Utility immediately after DVT	0.72	SE=0.006	Beta(3977, 1565)	Monreal 2019[23]
Utility immediately after PE	0.72	SE=0.007	Beta(2741, 1080)	Chuang 2019[22] [assumed same SD as observed for patients having DVT in Monreal 2019]
Utility for DVT without PTS	0.86	95% CI 0.823 to 0.903	Beta(248,40.3)	Enden *et al (*2013) [24]
Disutility for PTS versus no PTS after DVT	0.09	95% CI 0.03 to 0.15	Beta(7.78, 78.6)	Enden *et al (*2013) [24]
Utility for CTEPH	0.56	SD=0.29, N=308	Beta(505, 397)	Meads *et al* (2008)[27]
Utility for NYHA class 1	0.86	SD=0.17, N=35	Beta(105, 12.9)	Meads *et al* (2008)[27]
Utility for LMWH	0.993	SD=0.016	Beta(27.5, 0.205)	Marchetti *et al* (2001) [26]
Utility for warfarin	0.989	SD=0.024	Beta(17.6, 0.195)	Marchetti *et al* (2001)[26]
Utility regression for age related decrement – coefficients for Age Age x Age constant	 -0.000172 -0.000034 0.9584588	 SE=0.0003737 SE=3.96 x 10^{-6} SE = 0.0077431	Multivariate normal	Ara and Brazier (2011)[20] Variance – covariance matrix Age: Age 1.4 x 10^{-7} Age x Age: Age -1.5 x 10^{-9}, Age x Age 1.6 x 10^{-11} constant: Age -2.80 x 10^{-6}, Age x Age 2.8 x 10^{-8}, constant 6 x 10^{-5}

Abbreviations: CC, complications and comorbidities; CI, confidence interval; CG, clinical guideline; CTEPH, chronic thromboembolic pulmonary hypertension; CODA, convergence diagnostics and output analysis; CTPA, computerised tomography pulmonary angiography; DVT, deep vein thrombosis; ED, emergency department; GI, gastrointestinal; GP, general practitioner; HR, hazard ratio; HRG, healthcare resource group; ICH, intracranial haemorrhage; IQR, interquartile range; LMWH, low molecular weight heparin; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; ONS, Office for National Statistics; OR, odds ratio; PE, pulmonary embolism; PTS, post-thrombotic syndrome; RCT, randomised controlled trial; SD, standard deviation; SE, standard error; SPECT, Single Photon Emission Computed Tomography; V/Q, ventilation – perfusion VTE, venous thromboembolism

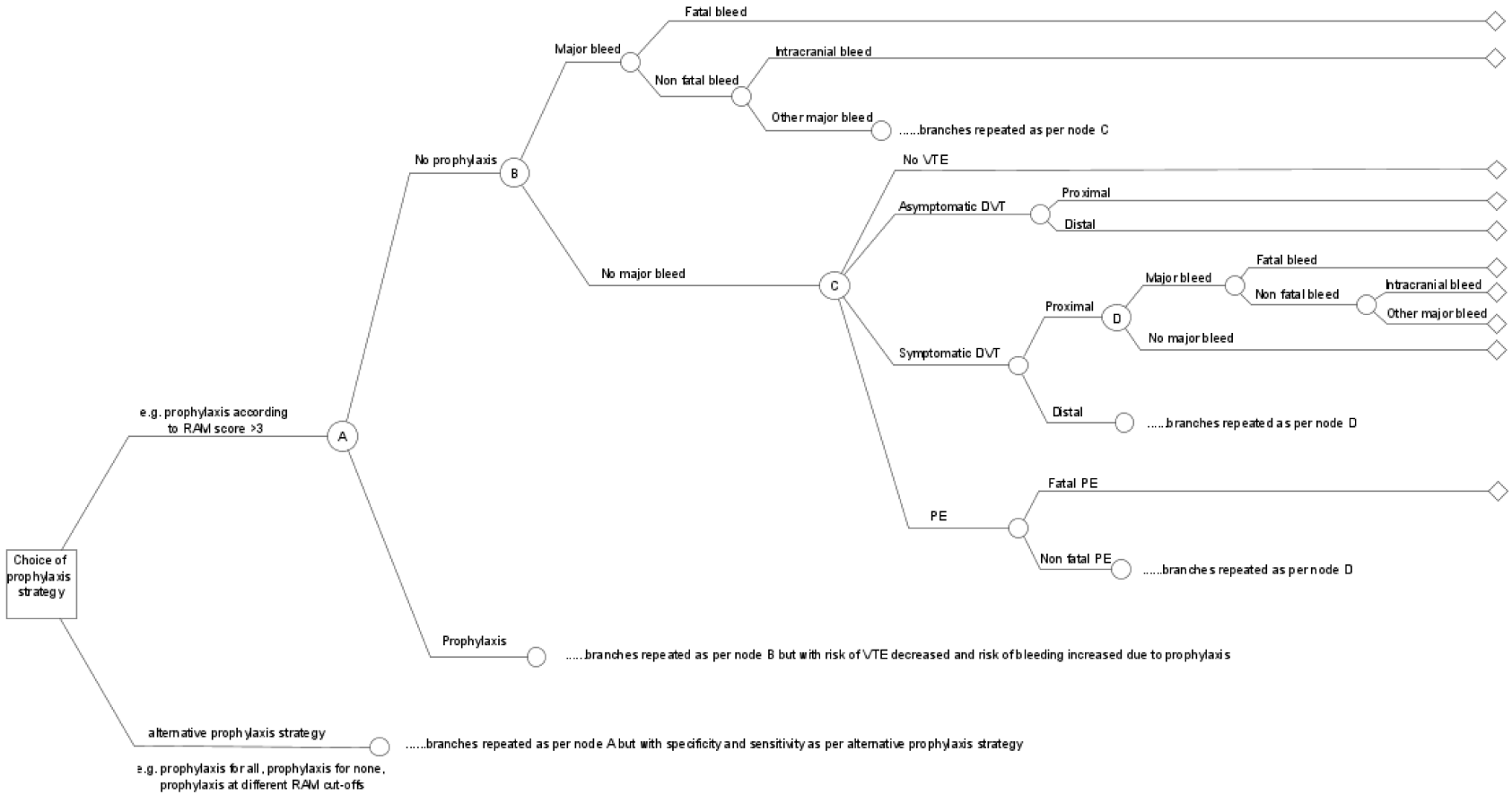
Appendix Table 8: Deterministic one-way sensitivity analyses (assumes RAM is Padua and performance is based on Greene et al.)

Scenario	Parameter varied	Parameter value in basecase scenario	Parameter value in current scenario	Optimal strategy in current scenario*
Basecase	N/A	N/A	N/A	PPX for all
Younger patients	Age	65.8	20	PPX for all
Older patients	Age	65.8	80	PPX for all
Double utility decrement for PPX	Utility decrement	0.007	0.015	PPX for all
Low discounting rate for costs and QALYs	Discount rate	3.5%	1.5%	PPX for all
High discounting rate for costs and QALYs	Discount rate	3.5%	6.0%	PPX for all
Utility decrement of PTS is halved	Utility decrement	10%	5%	PPX for all
Utility decrement of PTS from Lenert et al.	Utility decrement	10%	2%	PPX for all
PTS cost from Caprini	Year 1 cost Year 2 cost	£293 £78	£1022 £423	PPX for all
Lower case-fatality rate of PE	Case-fatality rate of PE	26.8%	13%	PPX for all
Higher case-fatality rate of PE	Case-fatality rate of PE	26.8%	67%	PPX for all
Increased use of DOACs to treat VTE	% of VTE treatment that is DOACs	40%	100%	PPX for all
No asymptomatic DVTs	Asymptomatic DVT risk	30.5%	0%	PPX for all
No PTS risk in asymptomatic DVT (proximal or distal)	Risk of PTS in; - Proximal - Distal	 57.5% 15.6%	 0% 0%	PPX for all
Low risk of VTE (one sixth of baseline risk)	Risk of symptomatic VTE	3.4%	0.6%	Padua ≥2

Higher bleed risk during PPX (six times higher)	Risk of bleeding without PPX	0.67%	4.00%	Padua ≥1
Low risk of VTE (one half of baseline risk) combined with higher risk of bleeding (three times higher than baseline)	Risk of symptomatic VTE Risk of bleeding without PPX	3.4% 0.67%	1.7% 2.00%	Padua ≥1
Low risk of VTE (one half of baseline risk) combined with higher risk of bleeding (six times higher than baseline)	Risk of symptomatic VTE Risk of bleeding without PPX	3.4% 0.67%	1.7% 4.00%	Padua ≥4 †
Bleed risk during VTE treatment reflects any HAS-BLED score	Risk of major bleeding during anticoagulation	0.9%	2.0%	PPX for all
7 days of LMWH (including 2 days post-discharge)	Cost of PPX	£23.91	£101.03	PPX for all
Higher risk of death in year of admission	Risk of death in year 1	10%	22%	PPX for all
No additional cost for administering RAM	Cost of RAM administration	£9.08	£0	PPX for all
Quadruple cost of administering RAM	Cost of RAM administration	£9.08	£36.33	PPX for all
No increase in inpatient care due to VTE	Distal DVT cost Proximal DVT cost PE cost	£644.88 £765.05 £1850.68	£386.10 £386.10 £476.57	PPX for all
VTE occurs 3 days after admission	Time of VTE	42	3	PPX for all
VTE occurs 90 days after admission	Time of VTE	42	90	PPX for all

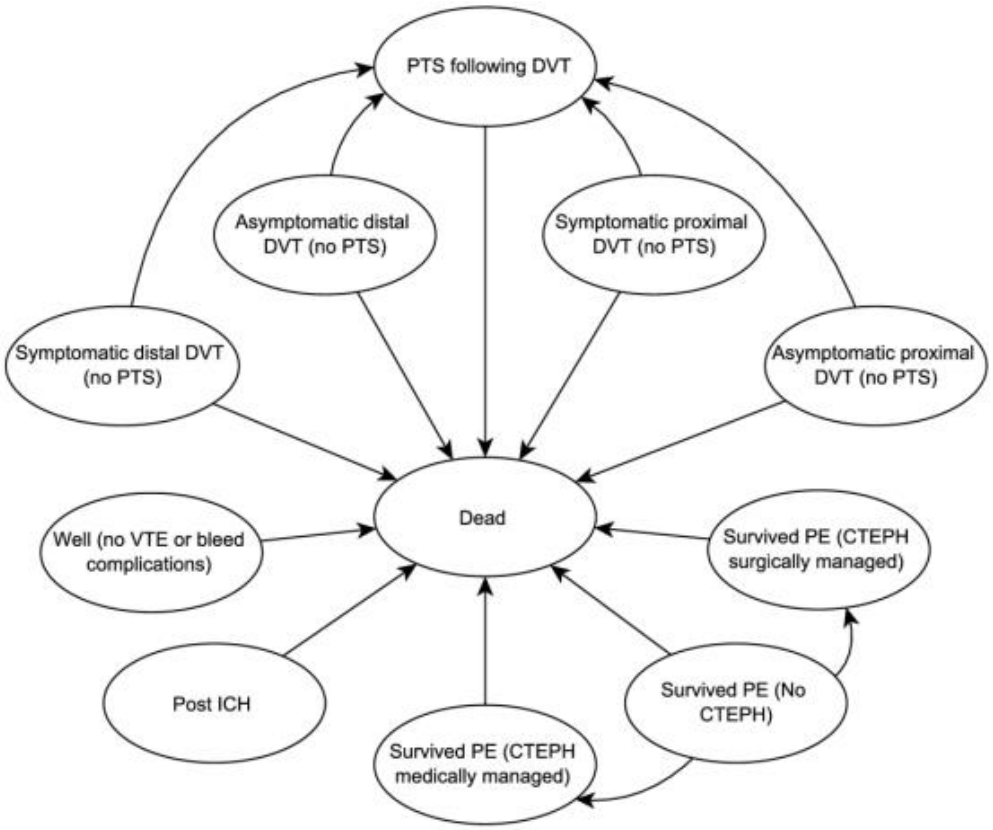
* Optimal strategy when valuing a QALY at £20,000; † PPX for all has lower QALYs than PPX for none in this scenario

Appendix Figure 1: Short-term (six month) decision tree model structure



Footnote: Node B captures the risk of bleeding related to prophylaxis whilst Node D represents the risk of bleeding in patients during therapeutic dose anticoagulation given following a symptomatic VTE.

Appendix Figure 2: Long-term Markov model (reproduced from Pandor et al.[21])



Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial haemorrhage; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism

Figure 2 is reproduced from Pandor A, Horner D, Davis S, Goodacre S, Stevens JW, Clowes M, et al. Different strategies for pharmacological thromboprophylaxis for lower-limb immobilisation after injury: systematic review and economic evaluation. Health Technol Assess 2019;23(63)

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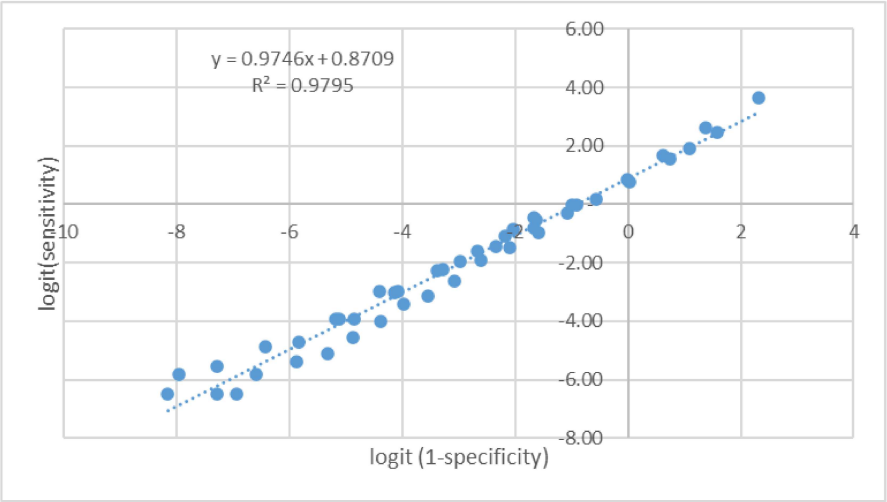
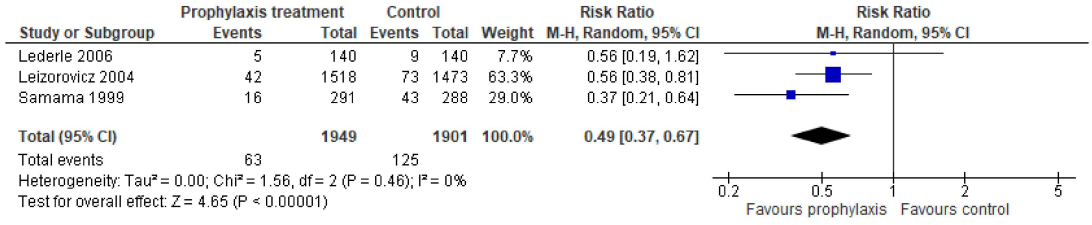
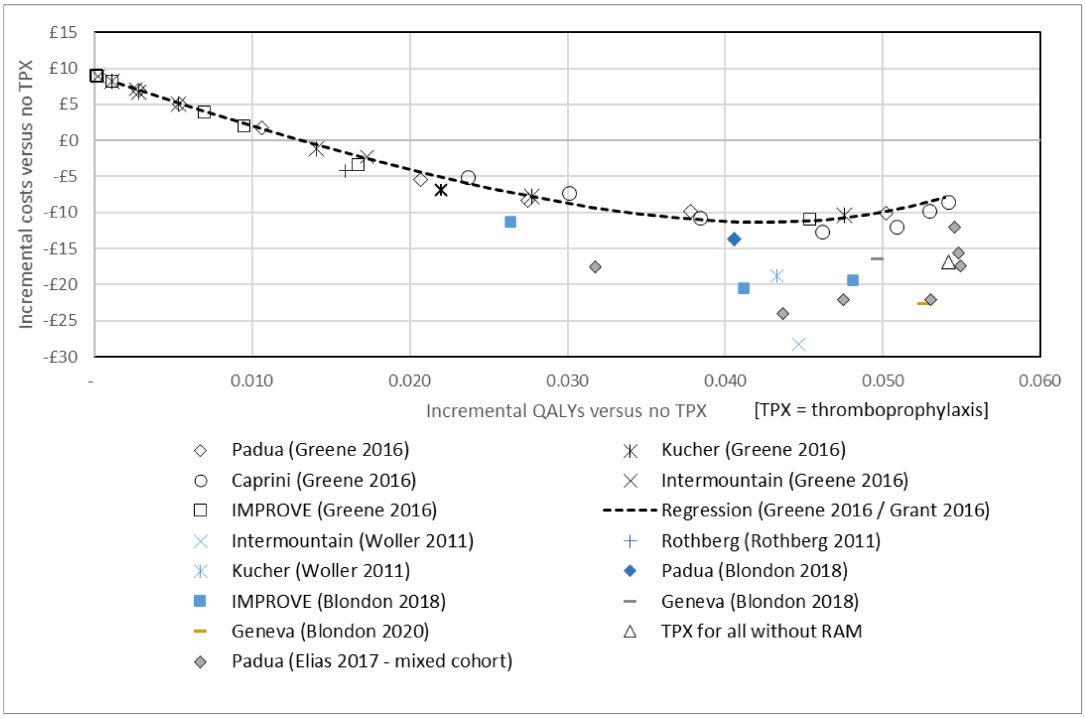
Appendix Figure 3: Regression to estimate performance of a typical RAM in medical inpatients



Appendix Figure 4: Meta-analysis of VTE outcomes in medical inpatients



Appendix Figure 5: Cost-effectiveness plane for all RAMs validated in cohorts of medical inpatients and the Padua RAM in an alternative study (mixed cohort of medical and surgical inpatients)



References for supplementary materials

1. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost 2010;8(11):2450-7. doi: 10.1111/j.1538-7836.2010.04044.x [published Online First: 2010/08/27]

2. 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 (UK), 2010.

3. Lederle FA, Sacks JM, Fiore L, et al. The prophylaxis of medical patients for thromboembolism pilot study. Am J Med 2006;119(1):54-9. doi: 10.1016/j.amjmed.2005.03.049 [published Online First: 2006/01/25]

4. Leizorovicz A, Cohen AT, Turpie AG, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 2004;110(7):874-9. doi: 10.1161/01.CIR.0000138928.83266.24 [published Online First: 2004/08/04]

5. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med 1999;341(11):793-800. doi: 10.1056/NEJM199909093411103 [published Online First: 1999/09/09]

6. Decousus H, Tapson VF, Bergmann JF, et al. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. Chest 2011;139(1):69-79. doi: 10.1378/chest.09-3081 [published Online First: 2010/05/11]

7. Kooiman J, van Hagen N, Iglesias Del Sol A, et al. 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(4):e0122520. doi: 10.1371/journal.pone.0122520 [published Online First: 2015/04/24]

8. Nieto JA, Solano R, Ruiz-Ribo MD, et al. Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: findings from the RIETE registry. J Thromb Haemost 2010;8(6):1216-22.

9. Hach-Wunderle V, Bauersachs R, Gerlach HE, et al. 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(1):5-12. doi: 10.1016/j.jvsv.2012.07.003 [published Online First: 2013/01/01]

10. van Dongen CJ, Prandoni P, Frulla M, et al. Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome. J Thromb Haemost 2005;3(5):939-42. doi: 10.1111/j.1538-7836.2005.01333.x [published Online First: 2005/05/05]

11. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. Eur Respir J 2017;49(2) doi: 10.1183/13993003.01792-2016 [published Online First: 2017/02/25]

12. Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004;350(22):2257-64. doi: 10.1056/NEJMoa032274 [published Online First: 2004/05/28]

13. Delcroix M, Lang I, Pepke-Zaba J, et al. Long-Term Outcome of Patients With Chronic Thromboembolic Pulmonary Hypertension: Results From an International Prospective Registry. Circulation 2016;133(9):859-71. doi: 10.1161/CIRCULATIONAHA.115.016522 [published Online First: 2016/01/31]

14. Office of National Statistics. National Life Tables, England 1980-82 to 2016-18 London, UK: Office for National Statistics; 2019 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2016to2018 accessed 01/04/2020.

15. Moore E, Munoz-Arroyo R, Schofield L, et al. Death within 1 year among emergency medical admissions to Scottish hospitals: incident cohort study. BMJ Open 2018;8(6):e021432. doi: 10.1136/bmjopen-2017-021432 [published Online First: 2018/07/02]

16. Fogelholm R, Murros K, Rissanen A, et al. Long term survival after primary intracerebral haemorrhage: a retrospective population based study. J Neurol Neurosurg Psychiatry 2005;76(11):1534-8. doi: 10.1136/jnnp.2004.055145 [published Online First: 2005/10/18]

17. Harenberg J, Roebruck P, Heene DL. Subcutaneous low-molecular-weight heparin versus standard heparin and the prevention of thromboembolism in medical inpatients. The Heparin Study in Internal Medicine Group. Haemostasis 1996;26(3):127-39. doi: 10.1159/000217198 [published Online First: 1996/05/01]

18. Hull RD, Schellong SM, Tapson VF, et al. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. Ann Intern Med 2010;153(1):8-18. doi: 10.7326/0003-4819-153-1-201007060-00004 [published Online First: 2010/07/14]

19. Kleber FX, Witt C, Vogel G, et al. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. Am Heart J 2003;145(4):614-21. doi: 10.1067/mhj.2003.189 [published Online First: 2003/04/08]

20. 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(4):539-45. doi: 10.1016/j.jval.2010.10.029 [published Online First: 2011/06/15]

21. Pandor A, Horner D, Davis S, et al. Different strategies for pharmacological thromboprophylaxis for lower-limb immobilisation after injury: systematic review and economic evaluation. Health Technol Assess 2019;23(63):1-190. doi: 10.3310/hta23630

22. Chuang LH, Gumbs P, van Hout B, et al. 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(8):2111-24. doi: 10.1007/s11136-019-02175-z [published Online First: 2019/04/06]

23. Monreal M, Agnelli G, Chuang LH, et al. Deep Vein Thrombosis in Europe-Health-Related Quality of Life and Mortality. Clin Appl Thromb Hemost 2019;25:1076029619883946. doi: 10.1177/1076029619883946 [published Online First: 2019/12/17]

24. Enden T, Wik HS, Kvam AK, et al. 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(8):e002984. doi: 10.1136/bmjopen-2013-002984 [published Online First: 2013/08/31]

25. Luengo-Fernandez R, Gray AM, Bull L, et al. Quality of life after TIA and stroke: ten-year results of the Oxford Vascular Study. Neurology 2013;81(18):1588-95. doi: 10.1212/WNL.0b013e3182a9f45f [published Online First: 2013/10/11]

26. Marchetti M, Pistorio A, Barone M, et al. Low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous thromboembolism: a cost-effectiveness analysis. Am J Med 2001;111(2):130-9. [published Online First: 2001/08/11]

27. Meads DM, McKenna SP, Doughty N, et al. The responsiveness and validity of the CAMPHOR Utility Index. Eur Respir J 2008;32(6):1513-9. doi: 10.1183/09031936.00069708 [published Online First: 2008/09/05]

28. Joint Formulary Committee. British National Formulary (online) [Drug Tariff]: London, UK; [Available from: http://www.medicinescomplete.com accessed 06/04/2020.

29. Menakaya CU, Pennington N, Muthukumar N, et al. The cost of outpatient venous thromboembolism prophylaxis following lower limb injuries. Bone Joint J 2013;95-B(5):673-7. doi: https://dx.doi.org/10.1302/0301-620X.95B5.30555

30. NHS Improvement. National Cost Collection: National Schedule of NHS Costs - Year 2018-19 - NHS trust and NHS foundation trusts London, UK2020 [Available from: https://www.england.nhs.uk/publication/2018-19-national-cost-collection-data-publication/ accessed 02/03/2020.

31. Curtis LAB, A.;. Unit costs of health and social care 2019 Canterbury, UK: Personal Social Services Research Unit; 2019 [Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/ accessed 15/04/2020.

32. Luengo-Fernandez RY, G. S. C.; Gray, A. M.; Rothwell, P. M. Population-based study of acute- and long-term care costs after stroke in patients with AF. International Journal of Stroke 2012;8:308-14.

33. Curtis LAB, A.;. Unit costs of health and social care 2017 Canterbury, UK: Personal Social Services Research Unit; 2017 [Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/ accessed 15/04/2020.

34. Grant PJ, Greene MT, Chopra V, et al. Assessing the Caprini Score for Risk Assessment of Venous Thromboembolism in Hospitalized Medical Patients. Am J Med 2016;129(5):528-35. doi: 10.1016/j.amjmed.2015.10.027 [published Online First: 2015/11/10]

35. Greene MT, Spyropoulos AC, Chopra V, et al. Validation of Risk Assessment Models of Venous Thromboembolism in Hospitalized Medical Patients. Am J Med 2016;129(9):1001 e9-01 e18. doi: 10.1016/j.amjmed.2016.03.031 [published Online First: 2016/04/25]

36. National Guideline Centre. Venous thromboembolism in over 16s - Reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism: NICE guideline NG89. London, UK: National Institute for Health and Care Excellence, 2018.

37. Goodacre SH, K.; Shephard, N.; Pollard, D.; Hunt, B.; 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. Heath Technology Assessment 2018;22(47)

38. Lubberts B, Paulino Pereira NR, Kabrhel C, et al. 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(3):417-31. doi: 10.1160/TH16-02-0152 [published Online First: 2016/07/01]